

CLINICAL AND EXPERIMENTAL INVESTIGATIONS INTO THE
PREVENTION OF THE ACID ASPIRATION SYNDROME
(MENDELSON'S SYNDROME)

by

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PREFACE

One of the main complications associated with anaesthesia is aspiration of gastric contents into the tracheobronchial tree! This ill fortune is followed by pulmonary damage to the lung with a high morbidity and mortality rate¹. Data from obstetrical anaesthesia show this complication, next to toxæmia, to figure prominently in causing maternal deaths². Aspiration is however also a major complication to anaesthesia for general surgery³ and a life threatening danger to every comatose and debilitated patient⁴.

This review deals with the causes of tracheobronchial aspiration of acid gastric content. By highlighting these predisposing risk factors, the occurrence of acid aspiration can hopefully be minimized. First, however, historical aspects, clinical features, pathology, pathophysiology, predisposing factors and treatment will be discussed. Finally, studies developed to evaluate predisposing risk factors with recommendations as to improved prevention of this dreaded syndrome will be presented through a collection of personal publications.

This review is therefore based mainly on the above-mentioned studies reported in the enclosed papers, referred to in the text by their Roman numerals.

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DEFINITIONS

In this review, some words and expressions will have the following meaning when not otherwise stated.

Aspiration - Entering of foreign matter into the tracheobronchial tree.

Gastric Pressure - The hydrostatic pressure measured in the stomach in relation to the ambient atmospheric pressure.

Gastric Volume - The volume of gastric content which can be measured after evacuation of the stomach, using a gastric tube, gas not included.

Laryngeal Competence - A normal reacting larynx with intact reflexes preventing foreign matter from entering the tracheobronchial tree.

Lower Oesophageal Sphincter - A zone of increased intraluminal pressure localised in the lower part of the oesophagus at the gastro-oesophageal junction. The abbreviations LOS or LES refer to different spelling in English (oesophagus) or American (esophagus) literature.

LOS Pressure - The hydrostatic intraluminal pressure measured at the gastro-oesophageal junction.

Barrier Pressure - The difference in hydrostatic pressure recorded between LOS and gastric pressures.

Regurgitation - Passive reflux of gastric content into the oesophagus.

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ACID ASPIRATION SYNDROME

This syndrome describes a severe chemical pneumonitis caused when gastric content enters the lung. 'This may occur following regurgitation (passive) or vomiting (active expulsion) of gastric contents when a subject's laryngeal reflexes are depressed by excessive sedation of central nervous system (CNS) depression e.g. trauma, drugs or anaesthetic agents. Mendelson's classic paper in 1946 has made his name stick to this disease process so that acid aspiration syndrome is synonymous with the Mendelson's Syndrome⁵. In his work which included both human and animal experimentation, he clearly demonstrated that the primary etiological factor in aspiration pneumonitis was the acidity of the aspirate, and that a pH below 2,5 was needed to produce the pathognomonic picture of cyanosis, tachycardia, dyspnoea and expiratory wheeze.

Hall, however, was the first to draw attention to the frequency of aspiration pneumonitis in obstetrics in 1940. His paper was entitled "Aspiration pneumonitis - an obstetric hazard".⁶ The first published death under anaesthesia, caused by aspiration, occurred under chloroform in 1848⁷. In the first 51 cases of death under chloroform anaesthesia reported in 1861, at least two of them resulted from aspiration⁸.

CLINICAL FEATURES

The clinical picture produced by aspiration of gastric contents depends also on the nature of the material aspirated. When the aspirated material is of sufficient

size to cause acute respiratory obstruction, asphyxia and death may rapidly ensue. Chest x-ray will reveal collapse of lung tissue supplied by the involved bronchus and often a mediastinal shift towards the obstructed side. Liquid aspiration is however more common and may be silent or overt. If the aspirated material is liquid and acid, dyspnoea with cyanosis and tachycardia usually occur.

In some instances the signs of imminent vomiting are present, that is, irregular respiration, breath-holding, increased salivation and swallowing. Often, however, the first warning of aspiration is the appearance of gastric contents in the pharynx or mouth. Should the aspiration go unnoticed, it will not be before several hours later that cyanosis and tachycardia may be observed and a chest x-ray reveals the classical picture of aspiration. Some observers have described the immediate appearance of wheezes, rales and rhonchi over the involved area following aspiration and likened it to an asthmatic attack. Others however, describe few early auscultatory changes. Dines et al⁹ have reported that up to five hours may elapse between the time of aspiration and the onset of auscultatory findings. Cyanosis is a bad clinical sign and often refractory to oxygen therapy; hypotension is frequently present and the patient may die. With early treatment, the patient usually recovers and

remains stable for 24 to 36 hours. Subsequently, the patient may either improve or progressively deteriorate and die from respiratory failure.

The right lower lobe is most frequently involved because of the nearly linear path of the trachea and the right lower lobe bronchus. The right upper lobe is also frequently affected, probably caused by turning the patient to a Trendelenburg position permitting drainage of aspirate into the upper lobe. Both lungs can become involved if the aspiration is massive, leading to massive pulmonary injury and pulmonary oedema. In patients surviving for hours or days after aspiration, the extent of the radiographic abnormality does not necessarily parallel the clinical course. The mortality rate from aspiration is difficult to assess. In Mendelson's original report of 46 cases of aspiration, no deaths occurred. However, of the twenty who suffered airway obstruction, there were two fatalities. The mortality depends, as will be seen later, on the volume, the pH and the character of the material aspirated. Awe et al⁴ have reported 81 cases who had aspirated gastric contents, with a mortality of over 70%.

PATHOLOGY

Our knowledge of the pathological changes of acid aspiration is based on experiments done on animals. It

is important to realise that in a spontaneously breathing patient, the liquid aspiration is rapidly distributed throughout the lungs and damage occurs immediately. Acid gastric juice stained with methylene blue and aspirated into isolated dog lung can be seen on the surface of the lung within 12 to 18 seconds.¹⁰ Pathologic examination within the first few hours of acid aspiration reveals epithelial degeneration of the bronchi, haemorrhage and pulmonary oedema. Electron microscopy has shown necrosis of alveolar cells and the presence of free lamellated inclusion bodies in the pulmonary transudate. After four hours, there is an acute infiltration of polymorphonuclear cells, and fibrin can be seen in the alveolar space. Degeneration of alveolar cells and further necrosis of type I cells with detachment from the basement membrane are also seen. Marked polymorphonuclear infiltrations occur in the following 24 to 36 hours resulting in alveolar consolidation. After 48 hours hyaline membrane formation can be observed.¹¹ Examination of the lungs at this stage will show them to be boggy, oedematous and haemorrhagic. Usually resolution will have commenced 72 hours after aspiration. Lungs taken from experimental animals two to three weeks after aspiration of acid content have normal or slightly increased weight with parenchymal scarring and pleural reaction.¹⁰ The autopsy findings in humans show similar changes to those found in experimental animals.⁵

PATHOPHYSIOLOGY

All degrees of lung damage may be produced by the inhalation of gastric contents and, depending mainly on the pH of the aspirate. If the pH is 2,5, or lower, damage to the alveolar capillary membrane and exudation of fluid and proteins into the alveoli and bronchi will occur¹. An increase in lung weight and decreased pulmonary compliance with or without pulmonary oedema are seen¹⁰. The accompanying loss of intravascular volume, which may be large, may cause severe hypotension¹⁰.

The interference with the alveolar capillary membrane causes hypoxia. However, hypoxia is initially caused by the reflex airway closure in response to the aspiration of the fluid, secondly the surfactant factor is destroyed or altered by acids, leading to alveolar collapse¹². Thirdly, the loss of fluid and proteins into the damaged tissues causes interstitial and alveolar oedema, resulting in further interference with diffusion of oxygen. Lastly, alveolar haemorrhage and consolidation lead to hyaline membrane formation which contributes to a large alveolar/arterial oxygen difference.

The aspiration of acid content also changes the pulmonary vasculature. Initially the pulmonary arterial pressure rises rapidly but because of the decrease in cardiac output, due to the loss of intravascular volume, the pulmonary arterial pressure falls leading to a decreased perfusion of an already hypoxic lung¹⁰.

PREDISPOSING FACTORS

The predisposing factors to aspiration of gastric contents can be divided into three main groups.

I. Physiological factors predisposing to regurgitation and/or vomiting, with possible acid aspiration resulting, depends upon : 4,10,13

- (a) Stomach content : More than 25ml of either acid or nonacid composition.
- (b) Decreased stomach emptying rate leading to increased intragastric pressure.
- (c) Decreased lower oesophageal sphincter (LOS) tone (hence reducing the physiological barrier to reflux).
- (d) Increased intragastric pressure overcoming the resting LOS tone, leading to possible regurgitation into the oesophagus.
- (e) Decreased pH of stomach content.

II Factors reducing the level of consciousness, leading to decreased protection of the laryngeal inlet.¹⁰

- (a) Sedation.
- (b) General anaesthesia.
- (c) CNS depression by trauma.
- (d) Bulbar palsy.
- (e) Spraying the mucous membrane of the pharynx with local anaesthetic.

III Mechanical factors.¹⁰

- (a) Nasogastric tubes making both upper and lower oesophageal sphincters incompetent.
- (b) Tracheostomy. This, theoretically anyway, contributes to aspiration by interfering with the normal mechanism of glottic closure.
- (c) Positioning of the patient (Trendelenburg).
Gravitational forces.

Experimental work performed using animals^{4,12,14-18}

indicates that :

1. Gastric contents instilled in the tracheal-bronchial tree causes irritation reactions to lung parenchyma, the severity of which is directly related to the acidity.
2. Reactions become progressively severe with a pH below 2,5.
3. Food particles are irritant regardless of the pH.
4. Alkalis such as magnesium trisilicate and aluminium hydroxide can cause reactions unless diluted 5 to 10 times (vol/vol).
5. Magnesium trisilicate mixed with gastric contents giving a pH >3 is only slightly irritant while aluminium hydroxide is very irritant.

Clinical studies and case reports in man^{17,19-23} have shown that :

1. Silent regurgitation of gastric contents is not uncommon since one study reports a 26% incidence

during anaesthesia.

2. Only a small quantity of gastric content inhaled is needed to develop the syndrome. From animal experimentation, the critical volume in man has been calculated to be 25 ml.
3. The death rate following aspiration is greater than in the original description by Mendelson.
4. Alkalis, given during labour, can substantially raise the pH of stomach contents and hence decrease the chances of acid aspiration syndrome in all presenting for general anaesthesia.
5. Pre-anaesthetic cimetidine administration increases gastric pH and results in a reduced dangerous pulmonary reaction, should aspiration occur.

Aspiration is often the result of regurgitation, which is usually clinically silent and is common in patients with depressed CNS states and may often be difficult to recognize.¹⁰ Vomiting is a complex and co-ordinated series of active reflex manoeuvres which may occur during the excitement state of inhalation anaesthesia. However, the current practice in anaesthesia, using ultra shortacting barbiturate or another intravenous induction agent with succinylcholine for induction of anaesthesia, has virtually eliminated this stage. Therefore, the incidence of active vomiting during anaesthesia has dramatically decreased. Regurgitation of stomach contents, on the other hand, is more common and can be equally hazardous as vomiting. The mechanism of regurgitation

is not well understood. Culver, Mackel and Beecher²⁴ and Berson and Adriani²⁵ have shown that regurgitation leading to occult aspiration occurs frequently during otherwise uneventful general anaesthesia. These investigators placed dyes in the stomach of their patients preoperatively, and observed subsequent appearance of dye in the tracheo-bronchial tree in 26% and 7% of cases, respectively.

The special hazardous clinical situations which may produce significant regurgitation deserve special emphasis. Anaesthesia is most commonly produced by the intravenous administration of an intravenous induction agent and the lungs then inflated intermittently with oxygen by positive pressure to a tight fitting face mask before the muscle relaxant is given. If the airways are partially closed, oxygen can be forced into the stomach, producing increased gastric pressure which may result in regurgitation. The administration of muscle relaxants, especially succinylcholine, after the intravenous anaesthetic induction agent and before tracheal intubation has been shown to increase pressure during fasciculation which could predispose to regurgitation of gastric contents into the oesophagus²⁶ However, recent studies by Smith, Dalling and Williams (1978)²⁷ have shown that, during the induction phase of anaesthesia, succinylcholine does not increase the incidence of regurgitation through the LOS since a

modest increase in gastric pressure always leads to a corresponding increase in LOS. The premedication in the above study consisted of morphine i.m. one hour preoperatively, a drug also known to decrease LOS tone.²⁸

Another hazard results from the irresistible impulse of the unwary to palpate the abdomen shortly after the muscle relaxing drug has been given so as to ascertain its onset of action. External compression of this nature can produce surprising amounts of regurgitation, even from a fairly well emptied stomach.

NON ACID ASPIRATION

Non acid or neutral aspirates with higher pH than 2,5 can cause either transient or sustained damage to the lung. The nature and extent of this damage depends not only on the volume of the aspirate but also on its composition especially its tonicity, and the presence of large food particles.¹⁰ Schwartz and co-workers²⁹ have shown that aspiration of partially digested food, even at pH greater than 2,5, produces physiological, histological and x-ray derangements at least as severe as those caused by hydrochloric acid at pH 1,8. This finding supports the recent implication that aspiration of acid is not the sole cause of Mendelson's syndrome.³⁰

PREVENTION OF ACID GASTRIC REGURGITATION

Prevention can be made effective, by decreasing the stomach content either by fasting at least six hours or by emptying the stomach of its gastric content. Furthermore, increasing the stomach emptying rate, increasing the lower oesophageal sphincter tone, increasing the pH of the stomach content either by alkalis, vagolytic or histamine receptor drugs, prevention of vomiting during induction or recovery from anaesthesia and safeguarding the airway for as long as the level of consciousness is abated, are means of preventing the dreaded syndrome. The risk associated with general anaesthesia in patients requiring emergency surgery may be reduced by the use of a purely regional anaesthetic technique or by endotracheal intubation preceding the induction of general anaesthesia. The last mentioned method can not always be used and a rapid induction/intubation of the trachea sequence with simultaneous application of cricoid pressure (Sellick's manoeuvre) to protect the patient's airway is more appropriate in these cases.³¹ Although antacids have never been shown to reduce morbidity or mortality rates, a standard dose of an effective antacid given 30 minutes to an hour before surgery has been shown to raise the gastric pH above the dangerous level of 2,5.^{16,32} In obstetric patients whose time of receiving anaesthesia cannot be predicted, routine administration of antacids during labour at intervals of 2 to 3 hours, and a dose given shortly before induction of anaesthesia, has been recommended.³³

Recently the same author has recommended Sodium Citrate as a better mixer with gastric juice than magnesium trisilicate and also recommended the turning of the patient from left to right and back again to ensure adequate mixing.³⁴ Unfortunately, despite all preventive measures taken, aspiration may still occur - in that event proper therapy is of the greatest importance.

THERAPY

In case aspiration has occurred, the therapy, where indicated should consist of :

1. Endotracheal intubation with suctioning.
2. Bronchoscopy and lavage.
3. Oxygenation.
4. Antibiotics.
5. Corticosteroids.
6. Other supportive measures.

ENDOTRACHEAL SUCTIONING

If aspiration is observed, endotracheal intubation and suction should always be performed to prevent further aspiration and to suck aspirated material out. However, under the best conditions, suctioning will only remove part of the aspirate as the aspirate disperses itself into the lung immediately (in a breathing patient) causing damage nearly instantaneously. Therefore, suctioning cannot guarantee a total removal of the aspirate or prevent lung injury and should be supplemented by other forms of therapy. It is very important to

remember that failed or clumsy intubation is itself an important cause of further aspiration. In a paralysed patient who has aspirated, a thorough suction through the endotracheal tube is imperative before ventilation of the lungs is commenced. This in order to prevent, as far as possible, the aspirated material being ventilated into the distal alveoli.

BRONCHIAL LAVAGE

Bronchial lavage with neutral or alkaline solution to neutralize aspirated acid has been done but the rationale for this therapy is questioned. Shortacting corticosteroids can also be added to the lavage.³⁵ Acid aspirate damages the lung almost instantaneously despite buffering within minutes after the insult of the bronchial aspirate.⁴ Most experimental studies of lavage have shown no improvement in lung damage. However, Simenstad, Galway and MacLean³⁵ have reported beneficial effects from large volume lavage, but their results were not statistically significant and adding to the problem of evaluating this work was the fact that all the animals received 100% oxygen.

BRONCHOSCOPY

Bronchoscopy should only be used to remove large aspirated material which produces collapse of the lung and when food particles have been aspirated.

OXYGENATION

Bronchospasm has been stated to be a particularly

troublesome feature after aspiration. Its relief may present a difficult therapeutic problem since most bronchodilators tend to cause cardiac dysrhythmias, a side effect made more prominent in the presence of hypoxia. Bronchospasm often responds to the relief of hypoxaemia and to steroid therapy. If additional treatment is necessary, aminophylline is a reasonable choice. However, if halothane or enflurane are available, these are powerful bronchodilators.

Hazards of prolonged mechanical ventilation are many, but following aspiration, intermittent positive pressure ventilation (IPPV) may be therapeutic in re-expanding damaged alveoli until normal surfactant production returns. The decision to ventilate the patient mechanically should be based on the evidence of deteriorating lung function as shown by rapidly increasing alveolar-arterial oxygen difference based on abnormal arterial blood gases and clinical judgement like watching for increasing dyspnoea and impending exhaustion often with facial signs of respiratory distress.³⁶ Any of these two parameters should alert the clinician that ventilation must be started without delay.

High inspired oxygen concentrations may be necessary to maintain an adequate arterial oxygenation but if continued for too long a time (more than 24 hours), pulmonary

oxygen toxicity may add to the grave pulmonary damage already present. The addition of positive end expiratory pressure (PEEP) is often useful for reducing alveolar-arterial oxygen differences and the effects of this manoeuvre should be assessed in any patient in whom an inspired oxygen concentration of 60% fails to provide adequate arterial oxygenation. For severe cases, extracorporeal membrane oxygenators have been used.³⁷ This technique, it was hoped, would ensure adequate arterial oxygenation and allow resolution of the lung inflammation without insults of high oxygen concentrations and large minute volumes. Preliminary experience in the United States suggests that though this technique could work well as a support device in acute respiratory failure, the improvements in pulmonary healing did not occur and subsequent weaning from the respirator became a major problem.³⁸ In any case, its use is confined only to highly specialized centres. Studies using the radical new concept of high-frequency ventilation is awaited with interest.

CORTICOSTEROIDS

These are often recommended in the treatment of aspiration pneumonia, although their use is controversial.¹⁰ The clinical impressions, however, are optimistic, but are only based on uncontrolled studies. There are no conclusive clinical or experimental data to justify the use of steroids in aspiration pneumonia. Experimental evidence indicates that there are minimal benefits.¹⁰

The effects of steroids on non acid aspiration are not known although recent studies in dogs³⁸ and humans³⁹ have shown that they are of no benefit in treating near-drowning patients. Hence, if steroids are used in the treatment of this disorder, one must weigh their unproven benefits against possible complications of the drug.

ANTIBIOTICS

Although gastric contents are often held to be sterile, pulmonary infection often becomes a problem after about 48 hours¹⁰. Studies have shown that the predominant organisms in the aspiration syndrome are staphylococci, pneumococci, coliforms, pseudomonas and bacteroides¹⁰. These bacteria are present in the mouth and pharynx, and may get carried down into the lungs at the time of aspiration.

The presence or absence of infection in a patient who has aspirated is difficult to ascertain. The development of fever, leukocytosis, pulmonary infiltrates, thick, tenacious sputum are non-specific responses that can result from uncomplicated chemical pneumonitis. If prophylactic antibiotics are to be used in aspiration, allowances must be made for coverage of all possible infecting organisms. Completeness would require protection against all anaerobes, including *Bacteroides fragilis*, as well as similar broad spectrum coverage for

anaerobes. Hence an approach would be to withhold antibiotics initially, monitor the patient clinically for evidence of infection, and treat on the basis of results from well collected smears and sputum specimens. However, the organisms *Bacteroides* are especially vicious and destructive, therefore a combination of gentamycin and metronidazole would be a reasonable choice should aspiration have occurred. This regime can always be modified later when the organisms and their sensitivities are known. One study which is often quoted, claims to show that the use of prophylactic antibiotics did not improve prognosis and was more likely to lead to the growth of resistant organisms.³⁷

Other supportive measures include general measures like :

1. Correction of acid-base disturbance.
2. Correction of cerebral oedema - if hypoxaemia has been severe, steroids, mannitol and a moderate reduction of arterial pCO₂ (26-32 mmHg) may be required.
3. Adequate fluids, electrolytes and albumin levels must be maintained providing an adequate circulatory volume.
4. Hyperalimentation of the patient is essential since treatment is often prolonged.

However, it has been suggested that patients with aspiration should be "run dry" with very careful restoration of the plasma osmotic pressure.³⁷ This is a

problem, as reduction in albumin levels will decrease the pulmonary capillary pressure at which pulmonary oedema occurs, and infused albumin may simply leak out from damaged pulmonary capillaries, leading to an increased interstitial pulmonary oedema.³⁷

SUMMARY

In summary, the optimum management of patients with documented aspiration syndrome should entail immediate endotracheal intubation with suctioning and bronchoscopy if large particles are seen or suspected. If ventilation is insufficient, ventilatory support with supplemental oxygen and possibly positive end-expiratory pressure and an adequate fluid replacement, are essential. Lavaging with large volumes of neutral or alkaline solutions and corticosteroids are of unproven benefit. The administration of prophylactic broad spectrum antibiotics would seem indicated.

AIM OF PRESENT STUDIES

The aim of this review is to highlight the predisposing risk factors involved in the production of the acid aspiration syndrome and how these can be minimized. A more detailed knowledge of the underlying factors would seem imperative not only to anaesthetic practice but also to the management of the critically ill.

Gastric content with a low pH and of a certain gastric volume, inhaled into the lungs, causes this syndrome which

therefore can be considered to result from either :^{10,13}

1. Regurgitation, which depends upon -
 - (a) Decreased lower oesophageal sphincter (LOS) tone.
 - (b) Increased intragastric pressure overcoming the barrier of the LOS and thereby forcing stomach content to enter the oesophagus and pharynx.
 - (c) Faulty gastro-oesophageal sphincter mechanism.
 - (d) Decreased level of consciousness with diminished protective laryngeal and coughing reflexes.

2. Vomiting.

Here an active process propels the stomach content into the pharynx and with diminished protective laryngeal reflexes like the coughing reflex, aspiration can occur.

It is generally accepted that the acid aspiration syndrome may follow the inhalation of as little as 25 ml of gastric juice of pH less than 2,5⁴⁰ but it has also been reported in an obstetrical patient after inhalation of stomach content with a pH of 3,5.⁴¹

In anaesthetic practice, patients presenting for elective surgical procedures are starved from the night before. There is little information in the anaesthetic literature on the volume and acidity of gastric juice after such a fast, despite its obvious relevance to patient safety during general anaesthesia. This problem

was elucidated in our study of fasting patients with gastrointestinal symptoms by measuring the early morning volume and acidity of stomach contents (Paper I).

Furthermore, the duration of action of magnesium trisilicate in neutralizing gastric juice was reported in the paper entitled "Gastric Volume and Acidity at Caesarean Section" (Paper II).

The effects of various anaesthetic drugs on the LOS were elucidated in the studies presented in Papers III to XII. Intra-gastric pressure studies in pregnant patients at term (Papers VI, VII and XI) confirming the work of Lind⁴² where an increased intra-gastric pressure is seen. This increase can be partly responsible for the increased incidence of oesophageal reflux in these patients. Recently we have shown that pregnant women in the first trimester have an increased intra-gastric pressure, making these patients too susceptible to regurgitation of gastric content into the oesophagus.⁴³

Decreased level of consciousness with ensuing diminished protective laryngeal reflexes has been discussed in Papers XIII and XIV.

Since aspiration of antacids are shown to be noxious to the lung,⁴⁴ the development of cimetidine, a histamine H₂ receptor antagonist, would seem an appropriate drug

in the prevention of acid aspiration.²³ Cimetidine reduces the acidity and gastric volume, probably attributable to reduced gastric secretion.²³ However, it is important that the safety of the drug is established in as much as it does not cause any adverse interaction with the general anaesthetic techniques. Recently, long term cimetidine therapy has been associated with thrombocytopenia.⁴⁵ Further studies in this field are awaited with interest. Our own pilot study shows cimetidine's effectiveness in reducing gastric acidity and is reported in the Result and General Discussion sections (Pages 41 - 42). Cimetidine has been found by us to have no respiratory or cardiovascular depressive effects in normal healthy volunteers.⁴⁶ Further studies elucidating both respiratory and cardiovascular effects following cimetidine in the critically ill patient are at present being studied. We have recently completed a study using a new long acting H₂ receptor antagonist, Ranitidine.

METHODOLOGICAL CONSIDERATION

The investigations done are all concerned with elucidating the predisposing factors responsible in developing the acid aspiration syndrome. Different experimental methods have been used to attain this goal, namely :

1. Oesophageal manometric measurements to establish the effects of various drugs and one hormone (prolactin) on the LOS tone.⁴⁷
2. pH electrodes to establish the incidence of gastro-

oesophageal reflux with the various drugs' effect on LOS tone.

3. Screening gastric tubes into the stomach with volume and pH measurements. This to establish -
 - (a) Percentage of patients at risk after an overnight fast.
 - (b) The effectiveness of antacids and cimetidine in the reduction of gastric acidity.
4. Radio-opaque dye instilled into the pharynx to establish the incidence of tracheobronchial aspiration.
5. Double-blind postoperative trial in 210 patients to establish the incidence of nausea and vomiting following general anaesthesia and the effectiveness of a new antiemetic.⁴⁸

All studies were approved by the Ethical Committee of the University of Natal and informed consent was obtained from all patients and volunteers.

a. METHODS OF OESOPHAGEAL MANOMETRIC STUDIES.

Historical Perspective

Oesophageal motility studies were first performed in humans in 1883 by Kronecker and Meltzer.⁴⁹ They used two large balloons, 7 to 9 cm long, one positioned in the pharynx to monitor deglutition and the other at varying depths in the oesophagus. The oesophageal contractions were shown to occur as peristaltic waves moving in a caudad direction. They also convincingly demonstrated

the barrier pressure at the gastro-oesophageal junction. In 1923, Payne and Poulton,^{50,51} placed two small water filled balloons in different segments of the oesophagus and defined the peristaltic sequence in the oesophagus in response to swallowing. The first satisfactory recording of the responses of the gastro-oesophageal sphincter to swallowing was described by Burget (1936) and Zeller (1937).^{52,53} They placed balloons in the oesophagus, LOS and the fundus of the stomach through gastric and oesophageal fistulae in unanaesthetized dogs. Pressure sequences during induced distension and during spontaneous swallowing were recorded. Results showed that, in these dogs, relaxation of the LOS followed swallowing and oesophageal distension.

Different Manometric Techniques

These differ basically on the degree of deformity caused by the recording equipment. Although the term "resting" pressure is used, every tube or balloon will deform the sphincter differently. The degree of deformity depends upon the size and number of the tubes or balloons, and the rate at which these recording devices are pulled through the LOS.

The main variables in the techniques used will be discussed and thereafter, the technique selected for my studies described.

The main variables are :

- (a) Type of sensor.
- (b) Type of tubing.
- (c) Rate of perfusion of the sensor.
- (d) Intermittent or continuous pullthrough.

(a) Type of sensor

Theoretically, the device to measure pressure, the manometer, should be located best at the site of the desired pressure detection.⁵⁴ Miniature electrical pressure transducers that transform pressure changes to electrical signals have been designed and used for this purpose.^{55,56} The electrical signals from these manometers are carried over wire leads to a pressure recorder. Hydrostatic effects of differences between the point of pressure sensing and the position of the manometer are thereby eliminated, but the manometers have several practical disadvantages. They are expensive to purchase or build and require complicated electronic circuitry for their operation. Baseline shifts may occur due to temperature change around the sensor after insertion into the stomach. Hence few laboratories use such devices today. The more practical system, now widely used, is plastic tubing with lateral side orifices facing the oesophageal wall. These orifices act as peripheral sensors, of which four different types can be distinguished.

- (i) unperfused air filled.
- (ii) unperfused water filled.

- (iii) perfused with water at a constant, very slow rate.
(0,19 ml/min in our study).
- (iv) small water-filled balloon.

Air-filled tubes have been shown to give unreliable results⁵⁷ and have been discarded. It is now accepted that no matter what type of peripheral sensor is used, the common important principle is that the tubing must be completely water-filled⁵⁴. No bubbles of gas are permitted in the system, for even tiny volumes of gas will reduce the accuracy of pressure determinations.⁵⁴ In the early studies, the water-filled tubes were unperfused, but the recordings were "damped" and did not show the respiratory variation with inspiration and expiration evenly throughout the study period. Consequently it was decided to perfuse the tubes with water at a very low rate to keep the lateral orifices clear of obstructing food particles or mucus.⁵⁷ This perfusion has been successful in increasing the accuracy of the pressure determinations.⁵⁶⁻⁵⁸

Balloons unfortunately vary in diameter, length and resistance according to the type and thickness of latex rubber used. The use of small balloons (0,5 cm diameter) has increased reproducibility⁵⁷; but this technique still has serious drawbacks. Compared to open tipped perfused tubes, the primary disadvantage of the balloon method is that the balloon must be filled with air or water under positive pressure. This produces excessive distension of the oesophagus giving abnormally high positive pressure readings. The intraluminal oesophageal pressure

is normally considered to be negative. The resulting distension also provides a local stimulus for motor activity.⁵⁸ Furthermore, the balloon acts as an obstruction to either material swallowed or refluxed, leading to even higher pressures recorded in the LOS region. The open-end catheter slowly perfused with water was therefore selected since other workers^{31,42,56,59} have found the latter technique to be reliable and to give reproducible results.

(b) Type of Tubing

Two types of tubing are in common use - polyethylene and polyvinyl. The internal diameters range from 0,76 mm to 1,4 mm. In our original paper on oesophageal motility we used a multilumen polyvinyl catheter.^{III} However, polyvinyl tubing has the disadvantage of being distensible. Forty μ l of water must be used in a 150 cm length of polyvinyl tubing of internal diameter of 1,4 mm to increase the pressure within the tube from 0 to 150 cm H₂O, while polyethylene tubing is more stiff and virtually indistensible. In the latter tubing only 4 μ l of water increased the pressure from 0 to 250 cm H₂O in 150 cm long polyethylene tubing of 1,2 mm internal diameter.⁵⁴ The volume of displacement gives a measure of the distensibility of the tubing. With the polyvinyl catheter a larger volume is needed to prevent the occlusion of food bolus or mucosal folds. Since a larger volume of fluid gives abnormally high values of LOS pressure (discussed below), it is imperative that rigid tubes are used so that smaller volumes of liquid can be used at

the tip for continuous perfusion.⁵⁴ The advantage with polyvinyl catheters is that, according to our experience, they are easier for the subjects to swallow but the tube has a greater tendency to curl up in the oesophagus and may thus give totally misleading results. It is of interest to note however that our results, when polyvinyl tubes were used, are comparable to the results obtained using the polyethylene tubes. The reason for this could possibly be explained on the basis that the internal diameter of each lumen in the multilumen polyvinyl catheter was only 0,85 mm compared to 1,2 mm as reported by Code and Schlegel⁵⁴ and therefore our tube was less distensible.

(c) Rate of perfusion of sensor.

Pope⁶⁰ showed that when he measured the sphincter closing force with unperfused open-tipped catheters, he got abnormally low pressure readings. Large volumes of perfusion fluids act as a stimulus to the sphincter and give higher pressure measurements than normal. By infusing microliter quantities of fluid into an open-tipped catheter, the oesophageal motility measurements are more accurate in estimation of sphincter pressure. Furthermore, the height of the pressure in the sphincter correlates well with the sphincter efficiency, as defined by the presence or absence of reflux.⁶⁰

(d) Intermittent and continuous pull-through.

The motility catheter is withdrawn from the stomach until

the pressure recordings and their alterations in response to swallowing indicate that all three orifices lie within the oesophagus, above the LOS. This manoeuvre is termed a "pull-through".

There are two ways of pulling the pressure sensing tips through the LOS; either at a constant rate⁶¹ or intermittently, at 0,5 - 1 cm intervals with stops at each location for at least 4 respiratory cycles.⁵⁴

We elected to use the intermittent technique to obtain a plateau of constant pressure in the LOS, thereby increasing the accuracy of sphincter pressure measurement. However, the lower oesophageal sphincter normally contracts during swallowing⁵⁶ producing fluctuations in the pressure profile obtained, which initially gives an abnormally high and subsequently an abnormally low pressure value. The pressure changes recorded during deglutition have to be excluded and time allowed for the pressure profile to settle to pre-swallowing levels before continuing with the recording.

All tracings which gave an inadequate plateau of the high pressure zone due to swallowing were excluded. With the continuous method a spike wave is produced without a plateau, this makes measurements less accurate and less reproducible. Patients must refrain from swallowing during the period of continuous pull-through. If swallowing should occur, inaccurate peaks will result. Previous studies have shown that the

pressure obtained by the continuous method is not always midway between the pressures recorded during the inspiratory and expiratory phases of respiration as it is in the intermittent method, unless the patient stops breathing during the expiratory phase.⁶² Experience has shown that total arrest of breathing is difficult to obtain. Breath holding can occur at various stages of the respiratory cycle with various pressure gradients and hence inaccuracies are produced in the measurements with the continuous pull-through technique.

Our Manometric Technique (Best described in publication No. XI)

The motility tubes used consisted of three PORTEX polyethylene No.54 (5 mm diameter) plastic tubes assembled together at the distal end. Each tube has a single lateral orifice 2 mm in diameter situated 5 cm, 10 cm and 15 cm respectively from the distal tip. The lumen of each tube immediately distal to the lateral opening was occluded by a small plastic plug. The triple lumen catheter is swallowed orally until all the recording orifices are situated in the stomach. The proximal end of each tube is connected via a threeway stop cock to a Beckman Instrument Physiological Transducer Model 215071 linked to an 8-Channel Beckman R411 Dynograph amplifier and recorder*. The speed of the recording paper was variable from 0,25 mm/sec to 100 mm/sec and the deflection sensitivity of the recording adjusted to represent 10 cm H₂O per cm deflection. The recordings were done with

* Beckman Instruments Incorporated, 3900 River Road, Schiller Park, Illinois, 60176, U.S.A.

capillary ink pens on rectilinear standard folded chart paper.

Through the three-way stop cock, the physiological transducer chambers and recording tubes were filled with water at room temperature and perfused continuously at a constant rate of 0,19 ml/min using a Harvard Constant Infusion pump **. Each recording tube was connected separately via the three-way stop cock to its own individual transducer.

The transducers were calibrated between 0 - 80 cm H₂O above the level of the transducer before and after each test, using a water manometer connected to the transducer. The transducers were positioned at approximately the level of the lower oesophagus to eliminate the effect of hydrostatic pressure.

All motility studies were carried out with the patient in a supine position, except for pregnant women who had a left lateral tilt of 15°. Respiration was monitored by a tubular pneumograph placed about the chest and connected to an identical pressure transducer, as mentioned above. The inclusion of the pneumograph was done to monitor swallowing, respiration, and the pressure inversion point which indicates the location of the diaphragm in relation to the LOS. With the sensor in the abdomen, a positive swing is noted with inspiration, but if the sensor is placed above the diaphragm,

** Model 931, Harvard Apparatus, Millis, Mass.02054, U.S.A.

a negative deflection is seen. The pressure inversion point is normally sharp and the reason for this is that it is supposed to represent the point where the phreno-oesophageal ligament is attached.⁶³ The polyethylene tubes were swallowed without the use of local anaesthesia. Five to ten minutes were allowed to elapse to stabilize the gastric pressures. Thereafter, the catheter was withdrawn 0,5 cm at a time. At each location the recordings were made for 4 - 15 respiratory cycles. When the resting level of LOS had been recorded, the tubes were again advanced into the stomach and the identical procedure repeated after i.v. injection of the drug under investigation.

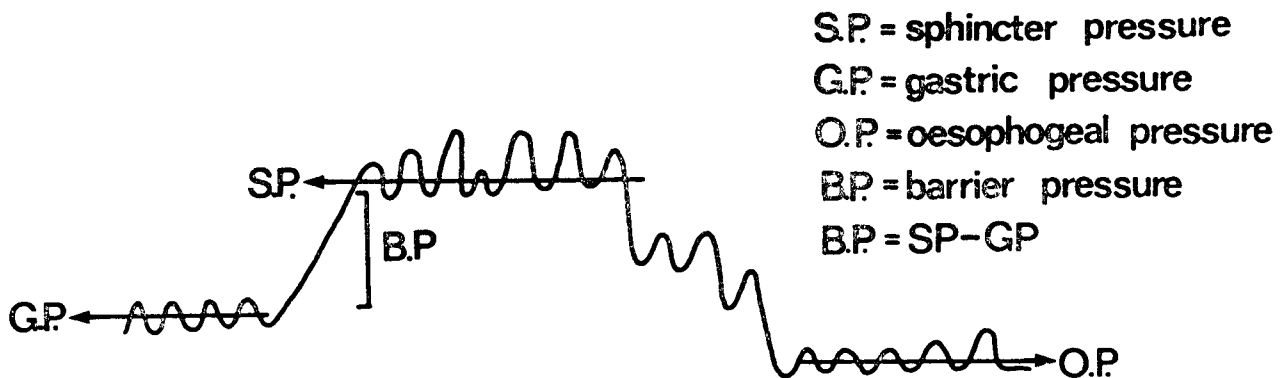
Measurement of pressures from the recordings.

The tracings obtained on the Beckman Recorder represent pressure changes from all three tubes. Hence, three pressure profiles are obtained for each pull-through, giving three values for gastric, sphincter and oesophageal pressures. One such pressure profile is shown in Fig.1 From these pressure profiles, the actual pressures were measured from the baseline (which represents the zero pressure) to the midpoint between the maximal end-inspiratory and end-expiratory points. The three measurements of gastric, LOS and oesophageal pressures prior to the drug administration and three measurements for each of these pressures after drug administration were compared. The gastric pressure (GP), the LOS pressure and oesophageal pressure (OP) were read

for each subject. The difference recorded between LOS and GP was termed the barrier pressure (BP). All pressures were expressed in cm H₂O above the actual atmospheric pressure. Only tracings which were without interference from movements, swallowing and gross respiratory changes were evaluated.

FIGURE 1

PRESSURES CALCULATED



b. MEASUREMENT OF GASTRO-OESOPHAGEAL REFLUX

Evidence of gastro-oesophageal reflux was measured using a Beckman Intestinal pH electrode No.39042. The pH electrode was attached 5 cm from the tip of the catheter at the level of the most distal orifice.

When a satisfactory sphincter profile had been obtained, the test for reflux was performed with the pH electrode 5 cm above the top of LOS. With the pH electrode in this position, the patient was instructed to increase his intra-gastric pressure by coughing, performing Valsalva manoeuvres with and without straight leg raising. The

increase in intra-abdominal pressure was not recorded since the catheter was out of the stomach.

Reflux was graded as follows :

1. Free reflux, i.e. reflux without stress was defined as a failure of the pH to rise above 3,5.
2. Stress reflux was considered to be present if the pH in the oesophagus dropped more than one pH unit during a stress test.
3. No reflux was present if neither free nor stress reflux were seen.

Statistical analysis was performed using Student's t-test for paired and unpaired data, and the Fisher Exact Probability Test, using a Hewlett Packard Desk Calculator No.98403*

c. ESTIMATION OF GASTRIC pH AND VOLUME

In Paper I (Fasting gastric volume and acidity associated with gastrointestinal symptoms) the technique consisted of introducing a radio-opaque nasogastric tube into the stomach. The stomach was emptied by continuous suction at 20 cm H₂O and augmented at 5 minute intervals with hand suction. This was done to minimize the chance that the holes could be blocked by aspiration of mucus or mucosa.

Gastric intubation is potentially dangerous. Even healthy

* Hewlett Packard Col, New York, U.S.A.

patients may develop arrhythmia and cardiac arrest has been described in a man with angina.⁶⁴ However, the risk of such an event is considered extremely small. A medically qualified doctor was always in attendance during these procedures, observing closely for any illness or evidence of arrhythmias.

The pH of the aspirate was measured with a Merck indicator and the results checked on an automatic titration device (Beckman Automatic pH Titrator). The correlation between these two methods was found to be good ($r = 0,92$)⁶⁵.

In Paper II (Gastric volume and acidity at Caesarean section) a 16 F.G. nasogastric tube was inserted during general anaesthesia. The position of the catheter tip in the stomach was verified by auscultation during insufflation of a few millilitres of air.

In a pilot trial, cimetidine 200 mg was given intravenously in 20 patients aged between 18 and 60 years. All patients were scheduled for emergency surgery and had fasted at least 5 hours and received no medication prior to anaesthesia. A nasogastric tube F.G.16 was passed nasally into the stomach and a small sample of gastric juice was taken and checked by Merck indicator paper and a Beckman pH electrode. The nasogastric tube was then withdrawn. Cimetidine was then given and anaesthesia induced with thiopentone and succinylcholine rapid induction

sequence. Cricoid pressure was applied and an endotracheal tube was inserted into the trachea. The pH electrode was then inserted into the stomach and the pH continuously read.

In another study recently completed using a long-acting histamine H₂ antagonist (Ranitidine), preoperatively, in which 90 patients were studied using a similar methodology to that in Study No.II, Ranitidine's effectiveness was shown.

d. ESTIMATION OF LARYNGEAL COMPETENCE

These studies (Nos. XIII, XIV) were done with a radio-opaque iodine containing liquid (Dionosil) injected at the back of the tongue with the patient anaesthetized with either neuroleptics with diazepam or relative analgesia. The use of Dionosil in this type of study is well established in medical literature.^{66,67} All facilities for resuscitation, including emergency drugs, were available. Volunteers with a previous history of iodine sensitivity, or any other allergy, were excluded from the study. Chest x-rays were taken prior to and after anaesthesia was induced. A positive result was indicated if dye was found in the respiratory tract.

e. INCIDENCE OF NAUSEA AND VOMITING IN THE POSTOPERATIVE PERIOD WITH OR WITHOUT ANTIEMETICS

Post-operative nausea and vomiting are common after general anaesthesia.^{48,68,69} The incidence varies from 30-68%. The use of antiemetics is recommended, especially in

patients most prone to vomiting. Without a previous history of anaesthesia with vomiting, however, there are few pinpointers to such patients. The importance of providing the patient with relief from nausea and vomiting are seen from the numerous studies to assess post-operative antiemetic effects of a variety of drugs. New, highly acclaimed, antiemetic drugs are frequently available, unfortunately without meaningful clinical trials to support claims of superior effects.

We tried to ascertain the antiemetic and antinauseant effect of a new highly acclaimed antiemetic, namely diphenidol (Vontrol^(R)), in 210 healthy patients.⁴⁸ The drug was compared in a double blind study with droperidol and placebo (0,9% saline). Diphenidol is an analog of trihexphenidyl HCl (Artane^(R)) (benzhexolichloride)* while droperidol is a neuroleptic butyrophenone compound.

RESULTS AND GENERAL DISCUSSION

Paper I describes the studies undertaken to establish the mean levels of acidity and volume of gastric juice after an overnight fast in patients with suspected upper gastrointestinal pathology. Four hundred and thirty patients with gastrointestinal symptoms and gastric analysis as part of their routine diagnostic workup were studied. According to observations made at fibro-optic gastroscopy, patients were divided into 4 groups :

* Felleskatalogen

Group I	:	No abnormality
Group II	:	Oesophagitis/gastritis
Group III	:	Gastric ulcers
Group IV	:	Duodenal ulcers

The volume of gastric juice varied from 0 - 400 ml and the pH from 0,8 to 8. The percentage of patients with overnight fasting gastric volume over 25 ml and a pH of less than 2,5 was high in all groups :

Group I : 38,6%	Group II : 51,2%
Group III : 40,0%	Group IV : 73,3%

This last figure is significantly greater than the group with no detectable abnormality. ($p < 0,001$). There was no significant difference between Groups I, II and III.

These results indicate that the stomach of a fasting patient often contains sufficient volume of acid gastric juice to place the subject at risk from acid aspiration during anaesthesia. Prophylaxis with antacid seems indicated preoperatively, with the possible inclusion of cimetidine. Consideration should also be given to preoperative gastric aspiration followed by ingestion of an antacid and/or cimetidine before induction of general anaesthesia, especially in patients with duodenal ulcers.

Criticism was raised against averaging the measured pH in the above study.⁷⁰ We did, however, follow the accepted convention of many other workers in the field.⁷¹

It is now generally accepted that the result of mean pH values gives the same result as when calculating the average of the H^+ ion concentration.⁷² Leach⁷³ reported an average overnight fasting stomach aspirate of 50 ml (no standard deviation was given) with a range of 0-180 ml, a result similar to our study (mean 55,2 ml and a range of 0-225 ml). However, the pH results reported by Leach were different, in his control, subjects' pH ranged from 1,1 to 2,6. Other studies in obstetrics,⁷⁴ the obese⁷⁵ and outpatients⁷⁶ have shown evidence of acidic and gastric volumes at potentially dangerous levels. These results indicate that both care and prophylaxis are indicated in these patients. It is further important to realize that anticholinergics, narcotics and barbiturates may seriously delay gastric emptying.⁷⁷

Study No.II was undertaken to establish the length of time the gastric juice pH was considered "safe" after pre-operative gastric aspiration and the administration of 15 ml magnesium trisilicate. The stomach contents of 70 mothers were aspirated at Caesarean section after preoperative gastric emptying and alkaline ingestion with magnesium trisilicate. The acidity of the gastric aspirate was analysed and volumes were measured. The patients were divided into 5 groups according to the time elapsed before the gastric aspiration was carried out. A "safe" gastric pH (pH >3,5) was found in all patients up to 2 hours after antacid ingestion. However, 2½ hours after the antacid ingestion, 50% patients had gastric volumes in excess of 25 ml and a pH of less than 3,5.

Many obstetrical departments do not perform gastric aspiration prior to general anaesthesia, while in our hospital (King Edward VIII Hospital, Durban, South Africa), with over 25000 deliveries a year, of which 4000-5000 mothers have Caesarean section, no one died of acid aspiration syndrome over a 2-year period under review. Following gastric aspiration, all patients now drink 30 ml of magnesium trisilicate prior to anaesthesia. Due to the good results obtained with this regime, one is reluctant to change.

A preinduction dose of magnesium trisilicate USP* (20 ml has been shown to act sufficiently rapidly to neutralize effectively reasonable quantities of stomach contents within two minutes.³³ However, the antacid may mix inadequately with the stomach content and may lie as a "layer" in the stomach.³⁴ Should regurgitation therefore occur, either the neutralized portion or the acid portion of the stomach content may be aspirated. Milk of Magnesia** has been suggested for introduction into obstetrical/ anaesthetic practice.⁷⁸ Clinical studies in our department are underway to confirm its efficacy. Some antacids, such as sodium citrate, which are available, have however been shown to be inefficient.⁷⁹ In conclusion therefore, active emptying of the stomach in patients in labour, followed by Milk of Magnesia to neutralize a small volume of gastric volume would seem an essential and safe method. However, Gibb et al (1979)⁸⁰ have recently demonstrated that when a dilute solution of * (USP) Aqueous suspension of magnesium hydroxide 7-8,5% ** Magnesium trisilicate contains not less than 20% magnesium oxide and 45% silicon dioxide

an antacid is introduced into the lungs of dogs, the resultant decrease in arterial oxygen partial pressure and increase in pulmonary shunting are as severe as those caused by instillation of hydrochloric acid, pH 1,8.

Morphological changes at 48 hours were severe in both antacid and acid treated groups. At one month, however, the lungs of animals that had aspirated acid were normal whereas those treated with antacid still demonstrated an extensive intra-alveolar cellular reaction. The focus for this florid response appeared to be the antacid particles, which were still visible in samples of lung tissue obtained 48 hours and one month after treatment. A group treated with alkalinized saline solution pH 5,8 showed only transient physiological disturbances and histological changes which were similar to those seen in the saline treated group.

Clinical reports of Bond, Stoelting and Gupta (1979)⁸¹ and Heaney and Jones (1979)⁸² describe severe physiological disturbances and, in one case, death following aspiration of gastric contents containing antacid. It is obviously essential to ascertain whether morbidity and mortality from Mendelson's Syndrome has decreased following the introduction of antacid. Nationwide statistics reporting maternal mortality from aspiration in relation to anaesthesia are difficult to obtain. Furthermore, the "Confidential Enquiry into Maternal Mortality in the United Kingdom" is not helpful as the number of deaths from aspiration during 1973-75, the period when antacid was used, were almost identical to that occurring during 1970-72 when virtually

no antacid was used.⁸³ To date we do not know if these data are of real clinical significance and further research using primate models would seem imperative.

Various methods of studying gastric emptying have been proposed, however, with the exception of the technique mentioned in Studies I and II, the perfect experimental model to be used in clinical anaesthesia has yet to be designed⁸⁴. Emptying experiments are difficult to evaluate as the volume in the stomach depends upon many factors :

1. The amount emptied from the stomach into the duodenum.
2. The amount returning to the stomach from the duodenum.
3. The amount absorbed by the gastric mucosa.
4. The amount secreted by the stomach and the salivary glands.
5. The presence or absence of intact gastric and duodenal muscles with their receptors and central nervous system connections, giving normal gastric motility.
6. The procedure. Even short term insertion of gastric tubes may cause major and/or unpredictable effects.
7. pH and osmolality of the resting gastric volume influence both gastric secretion and emptying.⁸⁴

In our pilot study using cimetidine 200 mg i.v. pre-operatively, the drug was effective in increasing the pH of the stomach content. Out of 20 patients, only 3 had a pH below 2,5 at 30 minutes while 2 had a pH below

2,5 at 60 minutes. After 90 minutes, the gastric pH was well above 2,5 in all patients. No side effect was noted with the use of this drug.

In Studies III - XII, the effect of various drugs on the LOS tone was studied. Tables I and II summarize the available information to date on the various drugs' influence on LOS tone in humans. The list of agents affecting the sphincter tone is becoming lengthy and will predictably grow as more drugs are studied.

Study III re-examined the effects of atropine and metoclopramide on the LOS. The decrease in LOS pressure noted after atropine confirms the findings of others.^{85,86} However, in anaesthetic literature, several authors recommend the administration of atropine as a premedication since Clark and Riddock⁹³ showed that atropine given intravenously (0,6 mg) markedly increased LOS tone. They suggested that the drug might reduce the likelihood of gastric reflux. Recent work^{85,86} including our own^{III} suggests that this advice would seem inappropriate. Atropine's detrimental effect on LOS has also been confirmed in pregnant subjects^{VI}. Study III confirmed the work of Heitman and Möller⁹⁴ that metoclopramide increased LOS pressure. Furthermore, the study showed that when metoclopramide and atropine were given together from the same syringe, intravenously, these two drugs antagonised each other's effect on the LOS. Thus metoclopramide reversed the relaxant effect of atropine on the LOS, maintaining the sphincter pressure at pre-

injection levels. The mechanism of action of atropine on the lower oesophageal sphincter remains to be elucidated. Atropine has been suggested to work partly by inhibiting the release of gastrins which again is thought to increase LOS tone, the latter physiological effect on LOS tone has however been seriously questioned.⁹⁵

Hyoscine, like atropine, (Study IV) decreased LOS pressure with an increased incidence of gastro-oesophageal reflux. The two drugs caused equal pressure drops. The results with atropine in this study, using the polyvinyl tube, was comparable to Study III when a polyethylene tube was used. The mechanism of action of hyoscine on the LOS remains to be elucidated. Crawford⁹⁶ recommends substituting hyoscine for atropine as a premedicant for obstetrical anaesthesia for several reasons, including the reduction of incidence of awareness. Unfortunately its effects on the LOS, demonstrated here, suggest that this advice might be inappropriate unless its effects on LOS tone can be countered. Metoclopramide would seem to be such a drug, however, in accordance with Laitinen's work⁹⁷, and our own unpublished results in humans, metoclopramide should be given prior to atropine administration. In this latter study, the effects of metoclopramide 10 mg i.v. on the LOS tone was studied in ten healthy volunteers. Metoclopramide increased the mean LOS pressure by 16,9 cmH₂O. Subsequent atropine administration did not influence LOS pressure significantly which was sustained at a level 13,9 cmH₂O higher than basal control levels. Results of this study suggest that metoclopramide should be

given prior to atropine administration in order to reduce the chances of regurgitation of acid gastric content during induction of general anaesthesia.

In Study XII, ten patients had randomly, two oesophageal motility studies performed at approximately weekly intervals. The study elucidated the sequence of domperidone 10 mg i.v. followed by atropine 0,6 mg i.v. effect on LOS tone and then in reverse order, namely atropine followed by domperidone. The results showed that domperidone increased LOS tone while later atropine administration caused only slight but statistically insignificant changes in both LOS pressure and barrier pressure which were sustained at 14 cmH₂O and 13 cmH₂O respectively, above basal values ($p < 0,005$). Atropine, on the other hand, decreased LOS tone and domperidone increased the tone to basal levels. Hence, domperidone should also be given prior to atropine in order to reduce the chances of acid aspiration syndrome. Domperidone would seem to be a more ideal agent to use prior to Caesarean section than metoclopramide since the former does not cross the placental barrier while the latter does.⁹⁸

In Study V, the effect of intravenous glycopyrrolate 0,3 mg on the LOS in normal healthy subjects was studied.

Glycopyrrolate decreased LOS pressure by 9 cmH₂O ($p < 0,005$) a result similar to atropine and hyoscine (III and IV).

Glycopyrrolate would seem an improved alternative to atropine and hyoscine in anaesthetic practice. Studies comparing it to atropine have shown it to be a better anti-

sialogue^{99,100} to provide more cardiovascular stability¹⁰¹ and to be of longer duration⁹⁹ (4-6 hours compared to 1-1½ hours for atropine and hyoscine). The drug hardly crosses the placenta¹⁰² or blood-brain barrier¹⁰³ hence no central anticholinergic syndrome is produced.¹⁰³ Finally, glycopyrrolate has been found to increase the gastric pH above 2,5 in paediatric patients¹⁰⁴ and obstetric patients⁷⁴. Other studies however have shown no such effect^{105,106}. The different studies are difficult to evaluate as varying doses of the drug and sampling times for pH measurement were used. However, an adequate dose given for a sufficient period of time 2 hours prior to induction of general anaesthesia would increase the pH of gastric content in most cases.¹⁰⁷ However, safety in obstetrical anaesthetic practice will hopefully be increased if the regime of prophylactic administration of a histamine H₂ blocker¹⁰⁸ and metoclopramide^{III,VII} or domperidone^{XI,XII} is included. The latter two, both increasing gastric emptying rate and LOS tone. Study VI also demonstrated atropine's detrimental effect on LOS tone in pregnant subjects. This decrease was accompanied by an increased incidence of gastro-oesophageal reflux as assessed by a pH meter.

Pregnant subjects with heartburn had a significantly lower barrier pressure compared to both non pregnant and pregnant subjects without heartburn.^{VII,43} Hence, pregnant subjects with heartburn exhibit a faulty compensatory mechanism of the LOS in response to the increased gastric pressure, giving rise to oesophagitis and possible heartburn. Pregnant subjects with heartburn also had a

greater tendency to both stress and free reflux, both before and after atropine, when compared to non pregnant and pregnant controls. However, the results were not statistically significant.

Studies VI and VII confirm previous observations that intragastric pressure is elevated during pregnancy,⁴² which was thought to be due solely to the presence of the enlarging uterus as pregnancy advances. We have recently concluded a study of pregnant women in the first trimester.⁴³ Gastric and sphincter pressures were measured in pregnant patients with and without heartburn. The gastric pressures in both pregnant groups were higher than controls but not as high as at term. It is possible that the difference in gastric pressure between both control and pregnant patients and between early and late stage of pregnancy could be a weight-related problem. The etiological factors precipitating oesophageal reflux and symptomatic heartburn in pregnancy remains unknown, however hormonal imbalance is the probable cause.¹⁰⁹ In Study XI, the mean barrier pressures of both the pregnant groups (Heartburn and No Heartburn) were significantly lower than controls and virtually identical. This finding was not unexpected since correlation between a decreased LOS pressure and symptomatic gastro-oesophageal reflux is not absolute.¹¹⁰ It is also possible that some of our patients without heartburn may have had a "weak" sphincter, even though they were symptom-free at the time of the study.

Study VII showed that metoclopramide increased LOS tone in

pregnant subjects, making it an important drug in obstetrical anaesthesia. The mechanism of action of metoclopramide on the LOS is poorly understood. There are three major current hypotheses for metoclopramide's mechanism of action on smooth muscle; enhancement of cholinergic excitation processes at the post ganglionic myoneural junction, inhibition of non-cholinergic, non-adrenergic motor inhibitory neurons¹¹¹ and direct action on the muscle.¹¹²

The method of anaesthesia we use routinely for Caesarean section includes the administration of atropine¹¹³ for the following reasons. A desensitizing dose of a non-depolarizing muscle relaxant is given prior to anaesthesia to avoid the increase in gastric pressure that occurs after a depolarizing muscle relaxant (succinylcholine).¹¹⁴ Since these two muscle relaxant antagonise each other, a larger than usual dose of succinylcholine is employed.¹¹⁵ This increased dose may have adverse effects on the cardiovascular system due to its muscarinic actions.¹¹⁶ These parasympathetic effects, in particular bradycardia with resultant lowered cardiac output, are blocked by atropine. In addition, a combination of concealed aortocaval occlusion, possible carotid body stimulations (cricoid pressure),³¹ and rapid endotracheal intubation in the absence of atropine premedication, may produce alarming hypotension and cardiac arrhythmias. Thus the exclusion of atropine as a pre-medicant appears unwarranted since placental perfusion and feto-placental exchange may be compromised.¹¹⁷ Furthermore, ketamine is sometimes used as an alternative to thiopentone

for anaesthetic induction.¹¹⁸ Due to its markedly increased salivation, the use of atropine preoperatively appears advisable. Significantly, in the most recent Confidential Report on Maternal Mortality from Great Britain, two women were deemed to have died because atropine was excluded from the preanaesthetic regime.¹¹⁹

Recently, Sehhati-Chafai (1980)¹²⁰ has reported his findings on intravenous induction agent's effect on LOS tone. Thiopentone, ketamine, etomidate and droperidol-fentanyl all produced a significant reduction in LOS pressure within 2 minutes, but well within the time of receiving the airway in a rapid induction sequence. Interestingly, all agents produced a drop in intragastric pressure and hence the barrier pressure could well have been maintained. Further studies would seem indicated.

Atropine is frequently given to parturients in labour to abolish reflex causes of fetal bradycardia.¹²¹ These patients may subsequently require urgent operative delivery of a distressed fetus under general anaesthesia. Thus, according to our results in Studies XI and XII, domperidone would seem to be a drug of choice by nullifying the deleterious effect of atropine on the LOS.

In another study from our department, ergometrine 0,5 mg increased LOS tone markedly by 24 cmH₂O ($p < 0,005$) during general anaesthesia for Caesarean section.¹²² This is an added beneficial effect of ergometrine. However, it is

important to remember that ergometrine is an emetic in approximately 20% of cases when given parenterally.¹²³ Further investigation in both unanaesthetized human volunteers and the pregnant patient at term, post-delivery, would seem indicated. Ergometrine can, however, never be recommended given prior to the induction of anaesthesia or before delivery.

Study VIII examined commonly used antiemetics' effect on the lower oesophageal sphincter. Promethazin decreased the LOS tone, probably due to its anticholinergic activity. However, prochlorperazine, also a phenothiazine derivative with only minimal anticholinergic activity, increased the LOS tone. The precise mode of action of the above drugs and the other drugs studied, cyclizine and droperidol, is unknown. Cyclizine increased LOS tone while droperidol caused no change in LOS tone in the dose used. One would expect droperidol, being an α -adrenergic blocker, to decrease LOS tone. Sehhati however, found that droperidol increased LOS tone while a combination of droperidol and fentanyl decreased the sphincter pressure.⁸⁷ Perphenazine (Trilafon^(R)) and thiethylperazine*(Torecan^(R)) effect on LOS tone has not to date been studied.

Antiemetic syrups are sometimes given orally, especially to children, as a premedicant. It is important to realize that drugs may be retained at the lower end of the oesophagus and cause oesophagitis,¹²⁴ with decreased LOS tone.¹²⁵

* Felleskatalogen

Study IX and X reported the effect of atropine/neostigmine and glycopyrrolate/neostigmine combinations on the LOS tone. These drug combinations are given at the end of a general anaesthetic to antagonize a non-depolarizing neuromuscular blockade. Regurgitation and inhalation of acid gastric content is associated, not only with induction, but also with recovery from general anaesthesia, hence information as to the effect these two drug combinations have on the LOS tone would seem imperative. Atropine 1,2 mg and neostigmine 2,5 mg decreased LOS pressure insignificantly, while atropine 1,2 mg and neostigmine 5 mg increased LOS pressure by a mean of 14 cmH₂O ($p < 0,001$). Glycopyrrolate 0,6 mg and neostigmine 2,5 mg increased LOS pressure insignificantly, while glycopyrrolate 0,6 mg and neostigmine 5 mg increased the LOS pressure by 12 cmH₂O ($p < 0,001$). Thus the combination using neostigmine 5 mg appears preferable if the integrity of the LOS is to be maintained at extubation and recovery from general anaesthesia. The characteristic pharmacological effect of neostigmine and other anticholinesterases is due primarily to inhibition or inactivation of acetylcholinesterase (ACHE) at sites of cholinergic transmission with consequent accumulation and increased action of endogenous acetylcholine (ACH), normally liberated by cholinergic nerve impulses.

Studies XIII and XIV reported the effect of neurolept

analgesia with diazepam and 50-50 nitrous oxide in oxygen on laryngeal competence. In Study XIII all eight patients were observed to have aspirated the dye, hence the technique of neurolept-analgesia with diazepam should not be used without safeguarding the airway in patients liable to regurgitate and inhale gastric contents. Prior use of gastric emptying, antacid and cimetidine would seem imperative. In Study XIV, two out of ten volunteers aspirated the dye when breathing nitrous oxide 50% in oxygen while no aspiration was apparent in the same group of volunteers in a similar study with the exception that nitrous oxide was omitted. The latter pilot study suggests that the inhalation of 50% nitrous oxide in oxygen differs little from other commonly used anaesthetic techniques with respect to suppression of pharyngeal and laryngeal reflexes. (Guedel's Stages of Anaesthesia)*. Care should therefore be taken during both obstetrical and dental anaesthesia and during induction of the critically ill when 50% nitrous oxide in oxygen is a commonly employed technique.

The postoperative incidence of nausea and vomiting was 30% in our study⁴⁸ which correlates well with that of other centres. A drug able to reduce postanaesthetic nausea and vomiting and thereby the chances of aspiration into the lung of gastric contents, would seem imperative in anaesthetic practice. In this double-blind trial, the

* Prof.A.E.Guedel (1883-1956) developed a classic table of the signs of anaesthesia into four stages. Laryngeal reflexes disappear in the 3rd stage (Surgical Anaesthesia).

antinauseant and antiemetic effect of droperidol and diphenidol were assessed against a placebo, under standard conditions. Droperidol appeared superior to both diphenidol ($p < 0,01$) and placebo ($p < 0,001$) in the prevention of vomiting and reduced the incidence of nausea when compared to saline ($p < 0,05$). Droperidol's superior action to metoclopramide and domperidone has also recently been described.¹²⁶ Perphenazine (Trilafon^(R)) would also seem to be an excellent antiemetic in the postoperative period.¹²⁷

In a preliminary study in pregnant patients at term, mothers with prolactin levels over 3000 $\mu\text{U/ml}$ had significantly higher mean barrier pressures than patients with hormone levels of less than 3000 $\mu\text{U/ml}$ ($p < 0,02$).⁴⁷ No direct correlation could however be demonstrated between barrier pressures and prolactin levels ($r = 0,34$). Little is known about the factors which regulate both a normal or decreased sphincter competence, although certain hormones and drugs are active on sphincter tone.¹²⁸ Plasma immunoreactive gastrin secretion increased in late pregnancy but plasma gastrin levels have not been found to be lower in parturients complaining of heartburn.¹²⁹

Lind et al, (1966),¹³⁰ showed that abdominal compression in normal non-pregnant subjects, caused an increase in GP which stimulated a committant increase in LOS tone. These authors postulated that some patients lack this LOS response to an increase in intragastric pressure and therefore

develop oesophageal reflux with dyspepsia. A similar hypothesis has been proposed to explain the occurrence of heartburn during late pregnancy in relation to the gravid uterus at term, causing an increase in intra-abdominal and hence GP.¹³¹ Intravenous prolactin has been shown to raise blood pressure in rabbits, possibly as a result of a direct action on smooth muscle tone in the peripheral vascular bed, or as a result of a central action.¹³²

Prolactin concentration in the blood rises progressively throughout pregnancy and reaches a peak at term¹³³ while heartburn is usually experienced by the parturient during the first trimester¹³⁴ and disappears spontaneously during the last weeks of pregnancy.¹³⁵ Metoclopramide increases blood prolactin concentrations in man¹³⁶ and increases the tone of LOS in both non-pregnant and pregnant women.^{VII}

Could metoclopramide increase LOS tone via prolactin ?

Further studies would seem indicated on an animal model to establish the importance of prolactin in the regulation of the LOS tone in both non-pregnant and pregnant subjects.

CONCLUSIONS

I. Conclusions concerning gastric pH and volume measurements.

1. The stomach content of a fasting patient often contains sufficient volume of acid gastric juice to place the subject at risk from acid aspiration during anaesthesia.
2. Antacid prophylaxis seems indicated and possibly cimetidine preoperatively - the latter to decrease gastric acidity.

3. The length of time the gastric juice pH is "safe" after preoperative gastric aspiration and administration of 15 ml magnesium trisilicate in mothers undergoing Caesarean section is 2 hours.
4. Cimetidine 200 mg. i.v. is effective in increasing the pH of the stomach content in fasting patients after 90 minutes.

II. Conclusions concerning various drugs' effect on the LOS tone.

1. Atropine, hyoscine, glycopyrrolate and phenergan all lowered LOS tone significantly.
2. Metoclopramide, domperidone, prochlorperazine and cyclizine all increase LOS tone significantly in non-pregnant subjects.
3. Metoclopramide or domperidone should be given prior to atropine before induction of general anaesthetic so as to prevent the deleterious effects of atropine on the LOS.
4. In pregnant subjects at term, atropine lowers LOS tone and metoclopramide and domperidone increased LOS tone.
5. Atropine 1,2 mg and neostigmine 5 mg increased LOS pressure significantly as did glycopyrrolate 0,6 mg and neostigmine 5 mg. Thus, the combination using neostigmine 5 mg for reversal of non-depolarising muscle relaxants appears preferable if the integrity of the LOS is to be maintained at extubation and recovery from general anaesthesia.

III. Conclusion regarding laryngeal competence.

1. Laryngeal incompetence was observed in all patients receiving neurolept analgesia with diazepam.
2. In patients receiving 50-50 nitrous oxide in oxygen, laryngeal incompetence was seen in 2 out of 10. Further studies are indicated.

IV. Conclusion regarding nausea and vomiting in the post-operative periods.

1. The incidence of nausea and vomiting was 35% correlating well with other centres. The need for an antiemetic in the perioperative period is indicated.
2. Droperidol is a superior antiemetic both to placebo and diphenidol.

V. Conclusion regarding cardiovascular studies.

1. Cimetidine in a dose of 400 mg i.v. is haemodynamically stable in normal subjects.

VI. Conclusion regarding the possible regulating effect of prolactin on the LOS in late pregnancy.

1. Pregnant patients with prolactin levels over 3000 uU/ml had significantly higher mean barrier pressures than patients with hormone levels at less than 3000 uU/ml ($p < 0,02$). No direct correlation could however be demonstrated between barrier pressures and prolactin levels ($r=0,34$). Further studies in this important field would seem indicated.

TABLE I : DRUGS DECREASING LOS PRESSURE IN MAN (cmH₂O) (BP - Barrier Pressure)

DRUG	DOSE	ROUTE	BASAL LOSP	POST DRUG LOSP	DIFFERENCE IN LOSP	INCREASE IN BP	REFERENCE
Atropine	0,6 mg	I.V.	60,5	50,9	- 9,6	- 10,0	IX
Atropine	0,015 mg/kg	Subcut.	35,9	28,0	- 7,9	- 6,0	86
Hyoscine	0,4 mg	I.V.	59,4	46,8	- 12,6	- 10,4	IV
Glycopyrrrolate	0,3 mg	I.V.	46,8	37,7	- 8,1	- 8,8	VII
Diazepam	2,5 - 10 mg	I.V.	16,1	10,8	- 5,3	* (-)	28
Morphine	7 - 10 mg	I.V.	17,6	10,5	- 7,1	* (-)	28
Meperidine	40 - 50 mg	I.V.	15,2	7,9	- 7,3	* (-)	87
Promethazine	25 mg	I.V.	57,5	43,4	- 14,1	- 14,3	VIII
Isoproterenol	0,03 mg/kg/min	I.V.	13,6	9,7	- 3,9	* (-)	88
Gastric Acidification	0,1 NHCl	into stomach	22,3	15,9	- 6,4	* (-)	89

Properidol and fentanyl also drops LOS pressure but no absolute figures are given ⁷⁷

* Information not available

TABLE II : DRUGS INCREASING LOS PRESSURE IN MAN (cmH₂O) (BP - Barrier Pressure)

DRUG	DOSE	ROUTE	BASAL LOSP	POST DRUG LOSP	DIFFERENCE IN LOSP	INCREASE IN BP	REFERENCE
Metoclopramide	10 mg	I.V.	50,8	71,8	21,0	20,0	VII
Metoclopramide	0,3 mg/kg	I.V.	26,0	52,0	26,0	* (-)	90
Metoclopramide	20 mg	Oral	19,4	62,4	43,0	* (-)	90
Prochlorperazine	12,5 mg	I.V.	44,9	55,6	10,7	10,1	VIII
Cyclizine	25 mg	I.V.	44,6	58,6	14,0	14,2	VIII
Edrophonium	80 mg/kg	I.V.	19,4	33,2	13,8	* (-)	91
Metacholine	40 mg/kg	Subcut.	19,4	38,8	19,4	* (-)	91
Domperidone	10 mg	I.V.	55,3	73,6	18,3	14,5	XI
Gastric Alkalinization	Aluminium Hydroxide 30 ml	per os	13,0	24,4	11,4	* (-)	92

Atropine 1,2 mg and neostigmine 5 mg IV increase LOS by 14 cm (V)

Glycopyrrolate 0,6mg and neostigmine 1mg IV increases LOS by 13cm (X)

* information not available

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Fasting volume and acidity of stomach contents associated with gastrointestinal symptoms

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J.M. SPITAELS AND R. STIEBEL

Pulmonary acid aspiration of stomach contents during the induction of or recovery from general anaesthesia is a serious hazard for both surgical and obstetric patients requiring urgent operation.^{1, 2, 3} Aspiration pneumonitis may follow the inhalation of as little as 25 ml of gastric juice of pH less than 2.5, but has been reported in an obstetrical patient after inhalation of more alkaline stomach contents, (pH 3.5).⁴ There is little information in the anaesthetic literature on the volume and acidity of gastric juice after an overnight fast, despite its obvious relevance to patient safety during general anaesthesia. This paper reviews, retrospectively, results of volume and pH measurements obtained after an overnight fast from patients investigated for gastrointestinal symptoms.

Material

The records of 430 patients aged 10-90 years were reviewed. All presented with symptoms suggestive of upper gastrointestinal pathology warranting investigation. All patients had gastric analysis performed in the Gastrointestinal Unit as part of their diagnostic work-up. After gastric analysis, all patients were subjected to endoscopy and upper gastrointestinal X-ray series. On the basis of evidence recorded after endoscopy, the patients were divided into four groups:

Group 1. Negative findings

Group 2. Oesophagitis and/or gastritis

Group 3. Gastric Ulcer

Group 4. Duodenal Ulcer

The clinical data of the groups studied are shown in Table 1.

Methods

Gastric analysis. After an overnight fast, a radio-opaque nasogastric tube was placed in the gastric antrum under fluoroscopic control in every case. All tests were done by two trained technicians who were in constant attendance. The stomach was emptied by continuous suction at 200 mmH₂O and augmented at 5-minute intervals with hand suction until the stomach was deemed to be empty. The volume was measured, and the pH of the aspirate was measured on an automatic titrator (Beckman Automatic pH Titrator). The test was then continued with a ½ to 1 hour basal collection, and a 1 hour collection after 6 µg/kg intramuscular pentagastrin. Results of basal and maximal acid output in our population have been previously reported and differ little from other population groups.⁵

Endoscopy was performed in all instances as far as the duodenum by a trained observer, utilising the Olympus end-view GIF-D, or oblique-view GIF-K endoscopes. Additional

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Table 1. Clinical data

Group	1 Negative findings	2 Oesophagitis/gastritis	3 Gastric ulcers	4 Duodenal ulcers
Males no.	108	24	23	134
Mean age	36.6	39.3	47.6	37.1
Range	10-90	17-58	28-76	17-71
Females no.	53	19	17	52
Mean age	38.4	40.4	41.3	38.6
Range	18-60	14-70	17-65	17-65

All differences are not significant.

examination with the side-view Olympus JFB and B2 endoscope was employed where indicated.

Results

The mean pH and the mean volume of the gastric aspirate after an overnight fast are shown for the various groups in Tables 2 and 3.

The pH of the gastric juice in the group with negative findings (Group 1), oesophagitis/gastritis (Group 2) and gastric ulcers (Group 3), were similar in males and females (Table 2). There was a significantly lower pH with duodenal ulcers in both sexes (Group 4) as compared to Group 1 ($P < 0.001$) (Table 2).

The volume of gastric aspirate obtained from both males and females in group 4 (duodenal ulcers) (Table 3) was significantly higher than in Group 1. ($P < 0.001$); males with oesophagitis/gastritis (Group 2) and gastric ulcers (Group 3) also had higher volumes of gastric juice than Group 1 ($P < 0.05$).

There was also a significantly higher volume of gastric aspirate obtained from males compared to females of all groups (Table 3). There

were no significant differences in sex or age. Forty per cent of controls of either sex had a fasting volume of over 25 ml with a pH of less than 2.5 and over 50% had a pH of less than 3.5 (Fig. 1). If any of the pathological conditions diagnosed (Groups 2-4) were present, a significantly greater percentage of patients had volume and pH levels in these potentially dangerous ranges. (Figs 1-3). There was no correlation between pH and volume.

Discussion

Pulmonary aspiration of gastric contents, with resultant chemical pneumonitis, remains a major cause of maternal death associated with obstetric anaesthesia. Teabeaut⁶ originally emphasised that the predominant insult from the aspiration of liquid gastric contents was related to volume and acidity; negligible roles were assigned to gastric enzymes and bacteria. The volume of gastric contents with a pH below 2.5 required to produce the acid aspiration syndrome has been stated by Roberts⁷ to be approximately 25 ml.

Table 2. Mean gastric pH values (s.e. mean)

Group	1 Negative findings	2 Oesophagitis/gastritis	3 Gastric ulcer	4 Duodenal ulcer
Males	3.9 (0.2)	3.1 (0.4)	3.9 (0.7)	2.4* (0.1)
Females	4.2 (0.3)	3.6 (0.4)	3.8 (0.6)	2.8* (0.2)
Males & females	4.0 (0.2)	3.3 (0.3)	3.9 (0.4)	2.7* (0.2)
Range	1-8	1-8.5	1-8	0.8-7.5

Levels of Significance from Group 1. * $P < 0.001$

Table 3. Mean gastric aspirate volumes in ml (s.e. mean)

Group	1 Negative findings	2 Oesophagitis/gastritis	3 Gastric ulcer	4 Duodenal ulcer
Males	59.6 (4.2)	86.0 (11.7)*	83.9 (10.9)*	82.7 (5.0)*
Females	46.3 (4.2)	42.5 (9.8)	51.2 (7.5)	67.8 (6.0)†
Males & females	55.2 (3.2)	53.2 (8.2)	70.0 (7.4)	78.5 (4.0)‡
Range	0-225	0-230	0-200	0-400

Levels of significance from Group 1. * $P < 0.05$; † $P < 0.005$; ‡ $P < 0.001$.

Significant difference between males and females in Groups 1, 2, 3 and 4: $P < 0.005$, $P < 0.001$, $P < 0.005$, and $P < 0.005$ respectively.

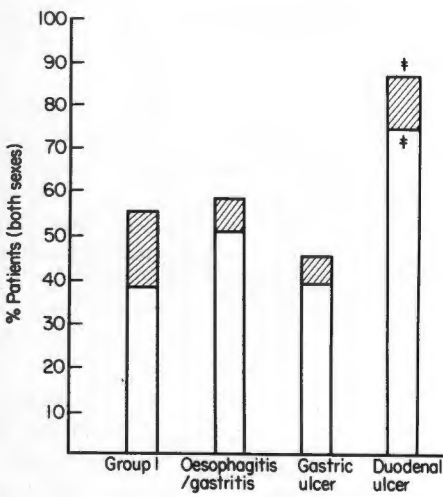


Fig. 1. Both sexes. Percentage of patients with overnight fasting gastric volume > 25 ml and pH < 2.5 (open column), or < 3.5 (hatched column). Differences from Group 1: ‡ $P < 0.001$.

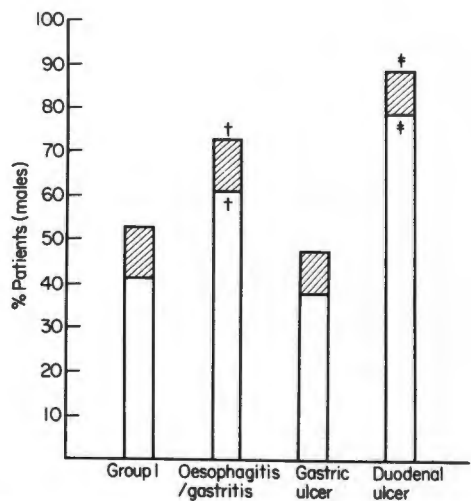


Fig. 2. Males. Percentage of patients with overnight fasting gastric volume > 25 ml and pH < 2.5 (open column), or < 3.5 (hatched column). Differences from Group 1: † $P < 0.005$, ‡ $P < 0.001$.

The present review was undertaken to establish the mean levels of acidity and volume of gastric juice after an overnight fast in patients with suspected upper gastrointestinal pathology. The results show that it is inappropriate to assume that the stomach of a patient is empty after an overnight fast.

Leach⁸ reported an average overnight fasting stomach aspirate of 50 ml with a range of 0-180 ml, a result similar to this study (mean 55.2 ml and a range of 0-225 ml). However, the pH results reported by Leach were different; in his control subjects, pH ranged from 1.1 to 2.6.

Fig. 1 indicates that over 40% of patients with 'negative findings' and 40-90% of patients with any one of the three pathological conditions

diagnosed had evidence of acidity and gastric volumes of potentially dangerous levels.

These results suggest, therefore, that more care should be exercised in the induction of anaesthesia, not only in obstetrics⁹ or obese patients,¹⁰ but also in patients with gastrointestinal pathology under investigation.

It is concluded that, in patients with upper gastrointestinal symptoms, the administration of oral antacid before induction of general anaesthesia appears mandatory. Further studies are recommended to establish the incidence of normal subjects with gastric pH of less than 2.5 or 3.5 associated with a volume of more than 25 ml after an overnight fast.

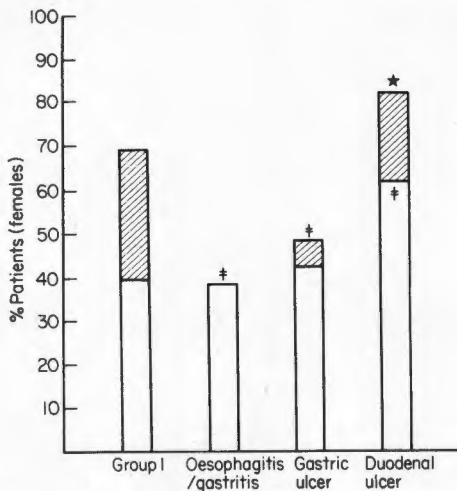


Fig. 3. Females. Percentage of patients with overnight fasting gastric volume >25 ml and pH <2.5 (open column), or <3.5 (hatched column). Differences from Group 1: † $P < 0.001$, * $P < 0.05$.

Summary

Acid aspiration is an important cause of anaesthetic mortality. 430 patients referred for gastric analysis were reviewed. According to observations made at endoscopy, patients were divided into 4 groups—no abnormality, oesophagitis/gastritis, gastric ulcers and duodenal ulcers. The volume of gastric juice varied from 0 to 400 ml, and the pH from 0.8 to 8. The percentage of patients with overnight fasting gastric volume over 25 ml and a pH of less than 2.5 was disturbingly high in all groups: controls 38.5%, oesophagitis/gastritis 51.2%, gastric ulcers 40.0%, duodenal ulcers 73.3%. This last figure is significantly greater than the group with no detectable abnormality.

These results indicated that the stomach of a fasting patient often contains sufficient volume of acid gastric juice to place the subject at risk from acid aspiration during anaesthesia. Antacid therapy in all these patients seems imperative

and consideration should also be given to pre-operative gastric aspiration before induction of general anaesthesia.

Key words

GASTROINTESTINAL TRACT; stomach, pH.

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Gastric Volume and Acidity at Caesarean Section

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SUMMARY

The pulmonary acid aspiration (Mendelson's) syndrome may present after regurgitation and inhalation of acid gastric content during obstetric anaesthesia.

The stomach contents of 70 mothers were aspirated at caesarean section after pre-operative gastric 'emptying' and alkaline ingestion. The acidity of the gastric aspirate was analysed and volumes were measured. The patients were divided into 5 groups according to the time when gastric aspiration was carried out.

A 'safe' gastric pH ($\text{pH} > 3,5$) was found in all patients up to 2 hours after antacid ingestion (groups 1-3). However, $2\frac{1}{2}$ hours after antacid ingestion (group 4), 50% of patients had gastric volumes in excess of 25 ml and a pH of less than 3,5.

We therefore recommend that, if general anaesthesia is to be induced or is in progress 2 hours after antacid therapy, the alkaline regimen should be resumed after repeated gastric aspiration.

S. Afr. med. J., 52, 182 (1977).

Pulmonary aspiration of acid gastric content during induction of/or recovery from general anaesthesia, is a serious hazard to patients who require urgent operation.¹⁻³ A chemical pneumonitis may follow the inhalation of as little as 25 ml of gastric juice with a pH of 2,5 or less,⁴ but it has also been reported in a pregnant patient after more alkaline stomach contents had been aspirated ($\text{pH} < 3,5$).⁵

Many methods, some controversial, have been employed to lessen the danger of regurgitation and inhalation of stomach contents during obstetric anaesthesia. At King Edward VIII Hospital, we routinely empty the stomach pre-operatively with a large-bore 28 FG stomach tube; thereafter magnesium trisilicate 15 ml is given orally to alkalize the gastric contents.

The value of antacids in preventing Mendelson's syndrome is well established.⁶ However, the duration of antacid action in maintaining a gastric juice pH above 3,5 after gastric aspiration has not been studied. The purpose of this investigation was to establish how long magnesium trisilicate BPC maintained the stomach pH at 'safe' levels ($\text{pH} > 3,5$) after gastric aspiration and to measure gastric volumes after pre-operative injection of metoclopramide.

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Date received: 29 March 1977.

PATIENTS AND METHODS

Seventy mothers referred for emergency caesarean section were included in this study. Gastric emptying was performed pre-operatively on all patients as described above, and thereafter 15 ml of magnesium trisilicate was administered and the time was noted. The method of anaesthesia, maintenance and supplementation before and after delivery of the fetus was similar to that described previously,⁶ and differed only in that metoclopramide was injected with atropine as a premedicant.⁷

Before anaesthesia ceased, a 16 FG nasogastric tube was passed through the nose into the stomach. The position of the catheter was verified by auscultation during insufflation of a few millilitres of air. Gastric contents were then sampled, the volume was recorded, and the pH was measured with indicator paper. Patients were divided into 5 groups (14 patients in each). In group 1 gastric aspiration was performed after 1 hour; in group 2 after $1\frac{1}{2}$ hours; in group 3 after 2 hours; in group 4 after $2\frac{1}{2}$ hours; and in group 5, 3 hours after initial aspiration.

RESULTS

The colour of the gastric contents ranged from clear to deep green. The latter suggested the presence of bile, but was not always associated with an alkaline pH. In 16 patients a recognizable suspension of antacid itself was retrieved. Since it was impossible to tell whether the stomach had been completely emptied by this aspiration, all volumes reported are therefore actual volumes obtained, and may not represent the maximum quantity of gastric contents present.

Magnesium trisilicate 15 ml maintained a 'safe' pH for at least 2 hours in all patients. However, at $2\frac{1}{2}$ hours 50% of patients had a $\text{pH} < 3,5$ and a gastric volume > 25 ml, and 28% of patients had a $\text{pH} < 2,5$ and a volume > 25 ml. The mean volumes are shown in Fig. 1, and the mean pH is shown in Fig. 2.

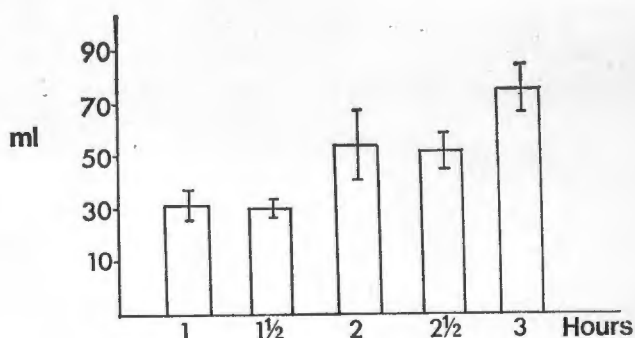


Fig. 1. Mean volumes (SEM).

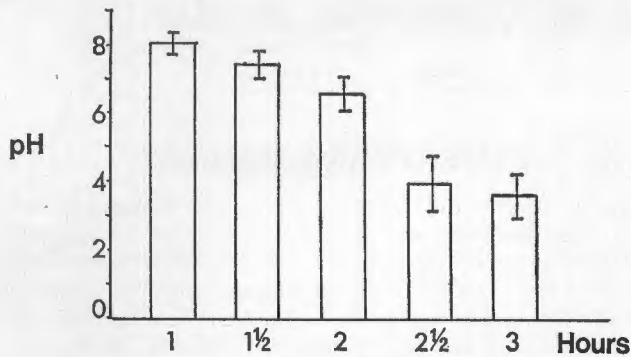


Fig. 2. Mean pH (SEM).

DISCUSSION

In 1951, Merrill and Hingson⁸ estimated that 100 maternal deaths a year were due to aspiration pneumonitis. Phillips *et al.*⁹ calculated an incidence of 1 maternal death per year per 1 million of the population as a result of aspiration.

Many methods for decreasing the incidence of acid aspiration during obstetric anaesthesia have been recorded, including pre-operative oral antacid therapy.⁴ We favour gastric aspiration before giving oral antacids, since they may not be effective in neutralizing large volumes of gastric juice. The neutralizing capacity of 15 ml of magnesium trisilicate has been reported to be adequate *in vitro* for a maximum of 140 ml of gastric contents.¹⁰ Peskitt¹¹ showed that the mean gastric volume of 131 women scheduled for caesarean section was 114.8 ml, with a range of 0-1 000 ml. In this series, the mean pH before antacid ingestion was 3.25 (range 0.5-7.5). This differs from our unpublished findings during manometric and pH studies of 30 pregnant women at term, when we recorded a mean pH of 2.4 (SEM 0.8). Gastric volumes were not measured in the latter study.

In 1966, Taylor and Pryse-Davies¹⁰ showed that oral administration of a magnesium trisilicate mixture markedly reduced gastric acidity. They postulated that pre-operative antacid therapy in obstetric practice would substantially reduce the incidence of the acid aspiration syndrome as described by Mendelson in 1946.¹

Inhalation of gastric juice with a pH higher than 2.5 causes little damage compared with the devastating effects of inhalation of stomach contents with a pH lower than 2.5.^{12,13} Recently, however, Taylor⁶ has reported a patient who was diagnosed as having Mendelson's syndrome after the inhalation of gastric contents with a pH of 3.5.

Thus, the critical value of pH < 2.5 in man should be considered arbitrary, as it is based solely on animal experimentation. A species difference exists with respect to the critical pH in rats, in which a pH of 1.7 may be lethal, compared with rabbits (pH 2.1-2.4).^{3,10} No information derived from clinical studies is available regarding the critical pH in man, to our knowledge.

Our results indicate that pre-operative gastric aspiration followed by administration of 15 ml magnesium trisilicate produces a 'safe' gastric juice pH for at least 2 hours. This is in keeping with the recommendation of Taylor and Pryse-Davies,¹⁰ who reported that the administration of 14 ml magnesium trisilicate to humans decreased the acidity of the gastric contents and raised the pH to above 2.5 for a period of at least 2 hours.

Crawford¹⁴ has titrated the recommended dose (14 ml) of magnesium trisilicate *in vitro* against a representation of the maximum amount of gastric acid secreted in a 2-hour period. He found that 15 ml of magnesium trisilicate given every 2 hours was adequate to maintain the pH above 2.5.

Thus, if induction of general anaesthesia is contemplated more than 2 hours after alkaline ingestion, we advise that antacid administration be repeated before operation. Furthermore, if anaesthesia persists for more than 2 hours after antacid treatment, repeat gastric aspiration followed by further administration of magnesium trisilicate would seem imperative. This is easily done via a nasogastric tube which is passed before extubation of the patient.

Our thanks are due to the Medical Superintendent and to Professor R. H. Philpott for permission to study patients in the department, to our obstetric colleagues for their help, and to Professor J. W. Downing for his advice and criticism of this paper.

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The administration of metoclopramide with atropine

A drug interaction effect on the gastro-oesophageal sphincter in man

J. G. BROCK-UTNE, J. RUBIN, J. W. DOWNING,
G. E. DIMOPOULOS, M. G. MOSHAL AND M. NAICKER

A zone of increased intraluminal pressure exists at the gastro-oesophageal junction in man, and is believed to act as a physiological sphincter. Contraction of this lower oesophageal sphincter (LOS), probably prevents reflux of acid gastric content.¹

The mechanisms involved in maintaining gastro-oesophageal competence remain controversial. Three mechanisms, independent of the LOS have been invoked in the prevention of reflux.² These are the pinch-cock action of the diaphragm, the flap valve effect of the angle of entry of the oesophagus into the stomach and the mucosal rosette at the gastro-oesophageal junction. These three mechanisms probably play a minor, supporting role in preventing gastric reflux compared to the mechanism which is probably of primary importance, the intrinsic LOS.¹

Pulmonary aspiration of gastric contents, with resultant chemical pneumonitis, remains a major cause of maternal death associated with obstetric anaesthesia.³ A decrease in LOS tone follows the administration of atropine,^{4,5} a drug routinely used in obstetric anaesthetic practice. Any drug which reverses this effect of atropine might enhance patient safety and prove a useful addition to the anaesthetist's armamentarium.

This paper presents the results of an investigation into the effects of a combination of atropine and metoclopramide on the LOS in normal control subjects. The methods employed are described in detail because it is intended that the results of a similar study concerning the effects of these drugs on the LOS of the parturient patient at term will be reported in the future.

Subjects and method

Oesophageal manometric studies were performed in three groups of healthy volunteers, aged between 18 and 55 years. All subjects gave informed consent. Any previous history of upper gastrointestinal surgery or disease precluded entry to the study. All

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the drugs were administered intravenously. The first group of eight volunteers received atropine 0.6 mg. The second group of 10 volunteers, received atropine 0.6 mg and metoclopramide (Maxolon) 10 mg given simultaneously. The third group of eight individuals was given 10 mg of metoclopramide alone.

Oesophageal motility studies were performed with the subject resting quietly in the supine position, after a fast of at least 5 hours.

A multilumen polyvinyl catheter (internal diameter of each lumen 0.85 mm) with three side orifices situated at the distal end set 5 cm apart, was used to measure intraluminal pressures at three different points. The catheter was passed orally until all the recording orifices lay in the stomach (Fig. 1). Throughout the entire procedure each

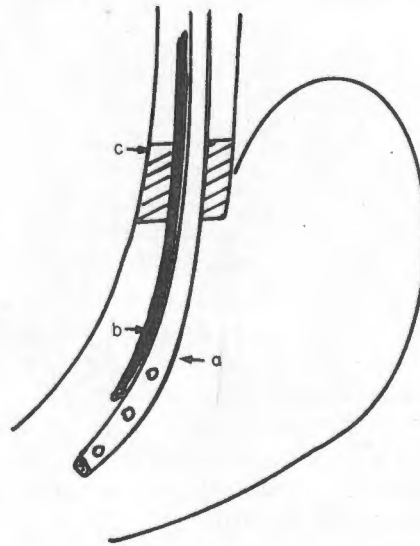


Fig. 1. (a) Polyvinyl catheter with side orifices. (b) pH electrode (not used in this study). (c) Lower oesophageal sphincter (LOS).

tube was continuously perfused with sterile water at a rate of 0.19 ml/min, using a Harvard constant infusion pump. Each tube was connected to a Beckman Instrument Physiological Transducer Model 215071 linked to an 8-channel Beckman R411 Dynograph amplifier and recorder.*

The catheter was withdrawn slowly, 0.5 cm at a time, until the pressure recordings, and their alterations in response to swallowing indicated that all three orifices lay within the oesophagus above the LOS. As each side orifice passed from the stomach into the oesophagus, a rise in pressure was usually observed (Fig. 2). This increase in pressure, or pressure profile, represents the passage of the catheter through the lower oesophageal sphincter.⁵ A mean pressure profile is established from the average of the three values obtained each time the tube is withdrawn. From the three tracings, a mean gastric pressure (MGP) and the mean LOS pressure (MSP), were calculated for each subject. The difference between these two readings, termed the barrier pressure (BP), was recorded.

The lower oesophageal sphincter normally relaxes and contracts during swallowing,⁶ producing fluctuations in the pressure profile obtained, which initially gives an

* Beckman Instruments Incorporated, 3900 River Road, Schiller Park, Illinois 60176, U.S.A.

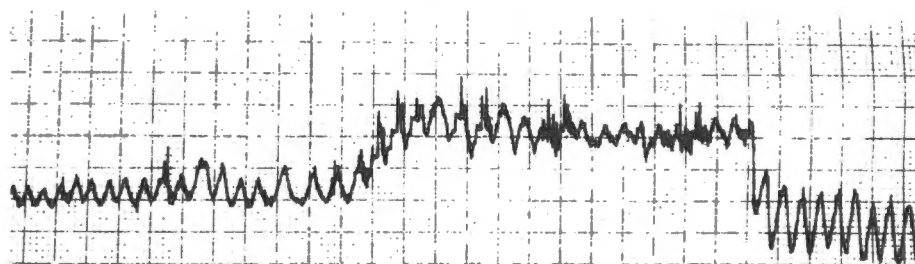


Fig. 2. From left to right. Gastric pressure, lower oesophageal sphincter (LOS) pressure and lastly oesophageal pressure (see text).

abnormally high value and subsequently, an abnormally low value. A pressure change recorded during swallowing is therefore deliberately excluded, and time is allowed for the pressure profile to settle to the previous pre-swallowing level before continuing with recordings. Pressures were expressed in cmH_2O above atmospheric pressure.

Respiration was monitored throughout using a tubular pneumograph placed round the subject's chest, connected to the Dynograph amplifier and recorder system.

Results

Changes in mean pressures of the three groups are shown in Fig. 3. Atropine decreased

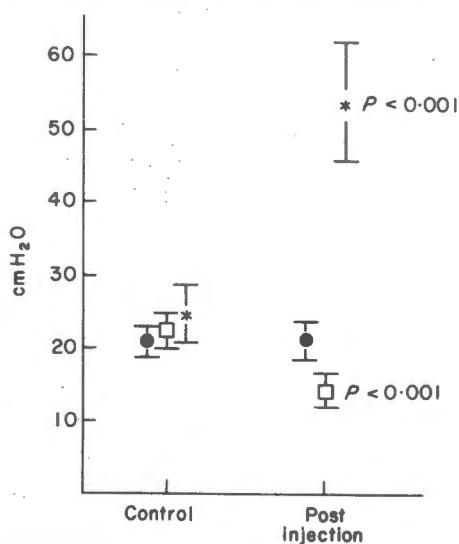


Fig. 3. Changes in mean barrier pressure of the three groups. ●, Atropine/metoclopramide; □, atropine; * metoclopramide.

the LOS pressure by an average of $8 \text{ cmH}_2\text{O}$ ($P < 0.001$). In contrast, no change in sphincter tone was noted following injection of the atropine–metoclopramide mixture.

Metoclopramide alone increased the LOS pressure by a mean of $29 \text{ cmH}_2\text{O}$ ($P < 0.001$).

Discussion

A zone of increased intraluminal pressure between the stomach and the oesophagus

has been identified,¹ but the precise anatomy and the functional importance of this physiological sphincter remain unresolved.

A physiological sphincter in the gastrointestinal tract may be defined as 'a segment of bowel which maintains a resting tone greater than that of the adjacent segments',⁷ a definition which is clearly applicable to the LOS. The mechanisms controlling lower oesophageal sphincter tone are complex and appear to be affected by neurotransmitter substance and hormones.⁸ LOS function may conveniently be considered as comprising two distinct phases.⁸ The fast component includes relaxation and contraction occurring during swallowing, and is probably initiated in the medulla via the mesenteric plexus. *In vitro* experiments indicate that the intrinsic nerves at the junction of the stomach and the oesophagus are predominantly cholinergic in nature, and that contraction of the LOS can be inhibited by atropine.^{4,5} The slow component, which is thought to be controlled by the hormone gastrin, is responsible for the maintenance of normal resting sphincter tone.⁹

The decrease in LOS pressure noted after atropine administration in this study, confirms the findings of Skinner & Camp⁴ and Lind *et al.*⁵ However, there is little information in the anaesthetic literature pertaining to the influence of drugs on gastro-oesophageal sphincter function, despite the obvious significance of this problem to the anaesthetist. Clark & Riddoch¹⁰ studied fifteen human subjects at operation using a Burge intra-gastric tube with an inflatable balloon cuff. They reported that atropine given intravenously in a dose of 0.6 mg markedly increased LOS tone, and suggested that the drug might thus reduce the likelihood of gastric reflux. This work has led several authors^{11,12} to recommend the administration of atropine as a pre-medicant drug to lessen the hazard of acid regurgitation and aspiration during the induction of emergency general anaesthesia. Recent work^{4,5} including our own results, suggests that this advice might be inappropriate.

The mechanism of action of metoclopramide on the LOS remains to be elucidated. *In vitro* experiments with human smooth muscle suggest that metoclopramide blocks adrenergic inhibitory nerve impulses,¹³ and enhances the response of smooth muscle to acetylcholine.¹⁴ The present study confirms that atropine relaxes and metoclopramide contracts the LOS in man. When given together, however, these two agents antagonise each other. It thus appears that metoclopramide can be used to reverse the relaxant effects of atropine on the LOS.

Increasing the resting tone within the LOS is currently believed to be the major barrier to gastro-oesophageal reflux. Hence metoclopramide should be the drug of choice in preventing gastro-oesophageal reflux in patients at risk, as it not only increases LOS tone, but also acts as a potent anti-emetic, and speeds gastric emptying.¹⁵

Metoclopramide is relatively free of undesirable side effects in adults,¹⁶ although extra-pyramidal symptoms have been described in psychiatric patients following very high doses.¹⁷ Dystonic reactions such as torticollis, oculogyric crises, and trismus, have also been observed in children receiving this drug. Metoclopramide appears to be unassociated with serious cardiac dysrhythmias,¹⁸ although one case of multifocal ventricular extrasystoles following a single intramuscular injection of 10 mg, has been reported.¹⁹

We conclude that the routine administration of metoclopramide to patients scheduled for emergency surgery and parturients presenting for general anaesthesia, appears indicated. Relaxation of the LOS induced by atropine is thus counteracted and the danger of acid aspiration reduced.

Summary

The effects of intravenous atropine 0.6 mg alone, metoclopramide (Maxolon) 10 mg alone and atropine 0.6 mg and metoclopramide 10 mg in combination, on the lower oesophageal sphincter (LOS) were studied in three groups of normal human volunteers. Atropine decreased the LOS pressure by an average of 8 cmH₂O ($P < 0.001$), whereas metoclopramide increased the LOS pressure by a mean of 29 cmH₂O compared to basal values ($P < 0.001$). In contrast, no change in sphincter tone was noted following injection of atropine-metoclopramide mixture.

These findings are relevant to the pre-operative preparation of patients presenting for emergency anaesthesia, since gastro-oesophageal reflux and pulmonary aspiration of acid gastric content continues to be a significant cause of morbidity and mortality.

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THE EFFECT OF HYOSCINE AND ATROPINE ON THE LOWER OESOPHAGEAL SPHINCTER

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SUMMARY

The effects of intravenous hyoscine 0.4 mg and atropine 0.6 mg on lower oesophageal sphincter tone were studied in normal human subjects. Hyoscine and atropine both decreased the lower oesophageal sphincter (L.O.S) pressure by approximately 11 cm H₂O ($p < 0.01$). There was also an increased incidence of reflux as seen by an indwelling pH electrode in the lower oesophagus.

These findings are relevant to the preoperative preparation of patients presenting for emergency obstetrical anaesthesia; since gastro-oesophagus reflux and pulmonary aspiration of acid gastric content continues to be a significant cause of morbidity and mortality.

A zone of increased intraluminal pressure exists at the gastro-oesophageal junction in man, which is alleged to act as a physiological sphincter. Contraction of this lower oesophageal sphincter (LOS) under normal circumstances prevents reflux of acid gastric contents (Cohen and Harris 1971).

Pulmonary aspiration of gastric contents, with resultant chemical pneumonitis remains a major cause of maternal death associated with obstetric anaesthesia. (Arthure *et al.* 1969). We have previously demonstrated that intravenous atropine 0.6 mg in fasting healthy volunteers decreases lower oesophageal sphincter (LOS) tone (Brock-Utne *et al.* 1976). Any drug that lessens the sphincter tone, might

increase the risk of pulmonary aspiration in patients requiring general anaesthesia.

This paper compares the effects of hyoscine and atropine on the LOS in normal control subjects.

SUBJECTS AND METHODS

Oesophageal manometric studies were performed in two groups of healthy volunteers aged between 19 and 45 years. All subjects gave informed consent. Any previous history of upper gastrointestinal surgery or disease, precluded entry to the study. The first group of eight volunteers received hyoscine 0.4 mg intravenously, and the second group of eight volunteers received atropine 0.6 mg by the same route.

Oesophageal motility studies were performed with subjects resting quietly in the supine position after a fast of at least six hours.

The apparatus and technique used for the motility investigation has been described in detail in a previous communication (Brock-Utne *et al.* 1976).

The motility tube used consisted of three portex polyethylene No. 54 plastic tubes assembled together at the distal end. Each tube has a single lateral orifice situated at 5 cm, 10 cm and 15 cm respectively from the distal tip.

The tube was passed orally until all recording orifices lay in the stomach. Throughout the

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entire procedure, each tube was continuously perfused with water at a rate of 0.19 ml/min., using a Harvard constant infusion pump. The tubes were connected separately to three separate transducers (Beckman Instrument Physiological Transducer, Model 215071) linked to an 8-channel Beckman R411 Dynograph amplifier and recorder.

The catheter was withdrawn slowly 0.5 cm at a time until the pressure recordings, and their alterations in response to swallowing indicated that all three orifices lay within the oesophagus above the LOS. The gastric pressure (GP), the LOS pressure (SP) and oesophageal pressure (OP) were recorded before and after intravenous injection of the drugs studied. The calculated difference recorded between SP, and GP, was termed the barrier pressure (BP). (Pressures were expressed in centimetres of water above atmospheric pressure.)

The LOS normally relaxes and contracts during swallowing, producing fluctuations in the pressure profile obtained, thus initially giving an abnormally low reading and then subsequently, an artificially high value. Any pressure change recorded during swallowing was therefore deliberately excluded, and time allowed for the pressure profile to settle to the previous pre-swallowing level, before continuing with the recording.

Respiration was monitored throughout using a tubular pneumograph placed round the subject's chest, connected to the Dynograph amplifier and recorder system.

MEASUREMENT OF REFLUX

The presence of gastro-oesophageal reflux was measured using an intestinal pH electrode (Beckman 39042,) attached to the motility

catheter at the level of the most distal orifice, 5 cm from the distal tip.

After a satisfactory sphincter profile was obtained, tests for reflux were performed utilising the pH electrode, placed 5 cm above LOS. With the electrode in this position the LOS was stressed by instructing the patient to cough and to perform valsalva manoeuvres with and without straight leg raising.

Reflux was Graded as Follows :

1. Free reflux, i.e. reflux without stress, was defined, as a failure of the pH to rise above 3.5 (5 cm above LOS).
2. Stress reflux, was considered to be present if the pH in the oesophagus dropped more than one pH unit during stress.
3. No reflux was present if pH was above 3, 5 even during stress.

RESULTS

The mean intraluminal pressure (\pm S.E.M.) obtained in all patients are shown in Table 1.

In Group I the basal resting pressures in the stomach, L.O.S., and oesophagus were 24.8, 59.4 and 4.0 cm H₂O respectively. The mean barrier pressure (sphincter pressure minus stomach pressure) was 34.6 cm H₂O. After administration of hyoscine there was a significant fall in the sphincter pressure (12.6 cm H₂O $p < 0.02$), and in the barrier pressure (10.4 cm H₂O $p < 0.01$) (Figure 1). Mean oesophageal pressure rose after hyoscine (3.5 cm H₂O $p < 0.1$).

In Group II the basal resting pressures in the stomach was 28.3 cm H₂O, in the L.O.S., was 59.5 cm H₂O, and in the oesophagus was 5.2 cm H₂O. The calculated mean barrier pressure was therefore 31.2 cm H₂O (sphincter minus stomach).

TABLE 1
Intraluminal Pressures (Mean \pm S.E.M.) (cmH₂O) in the Two Groups of Patients

	GROUP I		GROUP II	
	Basal	Post Hyoscine	Basal	Post Atropine
Gastric mean	24.8	21.2	28.3	30.7
Pressure \pm S.E.M.	1.09	0.90	1.28	1.81
Sphincter mean	59.4	46.8	59.5	50.9
Pressure \pm S.E.M.	2.84	3.08	4.55	3.3
Oesophageal mean	4.0	7.5	5.2	8.8
Pressure \pm S.E.M.	0.78	1.02	0.71	0.97
Barrier mean	34.6	24.2	31.20	20.0
Pressure \pm S.E.M.	2.86	2.74	4.39	2.86

After administration of atropine there was a fall in the sphincter pressure of ($8.6 \text{ cm H}_2\text{O}$ $p < 0.02$), and the barrier pressure ($11.2 \text{ cm H}_2\text{O}$ $p < 0.01$). The mean oesophageal pressure rose after atropine ($3.6 \text{ cm H}_2\text{O}$ $p < 0.1$).

The gastric pH was unaltered by injection of hyoscine or atropine administration. The stress test for reflux was negative under basal con-

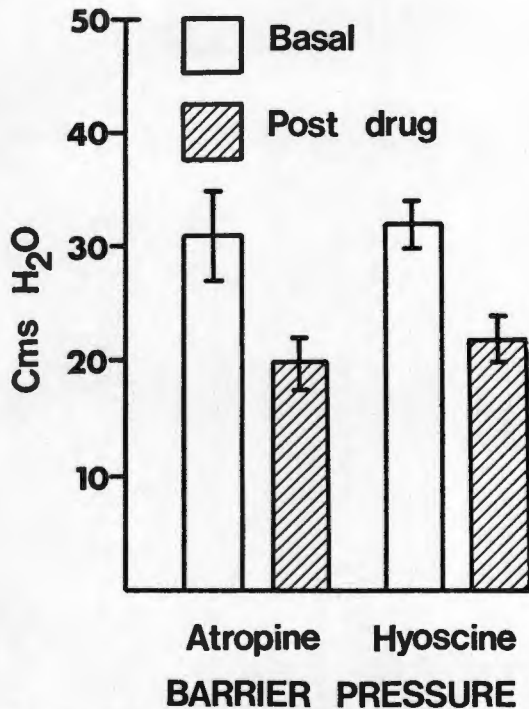


FIGURE 1.—Barrier pressure (mean \pm S.E.M.) before (basal) and after atropine and hyoscine.

ditions in both groups. However after the drug two subjects in both groups showed evidence of stress reflux, and free reflux was present in one subject, in both groups, after each drug.

DISCUSSION

The resting tone of the L.O.S., is currently believed to be the major barrier to gastro-oesophageal reflux (Cohen and Lipshutz 1971). In our study both hyoscine and atropine decreased L.O.S., pressure and increased the incidence of gastro-oesophageal reflux as seen by the lowered barrier pressure and pH results after these drugs. This suggests that there is an increased risk of acid regurgitation and aspiration during induction of general anaesthesia. Crawford (1972) recommends substituting hyoscine for atropine as a premedicant for Caesarean section since the former notably reduces the incidence of awareness. Unfortunately, its effects on the L.O.S., demonstrated here suggests that this advice might be inappropriate unless its effects on L.O.S., tone can be countered.

We have previously shown that when metoclopramide and atropine were given together, these two agents antagonise each other at the L.O.S., (Brock-Utne *et al.* 1976) reversing the relaxant effects of atropine, and we are at present studying the combined effect of hyoscine and metoclopramide.

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**THE EFFECT OF GLYCOPYRROLATE (ROBINUL) ON THE LOWER OESOPHAGEAL
SPHINCTER**

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THE EFFECT OF GLYCOPYRROLATE (ROBINUL) ON THE LOWER OESOPHAGEAL SPHINCTER

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PULMONARY ASPIRATION of gastric content with resultant chemical pneumonitis remains a major cause of obstetrical and surgical death.¹ The mechanisms of action of anticholinergic drugs on the lower oesophageal sphincter is of paramount importance to the anaesthetist and his patient. Previous studies have shown a decrease in lower oesophageal sphincter tone following the administration of atropine^{2,3} and hyoscine.⁴ Glycopyrrolate has been suggested as an alternative to atropine and hyoscine,⁵ but to our knowledge its effect on the lower oesophageal sphincter has not been elucidated. This paper concerns our investigations into the effect of glycopyrrolate on the lower oesophageal sphincter in normal control subjects.

SUBJECTS AND METHODS

Oesophageal manometric studies were performed on eight healthy volunteers, aged 18 to 38 years, with their informed consent. Previous history of upper gastro-intestinal surgery or disease precluded entry to the study.

Oesophageal motility studies were performed with the subjects resting quietly in the supine position after a fast of at least eight hours. The motility tube used consisted of three Portex polyethylene No. 54 plastic tubes assembled together at the distal end. Each tube has a single lateral orifice situated at 5 cm, 10 cm and 15 cm respectively from the distal tip.

The catheter consisting of the three tubes was swallowed orally until all recording orifices lay in the stomach. Each tube was continuously perfused with water at a rate of 0.19 ml per min-

ute, using a Harvard constant infusion pump. The tubes were connected separately to three transducers (Beckman Instrument Physiological Transducer, Model 215071) linked to an 8-channel Beckman R411 Dynograph amplifier and recorder.

The catheter was withdrawn slowly, 0.5 cm at a time, until the pressure recordings and their alterations in response to swallowing indicated that all three orifices lay within the oesophagus above the lower oesophageal sphincter. With the catheter in the stomach, three readings of gastric pressures were recorded. Similarly three readings were obtained with the catheter in the sphincter and similarly in the oesophagus. The mean gastric pressure, the mean lower oesophageal sphincter pressure and mean oesophageal pressure from the respective three readings were recorded before and after intravenous injection of glycopyrrolate 0.3 mg. The calculated difference recorded between mean lower oesophageal sphincter pressure and the mean gastric pressure was termed the mean barrier pressure. (Pressures were expressed in kPa above atmospheric pressure.)

The lower oesophageal sphincter normally first relaxes and then contracts during swallowing. This produces fluctuations in the pressure profile obtained, initially giving an abnormally low reading and then an abnormally high value. Any pressure change recorded during swallowing was therefore deliberately excluded and time was allowed for the pressure profile to settle to the previous pre-swallowing level, before continuing with the withdrawal of the catheter.

Respiration was monitored throughout using a tubular pneumograph placed around the subject's chest and connected to the dynograph amplifier and recorder system.

RESULTS

The mean intraluminal pressures obtained appear in Table I. Glycopyrrolate 0.3 mg decreased the mean barrier pressure by 0.88 kPa ($p < 0.005$) (Figure 1).

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TABLE I

MEAN OESOPHAGEAL, LOWER OESOPHAGEAL SPHINCTER, GASTRIC AND BARRIER PRESSURES BEFORE AND AFTER GLYCOPYRROLATE 0.3 mg (kPa)

Pressure site		Basal	Post drug
Oesophageal pressure	mean	0.32	0.43
	SEM	0.07	0.11
Sphincter pressure	mean	4.68	3.77
	SEM	0.30	0.20
Gastric pressure	mean	1.74	1.71
	SEM	0.13	0.15
Barrier Pressure	mean	2.94	2.06
	SEM	0.35	0.22

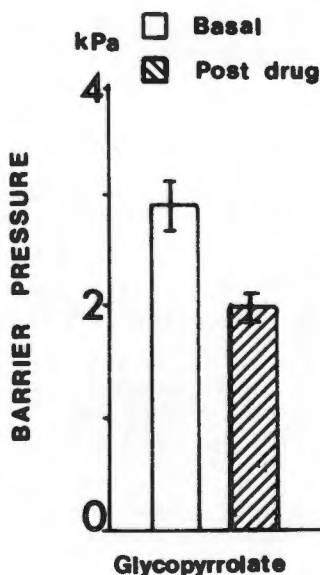


FIGURE 1 Mean barrier pressure in kPa before and after glycopyrrolate which produced a fall of 0.89 kPa ($p < 0.005$). The range around the mean is standard error.

DISCUSSION

The resting tone of lower oesophageal sphincter is currently believed to be the major barrier to gastro-oesophageal reflux.⁶ Our results show that glycopyrrolate decreases the barrier pressure (lower oesophageal sphincter pressure minus gastric pressure). Atropine and hyoscine have previously been shown to decrease lower oesophageal sphincter tone,^{2,4} whereas the effects of glycopyrrolate in this respect have not been previously reported. Clark and Riddock⁷ studied 15 human subjects at operation using a Burge intragastric tube with an inflatable balloon cuff. They reported that atropine given intravenously in a dose of 0.6 mg markedly increased

lower oesophageal sphincter tone, and suggested that the drug might thus reduce the likelihood of reflux of acid gastric content. This work has led several authors^{8,9} to recommend the use of atropine as a premedicant drug to lessen the dangers of acid regurgitation and aspiration during induction of emergency general anaesthesia. Recent work,^{2,10} including our own results in unanaesthetized subjects³ suggests that this recommendation might not be appropriate.

Glycopyrrolate is a quaternary ammonium compound which is an anti-cholinergic agent. Sun¹¹ and Moeller¹² reported the first clinical studies on its ability to control gastric acidity. All subsequent papers on glycopyrrolate continue to be related to gastroenterology in the management of peptic ulcers and other disorders associated with gastric hyperacidity. Glycopyrrolate has been found to be a potent antagonist of the increased salivation induced by neostigmine. As an anticholinergic agent it has, among other properties, the ability to cause dryness of the mouth and larynx. It appears to be free from side-effects. The detrimental effect it has on the lower oesophageal sphincter, demonstrated here, suggests that this drug and also atropine and hyoscine might increase the risk of pulmonary aspiration in patients requiring general anaesthesia. We have previously shown that metoclopramide and atropine when given together antagonize each other at the lower oesophageal sphincter,³ reversing the relaxant effects of atropine. We are at present studying the combined effects of glycopyrrolate and metoclopramide.

SUMMARY

Regurgitation and inhalation of acid gastric content, with resultant chemical pneumonitis,

remains a common cause of death during anaesthesia.

The effects of intravenous glycopyrrolate 0.3 mg on the lower oesophageal sphincter tone was studied in normal human subjects. Glycopyrrolate decreased lower oesophageal sphincter pressure by 0.88 kPa ($p < 0.005$).

This finding is of clinical importance in the pre-operative preparation of patients presenting for emergency surgery. A drug which decreases lower oesophageal sphincter tone would presumably increase the hazard of gastro-oesophageal reflux and pulmonary aspiration of acid gastric content.

RÉSUMÉ

La régurgitation de liquide gastrique avec bronchoaspiration et pneumonite chimique demeure une cause de mort anesthésique commune. Nous avons étudié, chez des sujets normaux, les effets d'une dose intraveineuse de 0.3 mg de glycopyrrolate sur le sphincter œsophagien inférieur. Cet agent a abaissé de 0.89 kPa ($p < 0.005$) la pression du sphincter œsophagien inférieur.

Ce résultat est d'importance clinique dans la prémédication anesthésique des malades opérés en urgence. En effet, un médicament qui abaisse le tonus du sphincter œsophagien inférieur peut présumément augmenter le risque de régurgitation gastrique avec bronchoaspiration.

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The Effect of Atropine on the Lower Esophageal Sphincter in Late Pregnancy

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Intraluminal gastroesophageal pressure and pH studies have been performed on 8 nonpregnant women, 10 pregnant women with heartburn, and 10 pregnant women without heartburn. Each patient was tested under resting conditions and after intravenous injection of 0.6 mg atropine. In both groups of pregnant patients the intragastric pressure was found to be higher than that of the nonpregnant subjects. The stomach to lower esophageal sphincter pressure (LESP) gradient under resting conditions was least in the pregnant patients with heartburn. After the administration of atropine, a fall in the LESP occurred in all 3 groups of patients which was most profound in the nonpregnant subjects and in the pregnant patients without heartburn. These changes and the pH recordings of the lower esophagus indicate the adverse effect that atropine has on the competency of the LESP both in pregnancy and in the nonpregnant state. Atropine should therefore be used with caution as a premedicant and preferably combined with metoclopramide (Maxolon).

RECENT ADVANCES in obstetric care have led to a steady decrease in maternal mortality during the last decade, but deaths due to anesthetic causes, in particular, aspiration of vomitus, have increased over the same period.¹ We have previously shown in nonpregnant control subjects, that atropine decreases the lower esophageal sphincter (LES) tone.² The LES is alleged to act as a physiologic sphincter preventing esophageal reflux of gastric content.³ Any premedicant drug that decreases the LES tone will increase the risk of regurgitation and pulmonary aspiration in patients requiring general anesthesia. Atropine, often used prior to cesarean section, is such a drug.² The present study was undertaken to compare the intraluminal pressure and pH changes at the gastroesophageal region before and after atropine administration in the pregnant and nonpregnant state.

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MATERIALS AND METHODS

Esophageal manometric studies were performed in 3 groups of women, with their informed consent. The first group consisted of 8 nonpregnant females, aged 17 to 46 years (mean 31.8 years), and acted as controls. The second group comprised 10 normal pregnant subjects without heartburn, aged 19 to 49 years (mean 30 years.) The third group consisted of 10 parturients aged 20 to 34 years (mean 25.3 years) who all complained of heartburn during their current pregnancy. Previous history of upper gastrointestinal surgery or disease, with the exception of heartburn in the third group of patients, precluded entry to the study. The 3 groups were comparable with regard to parity (36-40 weeks gestation).

Esophageal motility studies were performed with subjects resting quietly in the supine position, after a fast of 6 hours. Each group received atropine 0.6 mg intravenously after control values of gastroesophageal junction pressures and pH had been measured. The motility tube consisted of 3 portex polyethylene No. 54 plastic tubes assembled together at the distal end. Each tube has a single lateral orifice situated at 5 cm, 10 cm, and 15 cm, respectively, from the distal tip.

The catheter was swallowed orally until all the recording orifices lay in the stomach. Throughout the entire procedure each tube was continuously perfused with water at a rate of 0.19 ml/min, using a Harvard constant infusion pump. Each tube was connected to a Beckman Instrument physiological transducer Model 215071 linked to an 8-channel Beckman R411 Dynograph amplifier and recorder.

The tube was then slowly withdrawn, 0.5 cm at a time, until the pressure recordings, and their alterations in response to swallowing, indicated that all three orifices lay within the esophagus above the LES. The gastric pressure (GP), the LES pressure (SP), and the esophageal pressure (EP) were calculated for each subject before and after atropine. The difference between SP and GP was termed the barrier pressure (BP).

Normally, the lower esophageal sphincter relaxes and

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then contracts during swallowing, producing fluctuations in the pressure profile of the sphincter. These latter fluctuations result in an abnormally low reading at first, and then a substantially high value. Pressure changes recorded during swallowing were therefore excluded and time was allowed for the pressure profile to settle to preswallowing levels before continuing with the pull-through. All pressures were expressed in centimeters of water above atmospheric pressure.

Throughout the study, respiration was monitored using a tubular pneumograph placed around the subject's chest, and connected to the Dynograph amplification and recorder system.

Evidence of gastroesophageal reflux was measured using a Beckman intestinal pH electrode No. 39042. The pH electrode was attached 5 cm from the tip of the catheter at the level of the most distal orifice.

A satisfactory sphincter profile having been obtained, tests for reflux were performed with a pH electrode positioned 5 cm above the top of the LES. The patient was instructed to cough and perform Valsalva maneuvers with and without straight leg raising, and the changes in pH were observed. This latter constituted the stress test.

Reflux was graded as follows: 1) free reflux (occurring even without stress), defined as a failure of the pH to rise above 3.5, 5 cm above LES; 2) stress reflux, considered to be present if the pH in the esophagus dropped more than 1 pH unit during a stress test; and 3) nil—if neither free nor stress reflux was seen.

Statistical analysis was performed using the Student *t* test for paired and unpaired data, and the Fisher exact probability test.

RESULTS

The mean intraluminal pressures obtained in all patients are shown in Table 1 and Figures 1-4.

Control Group

Under basal resting conditions, the mean pressures in the stomach, LES, and esophagus were 28.3, 60.5, and

5.2 cm H₂O, respectively, giving a mean barrier pressure of 32.2 cm H₂O. After the administration of atropine, the mean ESOP pressure fell 9.6 cm H₂O ($P < 0.02$) and also the mean barrier pressure fell 12.0 cm H₂O ($P < 0.01$). Furthermore, after atropine the mean esophageal pressure rose by 3.6 cm H₂O ($P < 0.1$).

Pregnant Group

This group consisted of 10 asymptomatic mothers and 10 with heartburn. There was no significant difference in mean gastric pressures between the 2 groups under basal conditions. The LESP and the mean barrier pressures were significantly higher in the asymptomatic group, ($P < 0.05$ and $P < 0.005$, respectively). No change occurred in the mean gastric pressure after administration of atropine. However, the mean LESP fell 6.2 cm H₂O in the heartburn group and 17.1 cm H₂O in the asymptomatic group ($P < 0.1$ and $P < 0.005$, respectively). The mean barrier pressure fell in both groups particularly in the normal parturients, 6.8 (heartburn) and 18.3 (no heartburn) cm H₂O ($P < 0.025$ and $P < 0.005$, respectively). A rise in the mean esophageal pressure of 6.6 cm H₂O ($P < 0.005$) was observed in both groups.

Under basal conditions and after atropine, mean gastric pressures were significantly higher in both groups of pregnant patients compared to controls ($P < 0.01$ and $P < 0.005$, respectively). The fall in the mean LESP after atropine administration was similar in the control and pregnant heartburn group, but the significantly higher mean LESP found in the asymptomatic pregnant group fell by 17.1 cm H₂O to a level similar to that of the other 2 groups ($P < 0.05$). Mean barrier pressures before atropine in the control group and the asymptomatic pregnant group were similar and were significantly higher than in the pregnant heartburn group ($P < 0.01$). After atropine, however, the mean barrier pressures in both pregnant groups were particularly lower than in the control patients ($P < 0.01$). Mean esophageal pressure during basal conditions was also similar in the control group and asymptomatic pregnant group, while in the heartburn group it was twice the level found in the

TABLE 1. ESOPHAGEAL, LESP, GASTRIC, AND BARRIER PRESSURES BEFORE AND AFTER ATROPINE (cm H₂O)

	<i>Control (N = 8)</i>		<i>No heartburn (N = 10)</i>		<i>Heartburn (N = 10)</i>	
	<i>Basal</i>	<i>Post atropine</i>	<i>Basal</i>	<i>Post atropine</i>	<i>Basal</i>	<i>Post atropine</i>
Esophageal pressure (Mean ± SEM)	5.2 ± 0.71	8.8 ± 0.97	4.5 ± 0.75	11.1 ± 1.37	10.3 ± 0.97	16.9 ± 1.65
Sphincter pressure (Mean ± SEM)	60.5 ± 4.55	50.9 ± 3.3	68.7 ± 3.84	51.6 ± 2.74	58.1 ± 3.60	51.9 ± 2.93
Gastric pressure (Mean ± SEM)	28.3 ± 1.28	30.7 ± 1.81	37.2 ± 2.74	38.4 ± 2.58	39.0 ± 1.86	39.6 ± 1.42
Barrier pressure (Mean ± SEM)	32.2 ± 4.39	20.2 ± 2.86	31.5 ± 2.95	13.2 ± 1.43	19.1 ± 2.20	12.3 ± 1.84

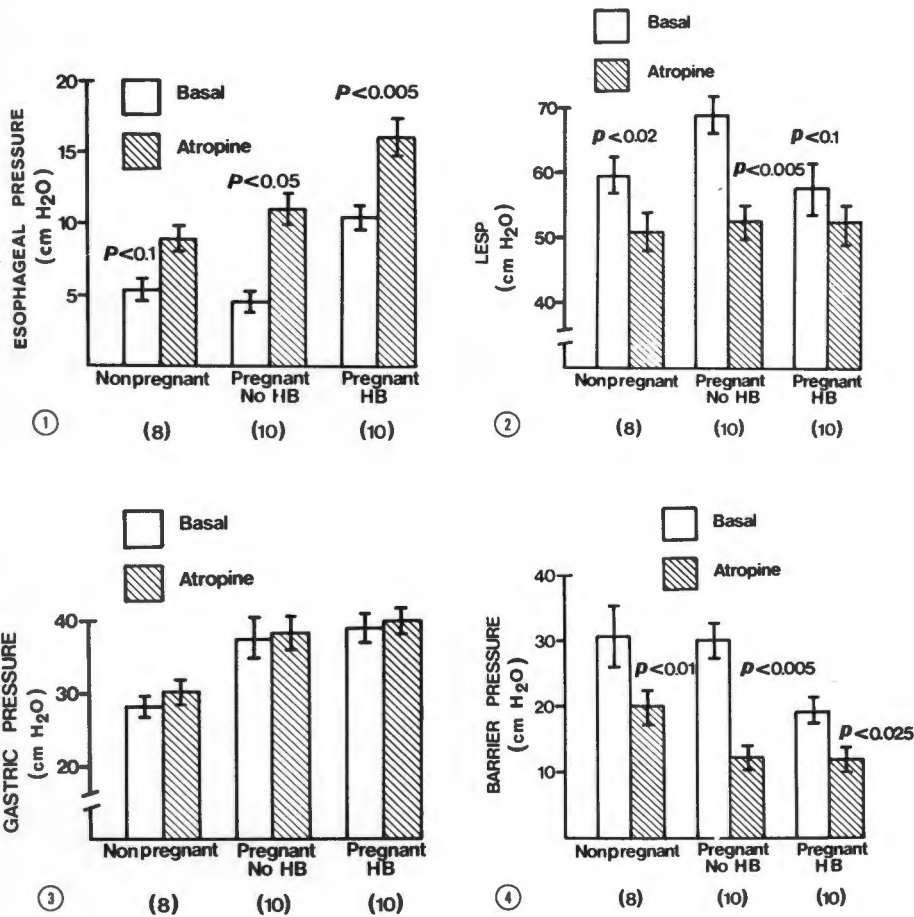


Fig 1. Mean esophageal pressure obtained before and after atropine. Fig 2. Mean LESPP before and after atropine. Fig 3. Mean gastric pressure before and after atropine. Fig 4. Barrier pressure obtained before and after atropine (HB = heartburn).

other 2 groups ($P < 0.005$). After atropine this difference was maintained.

pH Recordings and Reflux Status

There was no significant difference in the mean gastric pH of the 3 groups of patients before or after atropine. The mean esophageal pH (Figure 5) under basal conditions was significantly lower in the pregnant heartburn group when compared with the other 2 groups ($P < 0.05$). After atropine, each group showed a significant fall in pH which was least in the symptomatic pregnant group. Comparison of the mean esophageal pH values after the administration of atropine showed that the levels obtained were similar in all 3 groups of patients. In all patients in the control group under basal conditions, the stress test for reflux was negative (Table 2). It was, however, positive in 2 subjects after atropine administration. In the pregnant asymptomatic and pregnant heartburn groups the stress test was positive in 5 and 6 subjects, respectively, both before and after atropine. Free reflux was present in 1 control subject after atropine, in 2 subjects in the pregnant asymptomatic groups after atropine, and in 1 subject before and 3

subjects after atropine in the pregnant heartburn group. Statistical analysis of the reflux status before and after atropine in the 3 groups of patients was performed using the Fisher exact probability test. Differences were calculated within and between the groups, taking no reflux against stress reflux, combined stress and free reflux, and free reflux. No patients with stress reflux also demonstrated free reflux.

Under basal conditions the incidence of stress reflux compared to no reflux was significantly greater in the asymptomatic and heartburn groups than in the control group ($P = 0.02$ and 0.006 , respectively). These differences became more significant when no reflux was compared to combined stress and free reflux ($P = 0.02$ and 0.003).

After the administration of atropine, the incidence of stress and free reflux increased in the control subjects, but was only significant at the 10% level.

In the pregnant subjects, atropine did not produce any change in the occurrence of stress reflux but did show a greater, though not significant, incidence of free reflux. Stress reflux, however, was significantly more frequent in the pregnant patients with heartburn when

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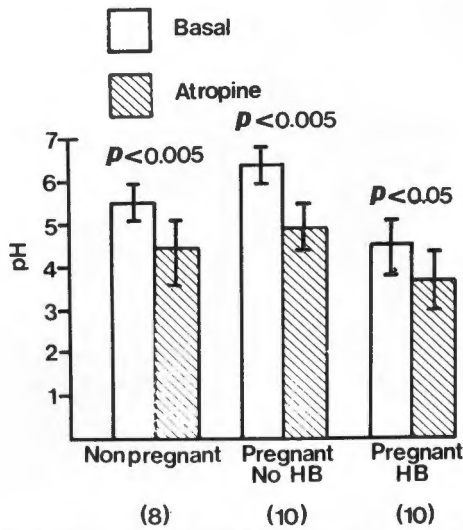


Fig 5. Esophageal pH values obtained before and after atropine (HB = heartburn).

these were compared to control subjects ($P = 0.04$). After atropine there was no difference in the incidence of stress or stress plus free reflux between the control group and the asymptomatic pregnant group.

DISCUSSION

Pulmonary aspiration of acid gastric content during general anesthesia is a major hazard in obstetric anesthetic practice.¹ Regurgitation and aspiration may be silent, but overt vomiting can also occur. Therefore, all patients who require general anesthesia for obstetric procedures in our unit, besides routinely emptying the stomach and thereafter giving magnesium trisilicate 15 ml orally preoperatively,⁴ have a cuffed endotracheal tube inserted into the trachea to safeguard the airway.

The method of anesthesia we use routinely for cesarean section includes the administration of atropine^{5,6} for the following reasons. A desensitizing dose of a nondepolarizing muscle relaxant is given prior to anes-

thesia to avoid the increase in gastric pressure that occurs after a depolarizing muscle relaxant (succinyl dicholine).⁷ Since these two muscle relaxants antagonize each other, a larger than usual dose of succinyl dicholine is employed.⁸ This increased dose may have adverse effects on the cardiovascular system due to its muscarinic actions.⁹ These parasympathetic effects, in particular bradycardia with resultant lowered cardiac output, are blocked by atropine. In addition, a combination of concealed aorticaval occlusion, possible carotid body stimulations (cricoid pressure), and rapid endotracheal intubation in the absence of atropine premedication, may produce alarming hypotension and cardiac arrhythmias. Thus the exclusion of atropine as a premedicant appears unwarranted, since placental perfusion and fetoplacental exchange may be compromised.¹⁰

Ketamine is sometimes used as an alternative to thiopentone for anesthetic induction.¹¹ Due to its markedly increased salivation, the use of atropine preoperatively appears advisable. However, atropine is known to decrease the LES tone² (as confirmed in this study). Thus there is an increase in the hazard of regurgitation and aspiration of gastric content. Recent studies in our unit have led us to include the routine injection of metoclopramide with atropine as part of the premedication before both emergency and elective operative obstetric anesthesia to counteract the relaxant effect of atropine on the lower esophageal sphincter (LES) tone.²

Atropine is frequently given to parturients in labor to abolish reflex causes of fetal bradycardia.¹² These patients may subsequently require urgent operative delivery of a distressed fetus, and general anesthesia and the use of metoclopramide is again indicated.

This study confirms previous observations¹³ that intragastric pressure is elevated during pregnancy, probably due to the presence of the enlarging uterus as pregnancy advances (Figure 3). In addition, mothers without heartburn exhibited significantly higher mean LES pressures (Figure 2) than those complaining of heartburn. Presumably, this pressure increase in the former group occurs in response to the raised intragastric pressure. Mothers without heartburn therefore maintain a mean barrier pressure (BP) similar to that found in nonpregnant subjects (Figure 4). However, in the pregnant patients with heartburn, the mean resting barrier pressure was low (Figure 4), indicating that the compensatory mechanism mentioned above is less efficient, or that the sphincter is weak.

The reason for the latter deficiency during pregnancy is unknown. Endogenous gastrin has been shown, but not conclusively, to increase LES tone, as has pentagastrin.³ Plasma immunoreactive gastrin secretion increases

TABLE 2. RESULTS OF REFLUX TESTING

	Basal			Post atropine		
	No reflux	Stress	Free	No reflux	Stress	Free
Control, nonpregnant	8	—	—	5	2	1
Pregnant, without heartburn	5	5	0	3	5	2
Pregnant, with heartburn	3	6	1	1	6	3

Numbers represent subjects studied.

in late pregnancy,¹⁴ but plasma gastrin levels have not been found to be lower in parturients complaining of heartburn.

The rise in the esophageal pressure (Figure 1), noted in the heartburn group, may reflect reflex esophageal contraction resulting from irritation by continual reflux of gastric content into the esophagus.

A decrease in mean LESP was present after atropine administration in all groups (Figure 2). The BP (Figure 4), after atropine, fell to the same level whether heartburn was present or not.

The adverse effect that atropine has on the competency of the LES is also well demonstrated in all 3 groups by the change in reflux status noted after atropine, and by the highly significant fall in esophageal pH associated with the drug. These changes are of particular importance to the patient undergoing elective or emergency obstetric anesthesia.

We conclude that, although atropine appears to have contraindication in the pregnant female at term, it does have an important role to play as a premedicant in parturients presenting for general anesthesia, for reasons discussed above. The deleterious effect of atropine on the LES tone is therefore routinely combated by the intravenous injection of metoclopramide in pregnant patients requiring either emergency or nonemergency obstetric anesthesia.¹⁵

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THE EFFECT OF METOCLOPRAMIDE ON THE LOWER OESOPHAGEAL SPHINCTER IN LATE PREGNANCY

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SUMMARY

The effects of intravenous metoclopramide (Maxolon) on the lower oesophageal sphincter (LOS) were studied in three groups of patients, one group being normal control and the other two being pregnant females, one without heartburn and the other with.

Metoclopramide increases the LOS pressure 20.5, 15.2 and 10.2 cm H₂O respectively ($p < 0.005$, $p < 0.005$ and $p < 0.05$).

These findings suggest that for patients undergoing elective or emergency obstetrical anaesthesia, intravenous metoclopramide may help reduce the incidence of regurgitation of gastric contents.

A zone of increased intraluminal pressure exists at the gastro-oesophageal junction in man which is alleged to act as a physiological sphincter.

Contraction of this lower oesophageal sphincter (L.O.S.) under normal circumstances prevents reflux of acid gastric content (Cohen and Lipshutz 1971).

Heartburn is a common and frequent distressing symptom of pregnancy (Donald 1964), the etiology of which is uncertain. It is, however, known to be associated with a weak LOS, and gastro-oesophageal reflux (Lind *et al.* 1968).

A steady decrease in maternal mortality due to advances in obstetrical care has occurred during the last decade, whilst deaths due to anaesthetic causes, in particular aspiration of vomitus, have increased over the same period (Arthur *et al.* 1969). Regurgitation and pulmonary aspiration

of acid gastric content gives rise to chemical pneumonitis and pulmonary oedema, a syndrome first described by Mendelson in 1946 (Mendelson 1946).

We have previously demonstrated in fasting healthy pregnant and non-pregnant volunteers, that intravenous atropine 0.6 mg decreases the intraluminal pressure of the LOS (Dow *et al.* 1977, Brock-utne *et al.* 1977); this might increase the risk of pulmonary aspiration in patients requiring general anaesthesia. Reversal of this effect by metoclopramide (Brock-utne *et al.* 1976) might enhance the patient's safety, and prove a useful addition to the anaesthetist's armamentarium.

This paper concerns our investigations into the effects of metoclopramide on the LOS in normal and pregnant subjects.

SUBJECTS AND METHODS

Three groups of women were studied, all of whom gave their informed consent. The first group of 8 non-pregnant subjects, ranging in age from 17 to 46 years, mean age of 31.8 (SEM 1.6), acted as controls.

The second group consisted of 10 normal pregnant women, without heartburn, aged between 17 and 36 years, mean age of 25.8 (SEM 1.9).

The third group comprised 10 pregnant women aged between 19 and 38 years, mean

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age 30.5 (SEM 1.9), all of whom complained of heartburn during their current pregnancy.

Patients with a history of upper gastrointestinal surgery or disease, with exception of heartburn, were excluded from the study.

The three groups were comparable in regard to parity and age. All pregnant patients were between 36–40 weeks gestation.

METHODS

Each group received metoclopramide 10 mg intravenously after control values of gastro-oesophageal junction pressures, and pH had been measured. The method of motility study and the measurement of reflux have been previously described (Brock-utne *et al.* 1977).

The gastric pressure (G.P.), the LOS pressure (S.P.) and the oesophageal pressure (O.P.) were calculated in each subject. The difference recorded between GP and SP was termed the barrier pressure (B.P.).

Respiration was monitored throughout using a tubular pneumograph placed around the subject's chest, connected to the Dynograph amplifier and recorder system.

MEASUREMENT OF REFLUX

Tests for reflux were performed after completion of the pressure measurements. A Beckman intestinal pH electrode No. 39042 was placed 5 cm above the LOS. The patient was instructed to cough, and then to perform Valsalva manoeuvres, with and without straight leg raising as a means of stressing the sphincter.

Reflux was graded as follows:—

Positive— If the pH in the oesophagus dropped more than one pH unit during a stress test (stress reflux).

Free reflux—defined as a failure of the pH to rise above 3.5 at any time.

Negative— if neither stress nor free reflux was seen.

Statistical analysis was performed using Student's tests for paired and unpaired data.

RESULTS

The mean intraluminal pressures obtained in all patients are shown in Table 1.

CONTROL GROUP

Under resting conditions the mean pressure in the stomach, LOS and oesophagus, were 29.7, 51.8 and 8.7 cm H₂O giving a mean barrier pressure of 22.1 cm H₂O. After the administration of metoclopramide, there was a significant increase in the lower oesophageal pressure of 21.4 cm H₂O ($p < 0.005$) and also in the barrier pressure of 20.5 cm H₂O ($p < 0.001$). The mean oesophageal pressure did not change after metoclopramide.

Pregnant group (10 asymptomatic patients and 10 patients with heartburn).

Under basal conditions there was no significant difference in the gastric pressures between the two groups. The barrier pressures were significantly higher in the asymptomatic group ($p < 0.02$) compared to the heartburn group.

After the administration of metoclopramide no change occurred in the gastric pressure. However, a rise in the LOS pressure of 13.8 cm H₂O was noted in the asymptomatic group and of 8.9 cm H₂O in the heartburn group ($p < 0.005$ and $p < 0.05$ respectively). Barrier pressure increased in both groups, although more significantly in the asymptomatic patients—15.2 and 10.2 cms H₂O ($p < 0.001$ and $p < 0.005$ respectively) (Figure 1). No change in oesophageal pressure was observed.

TABLE 1

Mean Pressure Readings (cm H₂O) in Three Groups of Patients Before and After Metoclopramide

	Non Pregnant Control		Pregnant no Heartburn		Pregnant Heartburn	
	Basal	Post Metoclopramide	Basal	Post Metoclopramide	Basal	Post Metoclopramide
Gastric Mean	29.7	30.6	41.9	40.5	45.0	43.7
Pressure Sem	2.6	2.5	1.3	1.3	1.7	1.8
Sphincter .. Mean	51.8	73.2	64.7	78.5	60.4	69.3
Pressure Sem	3.0	5.5	2.6	2.8	2.3	3.1
Oesophageal .. Mean	8.7	8.5	8.5	7.3	9.5	9.1
Pressure Sem	1.0	1.1	0.9	0.8	0.8	0.6
Barrier Mean	22.1	42.6	22.8	38.0	15.4	25.6
Pressure Sem	1.8	4.4	2.4	2.6	1.3	2.5

COMPARISON OF CONTROL AND PREGNANT GROUPS

In the basal condition and after metoclopramide, gastric pressures were significantly higher in the pregnant patients ($p < 0.001$). After metoclopramide both the non-pregnant control and the asymptomatic pregnant patients had a significantly higher barrier pressure than the heartburn group (both $p < 0.005$).

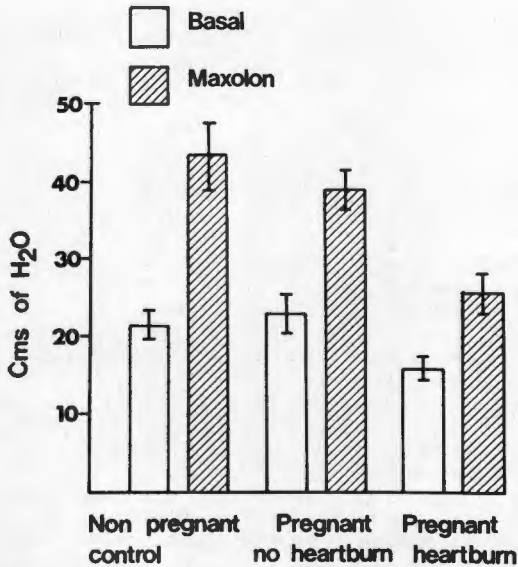


FIGURE 1.—Mean barrier pressures (gastric pressure—lower oesophageal pressure) obtained in the three groups of patients before and after metoclopramide (Maxolon).

REFLUX

No significant difference was found in the stomach and oesophageal pH of the three groups of patients before and after metoclopramide. Furthermore, no change in the oesophageal pH was noted between the groups.

Stress test for reflux was negative in all patients in the control group before and after metoclopramide. The test was positive in one case in each of the pregnant groups both before and after metoclopramide.

Free reflux was present in one patient in the asymptomatic group before and after metoclopramide and in the group of patients with heartburn 3 patients had free reflux before metoclopramide and only one patient had free reflux after metoclopramide. The latter finding just failed to reach statistical significance using the Fischer Exact probability test.

DISCUSSION

The present study confirms previous observations (Lind *et al.* 1968, Dow *et al.* 1977) that an increase in intragastric pressure occurs in pregnancy possibly due to the presence of the enlarging uterus as pregnancy advances.

In the pregnant patients without heartburn, the LOS pressure rose in response to raised gastric pressure as we have previously shown (Dow *et al.* 1977), thus maintaining a barrier pressure similar to that found in a non-pregnant patient. However, in the heartburn group, the resting LOS pressure remained at a lower level, when compared to the non-pregnant patients, and asymptomatic pregnant patients, indicating a "weak" sphincter. The lower barrier pressure noted in patients with heartburn may indicate that either the LOS response to raised intragastric pressure is altered or that decompensation has occurred during the course of pregnancy. The reason for such a difference in response seems speculative; endogenous gastrin has been implicated, but not shown to effect the LOS tone as does pentagastrin; nor have plasma gastrin levels been found to be lower in patients with heartburn (Cohen and Lipshutz 1971). The increase in the LOS pressure which was found after metoclopramide in all groups was least in the heartburn pregnant subjects. The incidence of reflux, as judged by the stress test and free reflux was greater in the pregnant groups. The significant increase in barrier pressure and the improvement in the free reflux status in the heartburn group, confirms the beneficial effect that this drug has on the competence of the LOS.

The mechanism of action of metoclopramide on the LOS remains to be elucidated. *In vitro* experiments with human smooth muscle suggests that metoclopramide blocks the adrenergic inhibitory impulses to acetylcholine (Birtley and Baines 1973). This present study confirms that metoclopramide increases the tone of the LOS man. We have previously shown, in non-pregnant controls, that metoclopramide can be used to reverse the relaxant effects of atropine on the LOS (Brock-utne *et al.* 1976). At present we are studying this effect in pregnant patients.

Increasing the resting tone within the LOS is currently believed to be the best method of preventing gastro-oesophageal reflux. Hence metoclopramide should be the drug of choice in preventing gastro-oesophageal reflux in patients at risk, as it not only increases LOS tone (Brock-utne *et al.* 1976) but also acts as a potent anti-

emetic (Handley 1967) and speeds gastric emptying (Howard and Sharp 1973). Metoclopramide is relatively free from undesirable side effects in adults (James and Hume 1968) although extrapyramidal symptoms have been described in psychiatric patients following very high doses (Borenstein and Bles 1965). Dystonic reactions such as torticollis, oculogyric crises and trismus have also been observed in children receiving this drug. Metoclopramide appears to be unassociated with serious cardiac dysrhythmias although one case of multifocal ventricular extrasystoles following a single intramuscular injection of 10 mg, has been reported (Shaklai *et al.* 1974). None of the patients in this study suffered any side effect of note.

This study demonstrates that metaclopramide increases the LOS tone. Thus the drug may help reduce the incidence of regurgitation of gastric content in patients undergoing elective or emergency obstetrical anaesthesia.

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THE ACTION OF COMMONLY USED ANTIEMETICS ON THE LOWER OESOPHAGEAL SPHINCTER

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SUMMARY

The effects of five antiemetic drugs on the lower oesophageal sphincter (LOS) were studied in five groups, each comprising eight healthy volunteers. Cyclizine, prochlorperazine and metoclopramide have a desirable functional effect on LOS, while promethazine and droperidol were associated with evidence of increased gastro-oesophageal reflux.

Aspiration of acid into the lungs remains a common cause of death associated with general anaesthesia (Harrison, 1968). The lower oesophageal sphincter (LOS) is said to be a major mechanism which maintains competence of the gastro-oesophageal junction (Cohen and Harris, 1971). Several drugs commonly used in anaesthetic practice may influence LOS tone and either decrease or increase the tendency to regurgitation (Hall et al., 1975; Brock-Utne et al., 1976; Brock-Utne, Rubin et al., 1977). Antiemetics are administered commonly both before and after surgery, but the effect of these drugs on LOS has not been investigated.

This paper compares the effects of metoclopramide, droperidol, promethazine, cyclizine and prochlorperazine on LOS in normal subjects.

PATIENTS AND METHODS

Five groups of eight healthy volunteers (aged 19–45 yr) were studied. None of the subjects gave a history of upper gastrointestinal surgery or disease, and informed consent was obtained.

The five antiemetic drugs studied were metoclopramide 10 mg, droperidol 5 mg, promethazine 25 mg, cyclizine 25 mg and prochlorperazine 12.5 mg. These doses are similar to those used in clinical practice and all the drugs were administered i.v.

The apparatus and technique used for measurement of lower oesophageal sphincter pressure have been described in detail in a previous communication (Brock-Utne et al., 1976).

After a fast of at least 8 h, the subjects rested quietly in the supine position and studies were performed according to our standard technique (Brock-Utne et al., 1976). The motility tube was passed orally until all recording orifices were in the stomach. The tube was then withdrawn slowly in increments of 0.5 cm until the pressure recordings, and their alterations in response to swallowing, indicated that all three orifices lay within the oesophagus above the LOS. In this manner basal values of gastric pressure (GP), lower oesophageal sphincter pressure (LOSP) and oesophageal pressure (OP) were obtained. All orifices were then reintroduced into the stomach and an i.v. injection given of one of the drugs under investigation. The tube was withdrawn again after 8 min to measure the LOS pressure. The calculated difference between the LOSP and GP is termed the barrier pressure (BP).

Measurement of reflux

The pH probe for detection of gastro-oesophageal reflux was introduced first by Tuttle and Grossman in 1958. We have adopted the method advocated by Skinner and Booth (1970) and placed the probe a set distance (5 cm) above the LOS. Oesophageal pH was measured both under resting conditions and after the patient had performed a series of respiratory manœuvres designed to increase intragastric pressure. The probe used was a Beckman intestinal pH electrode (no. 39042). The patient was instructed to cough and then to perform Valsalva manœuvres with and without straight leg raising. Reflux was graded as follows:

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TABLE I. Intraluminal pressures (\pm SD) obtained in all patients before and after drug administration

	Group										
	I Metoclopramide		II Cyclizine		III Promethazine		IV Droperidol		V Prochlorperazine		
	Basal	Post	Basal	Post	Basal	Post	Basal	Post	Basal	Post	
Gastric pressure (kPa)	mean	2.91	3.00	2.59	2.57	2.51	2.53	2.25	2.50	2.18	2.20
	SD	1.14	1.14	0.63	0.63	0.49	0.58	0.68	0.64	0.40	0.62
Sphincter pressure (kPa)	mean	5.08	7.18	4.46	5.86	5.75	4.34	5.38	5.69	4.49	5.56
	SD	1.29	2.45	1.05	1.26	1.06	1.04	1.66	1.58	1.14	1.64
Oesophageal pressure (kPa)	mean	0.85	0.83	0.53	0.56	0.46	0.56	0.36	0.34	0.51	0.53
	SD	0.45	0.48	0.46	0.49	0.36	0.36	0.33	0.33	0.39	0.20
Barrier pressure (kPa)	mean	2.17	4.18	1.87	3.29	3.24	1.81	3.13	3.19	2.31	3.36
	SD	0.79	1.99	0.97	1.05	0.92	0.70	2.01	2.10	0.86	1.30

TABLE II. Reflux testing

	Basal			After drug		
	No reflux	Stress	Free	No reflux	Stress	Free
Metoclopramide	8	—	—	8	—	—
Cyclizine HCl	8	—	—	8	—	—
Prochlorperazine	7	1	—	7	1	—
Droperidol	6	2	—	4	2	2
Promethazine	7	—	1	4	3	1

- (1) Free reflux (reflux without stress) was defined as a failure of the oesophageal pH to increase above 3.5 (5 cm above LOS).
- (2) Stress reflux was considered to be present if the pH in the oesophagus decreased more than 1 pH unit during stress.
- (3) No reflux was present if oesophageal pH was above 3.5, even during stress.

RESULTS

Metoclopramide

The mean barrier pressure before administration of metoclopramide was 2.17 kPa. After administration there was a significant increase in the mean barrier pressure to 4.18 kPa ($P < 0.005$). Oesophageal pressure was unaltered by the injection of metoclopramide (table I).

Cyclizine

The calculated mean barrier pressure of 1.87 kPa increased significantly to 3.29 kPa ($P < 0.005$) after the administration of cyclizine. The average pressure in the oesophagus remained unchanged after cyclizine administration.

Promethazine

After the administration of promethazine there was a decrease in the barrier pressure from 3.24 to 1.81 kPa ($P < 0.005$). Again, no change was observed in oesophageal pressure after injection of promethazine (table I).

Droperidol

After the administration of droperidol there was no change in either barrier or oesophageal pressures (table I).

Prochlorperazine

After the administration of prochlorperazine there was a significant increase in the barrier pressure from 2.31 to 3.36 kPa ($P < 0.005$). There was no change in the oesophageal pressure after prochlorperazine.

The results of reflux testing are shown in table II. There was no difference in reflux following metoclopramide, cyclizine and prochlorperazine. After droperidol and promethazine there appeared to be an increase in the frequency of gastro-oesophageal reflux, but statistical evaluation using χ^2 test could not be performed.

DISCUSSION

The role of the LOS in the prevention of reflux of acid into the oesophagus has been stressed in an earlier communication (Brock-Utne et al., 1976). It is of importance, therefore, to determine if drugs used commonly during anaesthesia have any action on the LOS.

The decrease in LOS pressure noted in this study after the administration of promethazine has not been reported previously. The drug possesses anticholinergic properties and therefore might be expected to decrease LOS tone. Droperidol has α -adrenergic blocking properties and therefore would be expected to decrease LOS tone. This was not confirmed in the present investigation. Both cyclizine and metoclopramide increased barrier pressure significantly, thus confirming previous reports indicating that these two drugs increase LOS tone (Heitman and Möller, 1970; Brock-Utne et al., 1976; Brock-Utne, Downing et al., 1977). Prochlorperazine also improved LOS tone significantly—a finding which has not been recorded previously. Although prochlorperazine is a phenothiazine derivative, it possesses minimal anticholinergic activity (C. C. D. Cowling, personal communication) in comparison with promethazine.

The mode of action of cyclizine hydrochloride on the LOS is unknown. *In vivo* experiments in cats suggest that the drug possesses vagolytic properties which are presumably mediated centrally at acetylcholine receptor sites, since peripheral acetylcholine receptors still respond to the injection of acetylcholine after the administration of cyclizine (Norton et al., 1954). Cyclizine is claimed to be a drug with low toxicity and minimal side-effects (Christie et al., 1958). Compared with the phenothiazine derivatives, cyclizine rarely causes drowsiness and does not potentiate the narcotic analgesics. In addition, extra-

pyramidal symptoms have not been reported after administration of cyclizine. Metoclopramide is also relatively devoid of undesirable side-effects in adults (James and Hume, 1968), although extrapyramidal symptoms have been described in psychiatric patients following very large doses (Borenstein and Bles, 1965).

The frequency of false positive reflux in normal subjects varies (Moossa and Skinner, 1976), but it depends upon factors including competence of the LOS and the force or effort with which these provocative manoeuvres are performed. In our study of 40 patients, six patients (15%) exhibited a "false" positive result, clearly indicating that the technique has drawbacks. We are, however, basically interested in changes occurring in reflux from basal levels.

Since only one dose of each of the individual drugs was used it is impossible to say whether there is a log dose-effect relationship on the functioning of the lower oesophageal sphincter.

In conclusion, this study demonstrates that prochlorperazine, metoclopramide and cyclizine, the last in half the recommended therapeutic dose, increase the barrier pressures. In contrast, promethazine and droperidol appeared to increase the incidence of gastro-oesophageal reflux.

Our results suggest, therefore, that the last two drugs might, by their action on LOS, increase the hazards of regurgitation and aspiration of acid gastric content during induction of and recovery from general anaesthesia.

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ACTION DES AGENTS ANTIVOMITIFS D'USAGE COURANT SUR LE SPHINCTER INFERIEUR DE L'ŒSOPHAGE

RESUME

On a étudié l'effet de cinq agents antiémétiques sur le sphincter inférieur de l'œsophage (LOS), sur cinq groupes se composant chacun de huit volontaires en bonne santé. La cyclizine, la prochlorpérazine et la métoclopramide ont un effet fonctionnel désirable sur le LOS, alors que la prométhazine et le droperidol ont donné des signes d'un reflux gastro-œsophagien plus fort.

DIE WIRKUNG ÜBLICHER ANTIEMETIKA AUF DEN UNTEREN SPEISERÖHREN-SCHLIESSMUSKEL

ZUSAMMENFASSUNG

Die Wirkung von fünf antiemetischen Drogen auf den unteren Speiseröhren-Schließmuskel wurde in fünf Gruppen studiert, von denen jede aus acht gesunden Freiwilligen bestand. Cyclizin, Prochlorperazin und Metoclopramid haben auf diesen Muskel eine wünschenswerte funktionelle Wirkung, während Promethazin und Droperidol Anzeichen eines verstärkten gastro-oesophagealen Rückflusses erkennen liessen.

LA ACCION EJERCIDA POR ANTIEMETICOS SOBRE EL ESFINTER ESOFAGAL INFERIOR

SUMARIO

Se estudiaron los efectos de cinco drogas antieméticas sobre el esfínter esofagal inferior (LOS) en cinco grupos compuestos por ocho voluntarios saludables. La ciclicina, procloroperacina y metoclopramida ejercen un efecto funcional deseable sobre el esfínter esofagal inferior, mientras que la prometacina y droperidol dieron señales de un aumento en el reflujo gastroesofagal.

Lower Esophageal Sphincter Tone During Reversal of Neuromuscular Blockade by Atropine and Neostigmine

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The effect on lower esophageal sphincter (LES) pressure of IV atropine and neostigmine, a drug combination routinely given to antagonize nondepolarizing neuromuscular blockade at the end of a general anesthetic, was studied in 22 patients undergoing cesarean section.

Atropine 1.2 mg and neostigmine 2.5 mg IV decreased LES pressure insignificantly by a mean of 0.7 kPa ($p < 0.1$). In contrast, atropine 1.2 mg and neostigmine 5 mg increased LES

pressure by a mean of 1.4 kPa ($p < 0.001$). The latter dosage of this drug combination, therefore, appears preferable in patients presenting for emergency surgery if the integrity of the lower esophageal sphincter is to be maintained during extubation and recovery from general anesthesia.

Key Words—GASTROINTESTINAL TRACT, esophagus. ANTAGONISTS, neuromuscular relaxants.

A ZONE of increased intraluminal pressure exists at the gastroesophageal junction in man, and is believed to act as a physiological sphincter. Contraction of this lower esophageal sphincter (LES) is the major barrier to reflux of acid gastric content into the esophagus.¹

Regurgitation and inhalation of acid gastric content, with resultant chemical pneumonitis, remains a major cause of maternal death associated with both the induction and recovery phases of general anesthesia.²

Esophageal manometric methods have

demonstrated that the administration of atropine preoperatively decreases LES tone, thus theoretically increasing the danger of esophageal reflux and subsequent pulmonary aspiration of acid gastric contents.³⁻⁵ Atropine is used routinely in combination with neostigmine to antagonize a nondepolarizing muscle relaxant at the end of an anesthetic. LES tone also appears to be influenced by this drug mixture.⁶ Our paper presents the results of an investigation into the effects of this common anesthetic drug combination on the LES in patients undergoing cesarean section.

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SUBJECTS AND METHODS

Twenty-two mothers, who gave their informed consent to the investigation, were studied during routine general anesthesia for elective cesarean section. The parturients were clinically free of serious systemic disease, with normal placental function. Gestational age was between 36 and 42 weeks and all fetuses were mature. Cases of multiple pregnancy were excluded. The patients were not in labor and their membranes were intact.

On the operating table, the mothers were tilted laterally toward the right side, by means of a 15° rubber wedge placed beneath the left hip.⁷ Patients inhaled 100 percent O₂ for 5 minutes through a nonbreathing anesthetic circuit. An IV infusion of balanced salt solution was commenced. Atropine 0.6 mg mixed with metoclopramide 10 mg (an antiemetic) was injected into the infusion tubing,⁵ followed by a small amount of a nonpolarizing relaxant, alcuronium (2.5 mg), to minimize the increase in gastric pressure caused by succinylcholine.⁸

Anesthesia was then induced IV with thiopental 3.5 mg/kg and succinylcholine 1.75 mg/kg freshly mixed in the same syringe.⁹ As the patients lost consciousness, an assistant applied pressure to the cricoid cartilage and a cuffed endotracheal tube was inserted into the trachea. Ventilation of the lungs was mechanically controlled using a Manley respirator delivering a minute volume of 120 ml/kg (Airco Ohio Vortex Respiration Monitor). Further muscle relaxation was obtained by injecting alcuronium 0.2 mg/kg IV. Anesthesia was maintained with 50 percent N₂O in O₂ with 0.6 percent enflurane.¹⁰

Following delivery of the fetus, narcosis was further augmented by the IV injection of meperidine 1 mg/kg and by increasing the inhaled N₂O concentration to 70 percent. An infusion of 20 units pitocin in 1000 ml of Ringer's lactate solution (10 ml/min) was also commenced after delivery of the infant.

Esophageal motility studies were commenced once general anesthesia was established. A motility catheter consisting of 2 Portex polyethylene No. 54 plastic tubes fused together at their distal ends was passed through the nose until the 2 recording orifices lay in the stomach. Each tube has a single lateral orifice situated at 5 cm and 10 cm respectively from the catheter tip.

Throughout the entire procedure, each tube was continuously perfused with H₂O at the rate of 0.19 ml/min, using a Harvard constant infusion pump. Each tube was connected to a Beckman Instruments physiological transducer (Model 215071) linked to a 4-channel Beckman R/511A Dynograph amplifier and recording system.

The catheter was withdrawn slowly, 0.5 cm at a time, until the pressure readings indicated that the recording lateral orifices were past the LES and in the lower esophagus. Pitocin infusion was halted 5 minutes before pressure measurements were started due to the relaxant effect of pitocin on smooth muscle.¹¹ Baseline gastric pressure (GP), lower esophageal sphincter pressure (LESP), and esophageal pressures (EP) were recorded 5 minutes before the IV injection of neostigmine and atropine. The calculated difference between LESP and GP was termed the barrier pressure (BP). Pressures were expressed in kilopascals above atmospheric pressure (kPa = cm H₂O × 0.098). Baseline motility recordings and post-drug motility recordings were taken during anesthetic maintenance with N₂O 70 percent in O₂ with enflurane 0.5 to 0.8 percent.

The 22 patients were randomly divided into 2 groups based upon dosages of drugs used to reverse the neuromuscular blockade. One group ($n = 11$) received atropine 1.2 mg and neostigmine 2.5 mg and the other group ($n = 11$), atropine 1.2 mg and neostigmine 5 mg. All drugs were mixed in the same syringe and were given rapidly IV as a bolus dose at the termination of surgery.¹² Withdrawal of the motility catheter from the stomach commenced 1 minute after the IV injection of the drugs. Results of the mean barrier pressure before and after injection of the drugs were analyzed using a paired *t*-test for 2 sample means, computed on a Hewlett Packard desk calculator No. 9815A.

The catheter was withdrawn 1 minute after relaxant reversal. This short interval was chosen for 2 reasons. First, the reversing action of atropine and neostigmine comes on rapidly after IV injection, and, secondly, any bucking or swallowing at the end of the surgical procedure, as may be seen following reversal, interferes with the tracing. After reversal anesthetic maintenance with N₂O 70 percent in O₂, with enflurane 0.5 to 0.8 percent, was continued. The lower esophageal sphincter normally

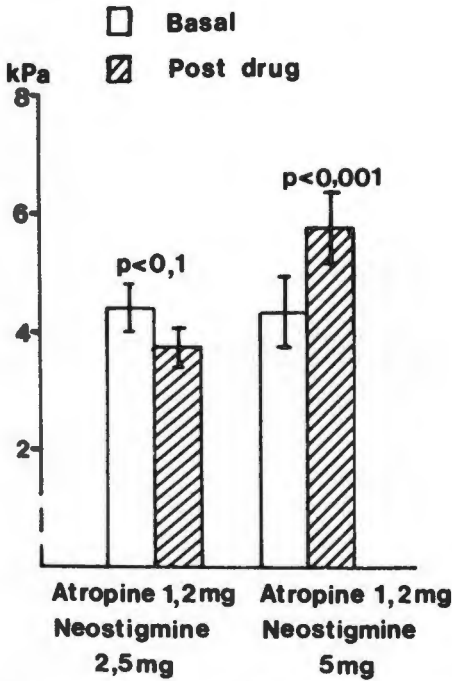


FIGURE. Mean barrier pressure obtained before and after atropine and neostigmine

relaxes and contracts during swallowing,¹³ producing fluctuations in local pressure profiles with initial abnormally high values and subsequent abnormally low values. A pressure change recorded during swallowing has to be excluded and time allowed for the pressure profile to settle to previous pre-swallowing level before continuing with the recording. Any patient studied whose tracing was interfered with by swallowing was excluded. Although the pullthrough started after 1 minute, the 2nd and last sphincter profile (tube No. 2) was obtained usually within 8 to 14 minutes after the relaxant-reversal mixture was given.

RESULTS

Group 1 (Atropine 1.2 mg + Neostigmine 2.5 mg)—Prior to injection of these drugs, the mean barrier pressure was 4.5 kPa (SEM 0.49). After administration of the neostigmine and atropine mixture, there was only a slight decrease in mean BP to a mean of 3.8 kPa (SEM 0.35) ($p < 0.1$). (See figure.)

Group 2 (Atropine 1.2 mg + Neostigmine 5 mg)—Prior to injection of these drugs, the mean barrier pressure was 4.3 kPa (SEM 0.63), but increased to a mean of 5.7 kPa (SEM 0.62) ($p < 0.001$) after atropine-neostigmine administration. (See figure.)

The difference noted between the control mean BP of the 2 groups was statistically not significant whereas a highly significant difference was apparent between the post-injection results obtained in the 2 groups ($p < 0.005$ —unpaired Student's *t*-test).

DISCUSSION

A zone of increased intraluminal pressure between the stomach and the esophagus has been identified,¹ but the precise anatomical and functional importance of this intrinsic lower esophageal sphincter remains unresolved. Atropine has been shown to lower esophageal sphincter tone,³⁻⁵ an effect which could well increase the hazard of acid regurgitation and pulmonary aspiration during induction or termination of general anesthesia. Kim et al⁶ demonstrated that atropine 0.017 mg/kg plus neostigmine 0.03 mg/kg, when used to reverse the effect of neuromuscular blockade, decreased LES tone. Our findings confirm their work. Using a similar dose of atropine and neostigmine, we found that LES tone decreased slightly. In contrast, increasing the dose of neostigmine to 5 mg with a similar dose of atropine (1.2 mg) raised the LES tone very significantly ($p < 0.001$). This effect has not, to our knowledge, been reported previously.

The characteristic pharmacological effect of the anticholinesterases, including neostigmine, is due primarily to inhibition or inactivation of acetylcholinesterase (ACHE) at sites of cholinergic transmission with consequent accumulation and increased action of endogenous acetylcholine (ACH), normally liberated by cholinergic nerve impulses.¹⁴

In man, neostigmine stimulates the lower portion of the esophagus to increase both organ tone and peristalsis. In addition, neostigmine enhances gastric contractions, an effect inhibited by atropine.¹⁴

Although measurement of LES pressure changes during general anesthesia introduces a number of variables which, in themselves, are liable to affect LES tone, we believe that our results, obtained during stable anesthetic conditions with a short interval between readings, are relevant to the clinical situation.

The beneficial effect of neostigmine 5 mg with atropine 1.2 mg would seem to be of clinical importance since the effect of this drug combination on LES tone lasts at

least 8 minutes. Therefore, the higher dose appears preferable for routine reversal of nondepolarizing neuromuscular blockade if the risk of regurgitation and/or pulmonary aspiration at the termination of general anesthesia is to be minimized.

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Reversal of neuromuscular blockade by glycopyrrolate and neostigmine

A study of the effects on lower oesophageal sphincter tone

J.G. BROCK-UTNE

The combination of glycopyrrolate with neostigmine, given to antagonize non-depolarising neuromuscular blockade, has been shown to result in fewer dysrhythmias than when atropine is given with neostigmine.^{1,2} However, the effect of a glycopyrrolate/neostigmine mixture on the lower oesophageal sphincter (LOS) pressure has not been elucidated. Previously it has been shown that atropine 1.2 mg and neostigmine 5 mg increased LOS pressure significantly, whereas atropine 1.2 mg and neostigmine 2.5 mg intravenously did not change LOS pressure significantly.³

Oesophageal manometric methods have demonstrated that the intravenous administration of atropine,^{4–7} hyoscine⁸ and glycopyrrolate⁹ pre-operatively decrease LOS tone. Since the LOS is thought to be the major barrier to reflux of acid gastric content into the oesophagus, the administration of any of these drugs preoperatively could increase the danger of oesophageal reflux and the possibility of pulmonary aspiration of acid gastric contents. The effects of glycopyrrolate and neostigmine mixture on the LOS, a drug combination used clinically to antagonize non-depolarising neuromuscular blockade at the end of a general anaesthetic, have been investigated.

Subjects and methods

Twenty women, who gave their informed con-

sent to the investigation, were studied during routine general anaesthesia for elective Caesarean section. The patients were all clinically free of serious systemic disease. All had single pregnancies (36–42 weeks gestation) with normal placental function, they were not in labour and their membranes were intact.

The general anaesthetic technique, including left lateral tilt,¹⁰ atropine 0.6 mg with metoclopramide 10 mg,⁷ a 'desensitizing' dose of a non-depolarizing muscle relaxant, rapid induction sequence using thiopentone 3–3.5 mg/kg together with suxamethonium 1–1.75 mg/kg, has been discussed recently in a review by Buley.¹¹

Oesophageal motility studies were commenced once general anaesthesia was established. The motility catheters, consisting of 2 'Portex' polyethylene No. 54 plastic tubes, were passed into the stomach. Each tube had a single lateral orifice and these were continuously perfused throughout the entire procedure. The technique used has been described in a previous communication.³

The twenty patients were randomly divided into two groups based upon dosages of drugs used to reverse the neuromuscular blockade. One group ($n = 10$) received glycopyrrolate 0.6 mg and neostigmine 2.5 mg, and the other group ($n = 10$) received glycopyrrolate 0.6 mg and neostigmine 5 mg. The drugs were mixed in the same syringe and given intravenously as

a bolus dose at the termination of surgery.

Oesophageal motility studies were performed before, and at the end of, the surgical procedure. The calculated difference between lower oesophageal sphincter pressure (LOSP) and gastric pressure (GP) was termed the barrier pressure (BP) and expressed in kilopascals above atmospheric pressure ($\text{kPa} = \text{cm H}_2\text{O} \cdot 0.098$). All recordings were taken during anaesthetic maintenance with N_2O (70%) and O_2 (30%) and enflurane (0.5–0.8%).

Results

Group 1 (glycopyrrolate 0.6 mg and neostigmine 2.5 mg)

Prior to injection of the drug mixture, the mean barrier pressure was 3.5 kPa (s.e. mean 0.41). After administration of the glycopyrrolate and neostigmine mixture, there was only a slight increase in mean barrier pressure to 3.7 kPa (s.e. mean 0.4) ($P < 0.1$) (Fig. 1).

Group 2 (glycopyrrolate 0.6 mg and neostigmine 5.0 mg)

Prior to injection of these drugs, the mean barrier pressure was 3.5 kPa (s.e.m. 0.31), but increased to a mean barrier pressure of 4.7 kPa (s.e.m. 0.35) ($P < 0.001$) after the glycopyrrolate/neostigmine administration (Fig. 1).

The effect on the LOS lasted at least 8 min. No adverse effect on cardiac rhythm was seen using these drug combinations.

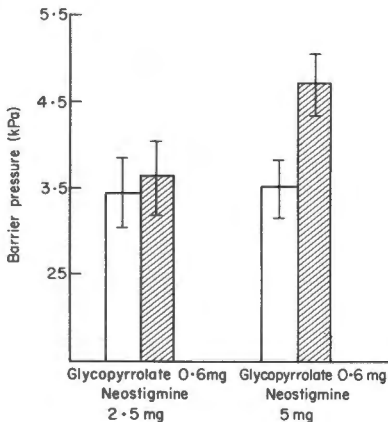


Fig. 1. Mean barrier pressure obtained before and after glycopyrrolate and neostigmine (kPa).

Discussion

This study has shown that increasing the dose of neostigmine to 5 mg with 0.6 mg of glycopyrrolate, raised the LOS tone significantly ($P < 0.001$) whereas LOSP was unaltered by a lower dosage of neostigmine. This effect has not, to the author's knowledge been reported previously. The rise in LOS tone with glycopyrrolate 0.6 mg and neostigmine 5 mg (1.2 kPa) is comparable to that seen with atropine 1.2 mg and neostigmine 5 mg (1.4 kPa).³

No untoward effects on cardiac rate or rhythm were seen when using glycopyrrolate and neostigmine, a finding similar to that of other workers.^{1,2,12} A glycopyrrolate/neostigmine mixture appears to cause less tachycardia and a smaller incidence of cardiac dysrhythmia when compared to the atropine/neostigmine combination, provided that adequate oxygenation is maintained.^{1,2} Furthermore, glycopyrrolate has a greater antisialogue effect than atropine^{1,2} and is longer acting than atropine. The duration of action of glycopyrrolate is 4–6 hr as compared to 1–1½ hr duration of atropine and scopolamine.¹² The desire of anaesthetists to have a long acting anticholinergic is emphasized in a recent survey.¹³

Glycopyrrolate possesses other theoretical advantages over the belladonna drugs. The latter are tertiary amines and hence readily cross the blood–brain barrier to enter the central nervous system and may cause the central anticholinergic syndrome.^{14–16} Glycopyrrolate, is a quaternary ammonium compound and therefore incapable of crossing the blood–brain barrier.

Finally, glycopyrrolate increases gastric pH above 2.5 in paediatric patients¹⁷ and parturients,¹⁸ thus reducing the chance of acid aspiration of gastric content with resultant chemical pneumonitis which is still a major anaesthetic cause of obstetric and surgical morbidity and mortality.¹⁹ In normal adult patients, however, glycopyrrolate does not appear to influence gastric acidity.²⁰

Theoretically, regurgitation of acid gastric content into the oesophagus can be due to one of three basic causes, namely a decrease in LOS tone, an increase in intragastric pressure above those normally resisted by the resting LOS and mechanical factors.²¹ The latter are now thought to be of little consequence.²²

A correlation between reflux and low sphincter pressure has been reported.^{2,3} Hence, a good sphincter will prevent gastro-oesophageal reflux in contrast to a 'poor' or 'weak' sphincter. However, this concept is not universally accepted⁴ because considerable individual variations in resting sphincter tone²⁴ have been reported. In order to ensure patient safety after the termination of anaesthesia, a higher dose of neostigmine in combination with glycopyrrolate would appear preferable for routine reversal of non-depolarising neuromuscular blockade in order to reduce the risk of regurgitation and/or pulmonary aspiration.

Summary

The effect of intravenous glycopyrrolate and neostigmine, a drug combination routinely given to antagonize non-depolarising neuromuscular blockade, on lower oesophageal sphincter tone was studied in twenty patients undergoing Caesarean section.

Glycopyrrolate 0.6 mg and neostigmine 2.5 mg i.v. increased LOS pressure insignificantly by a mean of 0.2 kPa ($P < 0.1$). In contrast, glycopyrrolate 0.6 mg and neostigmine 5 mg increased LOS pressure by a mean of 1.2 kPa ($P < 0.001$). The latter dosage of this drug combination thus appears preferable in patients presenting for emergency surgery, if the integrity of the lower oesophageal sphincter is to be maintained during extubation and recovery from general anaesthesia.

Key words

ANTAGONISTS, NEUROMUSCULAR RELAXANTS; atropine, neostigmine, glycopyrrolate.

GASTROINTESTINAL TRACT; oesophagus. LUNG; aspiration.

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Effect of Domperidone on Lower Esophageal Sphincter Tone in Late Pregnancy

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J. Rubin, M.B., B.Ch.,§ M. G. Moshal, M.R.C.P.¶

Increasing the resting lower esophageal sphincter (LES) tone is a useful method of preventing gastroesophageal reflux. The effects of a new antiemetic, domperidone, on LES were studied in 28 subjects. Group I included eight normal nonpregnant control subjects. The remaining 20 pregnant women were divided into two groups, Groups II and III—ten parturients without and ten with symptoms of heartburn. Domperidone increased LES pressure by 19, 11 and 10 cm H₂O in Groups I, II and III, respectively ($P < 0.05$). Domperidone may be a valuable premedicant in some patients to decrease the chance of gastroesophageal reflux. (Key words: Anesthesia, obstetric. Complications: aspiration. Gastrointestinal tract, esophagus. Lung: aspiration. Vomiting, antiemetics, domperidone.)

MENDELSON'S SYNDROME remains a major cause of death and morbidity in obstetric anesthesia. According to a confidential inquiry in the United Kingdom, there was no significant decrease in maternal mortality from aspiration during the years 1973-1975 (13 deaths) compared with the years 1970-1972 (14 deaths).¹ This disappointing finding may have many explanations. In medical literature, however, little emphasis has been placed on the importance of the lower esophageal sphincter (LES). Anesthetic drugs may decrease LES tone²⁻⁵ and thereby increase the incidence of gastroesophageal reflux.³⁻⁶ Regurgitation or vomiting and subsequent tracheobronchial aspiration, atelectasis, and hypoxia are recognized complications occurring in the perioperative period.⁷

Gastroesophageal relaxation with reflux is obviously the forerunner of overt aspiration. Silent regurgitation of gastric contents has been reported to occur in 25 to 70 per cent of patients receiving general anesthesia,⁸⁻¹⁰ with tracheal aspiration occurring in 76 per cent.¹¹ Theoretically, regurgitation of acidic gastric content into the esophagus may result from one of three causes¹²: decreased LES tone; intragastric

pressure increased to above levels normally withstood by the resting LES; and mechanical factors, now thought to be of little importance.¹³ Most current evidence supports the theory that the LES is the major barrier preventing gastroesophageal reflux.¹⁴

Domperidone, a benzimidazole derivative, is a potent antiemetic^{15,16} with gastrointestinal stimulatory properties.** Its chemical structure and pharmacokinetics has been recently described.¹⁶ The drug has been shown to increase LES tone in dogs and baboons.¹⁷ Hence, domperidone, by increasing LES tone, could have a prophylactic action in the prevention of the acid-aspiration syndrome. This paper concerns our investigation into the effects of domperidone on the LES in both normal and pregnant human subjects.

Materials and Methods

Three groups of subjects were studied. All subjects gave informed consent. The study was approved by the Ethical Committee of the Faculty of Medicine, University of Natal. The drug was cleared by the South African Medicines Control Council for full distribution with no restriction to pregnant patients, except in the first trimester. The first group (Group I) of eight nonpregnant volunteers, ranging in age from 18 to 55 years (mean 35 ± 4 SEM), acted as a control group. Group II consisted of ten normal pregnant women, without symptoms of heartburn, between 18 and 36 years of age (mean 26 ± 2); Group III included ten parturients between 17 and 29 years of age (mean 23 ± 2), all of whom complained of heartburn during their current pregnancy. Patients who had histories of gastrointestinal symptoms or surgical operations involving the gastrointestinal tract, with the exception of those with heartburn in Group III, were excluded from the study. All pregnant patients were between the thirty-sixth and fortieth weeks of gestation and were comparable in weight. Esophageal motility studies were performed with subjects resting quietly in the supine or left lateral position, after a fast of at least ten hours. Methods previously described were used.^{6,18}

In brief, a motility tube consisting of three No. 54 polyethylene tubes attached together at the distal

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TABLE 1. Esophageal, Lower Esophageal Sphincter, Gastric and Barrier Pressure (cm H₂O) before and after Domperidone (Mean \pm SEM)

	Group I Non-pregnant, Control		Group II Pregnant, No Heartburn		Group III Pregnant, Heartburn	
	Basal	After Domperidone	Basal	After Domperidone	Basal	After Domperidone
Gastric pressure	21 \pm 2	25 \pm 2	31 \pm 1	32 \pm 1	27 \pm 1	27 \pm 1
Sphincter pressure	55 \pm 3	74 \pm 3	51 \pm 2	62 \pm 3	45 \pm 3	55 \pm 4
Esophageal pressure	2 \pm 1	3 \pm 1	1 \pm 1	1 \pm 0.2	1 \pm 0.4	1 \pm 0.5
Barrier pressure	34 \pm 4	49 \pm 4	20 \pm 2	30 \pm 3	18 \pm 2	28 \pm 4

end was assembled. Each tube had a single lateral orifice situated 5, 10, and 15 cm, respectively, from the distal tip. The catheter was swallowed orally until all the recording orifices lay in the stomach. Throughout the entire procedure, each tube was continuously perfused with water at a rate of 0.19 ml/min, using a Harvard constant-infusion pump. Each tube was connected to a Beckman Instrument[®] physiologic transducer Model 215071 linked to an eight-channel Beckman R411 Dynograph[®] amplifier and recorder. The tube was then slowly withdrawn, 0.5 cm at a time, until the pressure recordings, and their alterations in response to swallowing, indicated that all three orifices lay in the esophagus above the LES. Normally, the lower esophageal sphincter relaxes and then contracts during swallowing, producing fluctuations in the pressure profile of the sphincter. These latter fluctuations result in an abnormally low reading at first, then a substantially higher reading. Pressure changes recorded during swallowing were therefore excluded, and time was allowed for the pressure profile to settle to preswallowing levels before continuing with tube withdrawal. Basal levels of gastric (GP), LES (SP), and esophageal pressures (EP) were determined initially for each subject. The difference between SP and GP was termed the barrier pressure. Each patient then received domperidone, 0.2 mg/kg (to as much as 10 mg maximum), intravenously. All pressures were expressed in cm H₂O above atmospheric pressure. Respiration was monitored using a tubular pneumograph placed around the subject's chest, and connected to the Dynograph amplification and recorder system.

All sphincter-profile recordings were analyzed independently by one experienced person (G.E.D.), whose sole function was to determine mean pressure values from the profiles. Unsatisfactory recordings were rejected and the subjects excluded from the study. Statistical analyses were performed using the Student *t* tests for paired and unpaired data. A *P* value < 0.05 was regarded as significant.

Results

In Group I (control) mean pressures in the stomach, LES, and esophagus were 21, 55, and 2 cm H₂O, respectively (table 1). After the administration of

domperidone, there were significant increases in both LES pressure and barrier pressure of 19 and 15 cm H₂O, respectively. Mean esophageal pressure did not change. The onset of drug effect on the LES was evident within 10 min and peaked within 30 min.

There was no significant difference in control gastric and barrier pressures between Groups II and III. After domperidone administration, there was no change in mean gastric pressure in either group. However, LES pressure increased significantly by 11 cm H₂O in Group II and 10 cm H₂O in Group III. Barrier pressure increased significantly in both groups after domperidone, 10 cm H₂O in each group. No change in esophageal pressure was observed.

Under basal conditions, mean gastric pressures were significantly higher in the pregnant patients than in the control group. After domperidone, the control group had a significantly higher mean barrier pressure than both pregnant groups.

Except for mild pain on injection of domperidone, which was experienced by three patients, no adverse side effect or serious complication was encountered in this investigation.

Discussion

This study confirms previous observations^{6,19} that intragastric pressure increases with pregnancy; presumably, this is caused by the presence of the enlarging uterus within the abdominal cavity. Normally, with the increase in gastric pressure, LES pressure also increases. In some patients, however, LES pressure is not seen to increase, and heartburn may result from acid regurgitation through a "weak" sphincter.^{6,18}

The mean barrier pressures of both the pregnant groups were significantly lower than control and virtually identical. This finding was not unexpected, since correlation between a decreased LES pressure and symptomatic gastroesophageal reflux and esophagitis²⁰ is not absolute. Also, some of our patients without heartburn may have had "weak" sphincters, even though they had been symptom-free at the time of study. The statistical significant difference in ages between the nonpregnant control and the pregnant heartburn group is probably of little consequence, since LES pressure is not age-dependent in this age range.²¹

Increasing the resting tone of the lower esophageal sphincter is currently believed to be the best method of obtunding gastroesophageal reflux.^{5,14} Hence, domperidone could be used as an antiemetic in patients at risk before operations and general anesthesia to help prevent aspiration of gastric content. The mechanism of action of domperidone on the LES remains to be elucidated. However, it is claimed that the action of domperidone is based on its dopamine-receptor blocking properties.¹⁷ Dopamine has been shown to cause a decrease in LES pressure in the opossum.²²

Domperidone does not belong to one of the well-known classes of antiemetics. Pharmacologically, it antagonizes apomorphine-induced vomiting in dogs, but it has no effect on the central nervous system, which indicates an inability to cross the blood-brain barrier.²³ Therefore, the drug does not affect the dopaminergic receptors in either the chemoreceptor trigger zone or the basal ganglia of the brain. The antiemetic action of domperidone is due solely to its peripheral dopamine blocking effect.**

Domperidone is rapidly redistributed to all body tissues after both oral and parenteral administration, and is effectively metabolized by the liver. Fecal excretion of metabolites is the main route of elimination after the drug's biodegradation. Domperidone has thus been claimed to be an effective antiemetic¹⁶ with a wide margin of safety.** Initial results comparing domperidone with metoclopramide, which does cross the blood-brain barrier, in patients undergoing elective cesarean section have shown no differences in fetal blood-gas values and Apgar scores (Brock-Utne *et al.*, unpublished observations). The drug has little effect on gastric acid secretion but does increase the rate of gastric emptying,** an obvious added advantage. Pharmacokinetic studies** have shown that the duration of antiemetic effect after intravenous injection of domperidone should last for at least two and possibly four hours. The drug's effect on the LES persisted for at least 60 min, but further studies may prove the duration of this action to be longer.

The intravenous injection of domperidone increases lower esophageal sphincter tone in both normal and pregnant patients without associated undesirable side effects. Domperidone's beneficial effect on the LES appears comparable to that of metoclopramide.¹⁸ Thus, the drug may prove useful in preventing regurgitation of acidic gastric contents in patients having elective or emergency anesthesia.

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Domperidone Antagonizes the Relaxant Effect of Atropine on the Lower Esophageal Sphincter

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BROCK-UTNE, J. G.: Domperidone antagonizes the relaxant effect of atropine on the lower esophageal sphincter. *Anesth Analg* 59:921-924, 1980.

A zone of increased intraluminal pressure exists at the gastroesophageal junction in man and is believed to act as a physiologic sphincter. Increasing this lower esophageal sphincter (LES) tone is an accepted and useful method in preventing gastroesophageal reflux. The effects of LES tone were studied in 10 healthy volunteers receiving sequential intravenous injections of atropine, 0.6 mg, or domperidone, 10 mg, followed by domperidone, 10 mg, or atropine, 0.6 mg. The order of drug administration was randomized during the first study. Each volunteer was studied a second time, 1 week later, when the order of drug administration was reversed from the first. Administration of atropine decreased mean LES pressure by 12.6 cm H₂O ($p < 0.001$). Subsequent injection of domperidone restored LES tone to near normal. In contrast, initial injection of domperidone approximately 1 week later in the same subjects, mean LES pressure increased by 18.5 cm H₂O ($p < 0.001$). Intravenous injection of atropine, thereafter, failed to decrease mean LES pressure significantly, LES pressure being sustained at a mean of 14.8 cm H₂O above basal control levels ($p < 0.005$). Results of this study suggest that domperidone given prior to atropine, before induction of general anesthesia, may counteract the potentially deleterious effect of atropine on LES tone, and thereby reduce the chances of regurgitation and pulmonary aspiration of acid gastric contents.

Key Words: GASTROINTESTINAL TRACT: esophagus; PARASYMPATHETIC NERVOUS SYSTEM: atropine; VOMITING, Antiemetics: domperidone.

PULMONARY aspiration of regurgitated acid gastric contents, with resultant chemical pneumonitis, remains the major cause of both maternal obstetric and surgical morbidity and mortality.^{1,2} The tone of the lower esophageal sphincter (LES) is a major barrier to esophageal reflux of acid gastric contents.³ Therefore, drugs that cause relaxation of the LES can be expected to increase the hazard of regurgitation, whereas pharmacologic agents that increase LES tone may decrease the risk.⁴

Atropine relaxes the LES, an effect which can be countered by prior administration of metoclopramide.⁵ Domperidone has also been shown to increase LES pressure.^{6,7} The purpose of this study was to ascertain the effects of sequential intravenous injections of atropine-domperidone and domperidone-atropine on LES tone and to establish the correct sequence of giving these drugs prior to general anesthesia. This is important information to the anesthetist striving to prevent the acid aspiration syndrome.

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Subjects and Methods

Esophageal manometric studies were performed on 10 healthy volunteers with their informed consent. The study was approved by the Ethics and Standards Committee of the Faculty of Medicine, University of Natal, Congella, South Africa. Any previous history of upper gastrointestinal surgery or disease precluded entry to the study. The average of the volunteers was 32.4 (± 2.9 SEM) years and their mean weight 68.7 (± 1.9 SEM) kg.

Volunteers received sequential intravenous injections of atropine, 0.6 mg, or domperidone, 10 mg, followed by domperidone, 10 mg, or atropine, 0.6 mg. Each volunteer was studied after a fast of at least 10 hours before the investigation. At the first study session, basal levels of gastric, LES, and esophageal pressures were recorded at rest. Thereafter, atropine, 0.6 mg, or domperidone, 10 mg, was given intravenously at random, and esophageal motility studies were repeated 7 minutes later.

Each volunteer was studied a second time 1 week later, in the same manner, but with the drugs being given in the reverse order from the first study i.e., domperidone, 10 mg, preceding atropine, 0.6 mg,

injection or vice versa. Selection of 7 minutes as the delay time before pressure recordings were made stems from our previous experience with these drugs,^{6,8,9} which confirmed that this interval was appropriate to allow their effects on the LES to be manifest.

The manometric technique employed in this study was similar to that previously described.^{6,9,10} Three polyethylene tubes bonded together at the distal end were swallowed by the volunteer. These catheters, continuously flushed by a Harvard constant infusion pump at a rate of 0.19 ml/min were attached to three separate transducers (Beckman Instrument physiologic transducer model 215071). The latter were calibrated from 0 to 80 cm H₂O before and after each study, using a water manometer. The transducers were positioned at approximately the level of the lower esophagus (midaxillary line) to eliminate the effects of hydrostatic pressure.

The above tubes were passed orally until all the recording orifices lay within the stomach. At least 7 minutes were allowed to elapse before the tube was slowly withdrawn, 0.5 cm at a time, measuring stomach and sphincter pressures until the pressure recordings and their alterations in response to swallowing indicated that all three orifices now lay within the esophagus above the LES. This maneuver is termed a pull through in gastroenterology literature.

The tracings obtained on the recorder, therefore, represent pressure changes in all three tubes. Hence, three pressure profiles were obtained for each single pull through, giving three consecutive values for gastric, sphincter, and esophageal pressures. For analysis of these pressure profiles, actual pressures were measured from the baseline (zero pressure) to the midpoint between maximal end-inspiratory and end-expiratory points of the respiratory fluctuations. The pre- and

postinjection tracings were compared. Each subject had three measurements of gastric, sphincter, and esophageal pressures before drug administration, and three after each drug was given. The mean pressures, gastric pressure (GP), LES pressure (LESP), and esophageal pressure (EP), were then calculated for each subject before and after receiving the drugs. The difference between LESP and GP, the barrier pressure (BrP), was also determined. All pressures are expressed in centimeters of water above atmospheric pressure. Only tracings that were without interference from movement, swallowing, and gross respiratory excursions, were evaluated.

One satisfactory pull through takes approximately 10 to 20 minutes. Hence, the time from the first drug administration to the second injection varied between 20 to 30 minutes. The peak effect of the study drugs on the LES would seem, according to our previous experience, to be between 20 to 40 minutes.

All pressure tracings were measured by an independent observer (G.E.D.). Statistical analyses were performed using Student's *t*-test for paired data on the Hewlett-Packard desk top calculator (No. 9815A). A *p* value of <0.05 was regarded as significant.

Results

The results are given in the Table. The mean pressures recorded under control conditions before the atropine-domperidone drug sequence were GP 15.4 cm H₂O, LESP 56.3 cm H₂O, and EP 3.6 cm H₂O. The average calculated BrP was thus 40.9 cm H₂O. Following atropine administration, a highly significant decrease both in LESP and BrP of 12.6 cm H₂O (*p* < 0.001) was observed. Subsequent domperidone administration restored both LESP and BrP to near basal levels. The mean control pressures recorded before

TABLE
Gastric, Sphincter, Esophageal, and Barrier Pressures before and after Atropine or Domperidone and Subsequent Domperidone or Atropine Administration*

	First drug administration			Second drug administration		
	Control	Atropine	Domperidone	Control	Domperidone	Atropine
	<i>cm H₂O</i>					
Gastric pressure	15.4 ± 1.8	15.4 ± 1.8	16.8 ± 1.5	16.5 ± 2.6	18.0† ± 2.5	18.0 ± 2.7
Sphincter pressure	56.3 ± 1.8	43.7§ ± 1.2	54.0‡ ± 2.4	53.4 ± 3.6	71.9§ ± 4.1	68.2‡ ± 4.4
Esophageal pressure	3.6 ± 0.5	4.1 ± 0.5	3.8 ± 0.6	2.9 ± 0.5	2.5 ± 0.6	3.0 ± 0.4
Barrier pressure	40.9 ± 2.8	28.3§ ± 1.8	37.2† ± 3.0	36.9 ± 2.9	53.9§ ± 2.1	50.2‡ ± 2.9

* Values are means ± standard deviation.
 † Level of significance from basal: *p* < 0.01.
 ‡ Level of significance from basal: *p* < 0.005.
 § Level of significance from basal: *p* < 0.001.

study of the domperidone-atropine order of drug injection were GP 16.5 cm H₂O, LESP 53.4 cm H₂O, and EP 2.9 cm H₂O. The average calculated BrP was 36.9 cm H₂O. These levels were similar to the control values reported after the first administration of drugs. After administration of domperidone, a significant increase in mean LESP of 18.5 cm H₂O ($p < 0.001$) was measured. Mean BrP increased 17 cm H₂O ($p < 0.001$). Later administration of atropine caused only slight but statistically insignificant changes in both LESP and BrP which were sustained at mean levels of 14.8 cm H₂O and 13.3 cm H₂O, respectively, above control values ($p < 0.005$).

The average GP also increased significantly after initial domperidone injection by 1.5 cm H₂O ($p < 0.01$) but was unaffected by atropine. EP was influenced by neither agent.

Discussion

Gastric reflux consists of the flow of gastric contents into the esophagus. The amount of reflux depends upon the competence of the antireflux mechanism. The LES is a specialized structure, physiologically different from the body of the esophagus, and presents the main barrier to gastroesophageal reflux.^{3, 11, 12}

Esophageal manometric measurements have shown that reflux occurs at BrP below 13 cm H₂O. Hence, if a patient with a basal BrP of 26 cm H₂O is given a drug that decreases the LES pressure by 14 cm H₂O the LES would be rendered incompetent.¹³ However, considerable individual variations in resting sphincter tone have been reported.¹⁴

In 1960, Bettarello and coworkers¹⁵ showed that the LES tone was reduced by atropine and increased by bethanechol. Furthermore, these workers demonstrated a marked increase in the incidence of gastroesophageal reflux after atropine injection, which was significantly reduced by bethanechol administration. This effect of atropine on the LES was later confirmed by other workers in both nonpregnant^{16, 17} and pregnant subjects.⁹ In the latter study by Dow et al (1978),⁹ a trend toward an increased incidence of gastroesophageal reflux was also noticed in parturients following atropine administration. However, the number of patients studied was too small to draw any firm conclusion.

Laitinen et al (1978),⁵ have shown in dogs that metoclopramide increases LESP significantly and that subsequent atropine administration fails to influence the LES tone. Domperidone has also been shown to

exert a strong tonic effect on the high pressure zone of the lower esophagus in baboons and in both non-pregnant and pregnant humans.^{6, 7} The present study using domperidone confirms this response in healthy humans. Laitinen et al also showed that when atropine was given before metoclopramide, the latter drug failed to elevate LESP previously reduced by atropine. In contrast, domperidone in the present study increased LESP to near normal basal levels after atropine injection. Hence, the timing and order of injection of atropine and both metoclopramide and domperidone before induction of anesthesia is important to anesthetists, especially since it has been previously advocated that metoclopramide and atropine be given together.⁸

Domperidone, a benzimidazole derivative, has been previously recommended for use as a premedicant because of its antiemetic effect¹⁸ and its ability to speed gastric emptying (unpublished research reports supplied by Janssen R & D Inc, Johannesburg, South Africa). The mechanism of action of domperidone on the LES and stomach is, however, unknown at present. Its chemical structure and pharmacokinetics have recently been described.¹⁸

The results presented here suggest that since the most likely effect of atropine on the LES is to block the effect of acetylcholine at postganglionic cholinergic myoneural junctions, domperidone could act as an antagonist at this site. A competitive drug receptor interaction would seem to occur; however, to be certain multiple doses of each drug must be studied. Atropine caused no statistically significant change in the elevated sphincter pressure induced by domperidone. However, if atropine is to be given prior to emergency operation, it would seem advisable to administer it approximately 20 minutes after domperidone injection and within a few minutes of induction of general anesthesia to avoid a possible significant decrease in BrP with time, as the effect of atropine on LES becomes maximal.

Despite the fact that atropine^{16, 17} and other cholinergic agents (hyoscine,¹⁰ glycopyrrolate¹⁹) are known to decrease LES tone, at the University of Natal the practice continues to be atropine or glycopyrrolate given intravenously to parturients before cesarean section for the following reasons: A desensitizing dose of a non-depolarizing muscle relaxant is routinely given before anesthesia to avoid the increase in gastric pressure associated with muscle fasciculation after injection of succinylcholine.²⁰ However, the importance of this increase in intragastric pressure, with respect to the risk of regurgitation, has been ques-

tioned.²¹ Since the two muscle relaxants antagonize each other, a larger than usual dose of succinylcholine is employed.²² This increased dose may have adverse effects on the cardiovascular system due to its muscarinic actions.²³ These parasympathetic effects, in particular bradycardia with resultant lowered cardiac output, are blocked effectively by atropine and glycopyrrolate.

In addition, a combination of concealed aortocaval occlusion, carotid body stimulation by cricoid pressure, and a rough or difficult endotracheal intubation in the absence of atropine or glycopyrrolate premedication, may produce alarming maternal bradycardia and hypotension. Hence, the exclusion of anticholinergic drugs as intravenous premedications appears unwarranted, especially if the fetus is at risk, since placental perfusion and fetoplacental gas exchange may be compromised. Significantly, in the most recent confidential report on maternal mortality from Great Britain,²⁴ two women were determined to have died because atropine was omitted from the preanesthetic medication.

In this and previous studies,^{6, 18, 25, 26} domperidone has been shown to be relatively free of undesirable side effects in adults. The present study suggests that when atropine is given before induction of anesthesia, its administration should be preceded by an injection of domperidone in order to increase LES pressure and thereby reduce the chances of pulmonary acid aspiration.

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LARYNGEAL INCOMPETENCE DURING NEUROLEPTANALGESIA IN COMBINATION WITH DIAZEPAM

J. G. BROCK-UTNE, T. J. WINNING, J. RUBIN AND H. G. G. KINGSTON

SUMMARY

In eight patients, following carotid angiography under neuroleptanalgesia, a radiopaque dye was instilled into the pharynx. The chest was x-rayed 15 min later. All eight patients were observed to have aspirated the dye. The technique of neuroleptanalgesia described should not be used without safeguarding the airway in patients liable to regurgitate and inhale gastric contents.

Neuroleptanalgesia is the combination of a neuroleptic drug with a potent short-acting analgesic, in order to obtain a state of mental detachment, indifference to the environment and profound analgesia. It is a widely used technique (Wylie and Churchill-Davidson, 1972), and has been advocated both for obstetric analgesia (Hutchinson and McQuillan, 1974) and neuroradiological procedures (Cane, 1973).

Conventional anaesthetic techniques may adversely affect laryngeal competence, exposing the patient to the hazard of regurgitation and aspiration of acid gastric content. The purpose of this study was to assess the efficiency of laryngeal closure during neuroleptanalgesia.

METHODS

Eight adult patients, who gave informed consent, were investigated. The age range was 33–54 yr, five patients were males and three were females. All the patients were undergoing carotid angiography; the indications for neuroradiological investigation were:

Cerebral tumour	5
Head injury	2
Cerebral aneurysm	1

There was no evidence of significant cardiopulmonary disease in any patient.

The subjects were starved for 6 h before the examination. On arrival in the x-ray department, an i.v. infusion of Ringer lactate solution was commenced. Atropine 0.6 mg was administered i.v. 5 min before the induction of neuroleptanalgesia.

Anaesthesia was then induced by injecting droperidol (Inapsin) 0.1 mg/kg into the infusion tubing,

followed 5 min later by diazepam 5–10 mg. Thereafter fentanyl 0.05 mg/ml was injected slowly i.v. until the patient's respiratory rate decreased to about 12 b.p.m. Cannulation of the carotid artery was performed by the radiologist, after initial local infiltration of the skin with lignocaine 1%. On completion of the angiographic investigation and while the patient lay supine on the x-ray table, 7 ml of a radiopaque liquid (Dionosil) was placed on the back of the tongue with a soft-tip plastic catheter. In four of the eight patients, the eyelid reflex had returned at this stage of the investigation.

All of the patients appeared to swallow the dye immediately. An antero-posterior chest radiograph was taken 15 min later, with the patient remaining in the supine position on the x-ray table.

The interval between instillation of the dye and the x-ray examination was 10–30 min.

RESULTS

All eight chest radiographs exhibited clear evidence of Dionosil aspiration. The amount of dye inhaled was sufficient to outline the bronchi in each patient. Two examples of the radiographs are shown in figures 1A and B.

DISCUSSION

In this study, all of the eight patients investigated inhaled Dionosil while under the influence of a neuroleptanalgesic technique. However, none developed pulmonary complication as a consequence of secretions or dye inhalation.

Taylor and Towey (1971) failed to demonstrate radiological evidence of pulmonary dye aspiration in conscious volunteers lying supine and premedicated with hyoscine. However, several investigators have shown that reflex laryngeal closure is depressed under general anaesthesia (Nunn, J. F., 1967, personal communication to Tomlin, Howarth and Robinson

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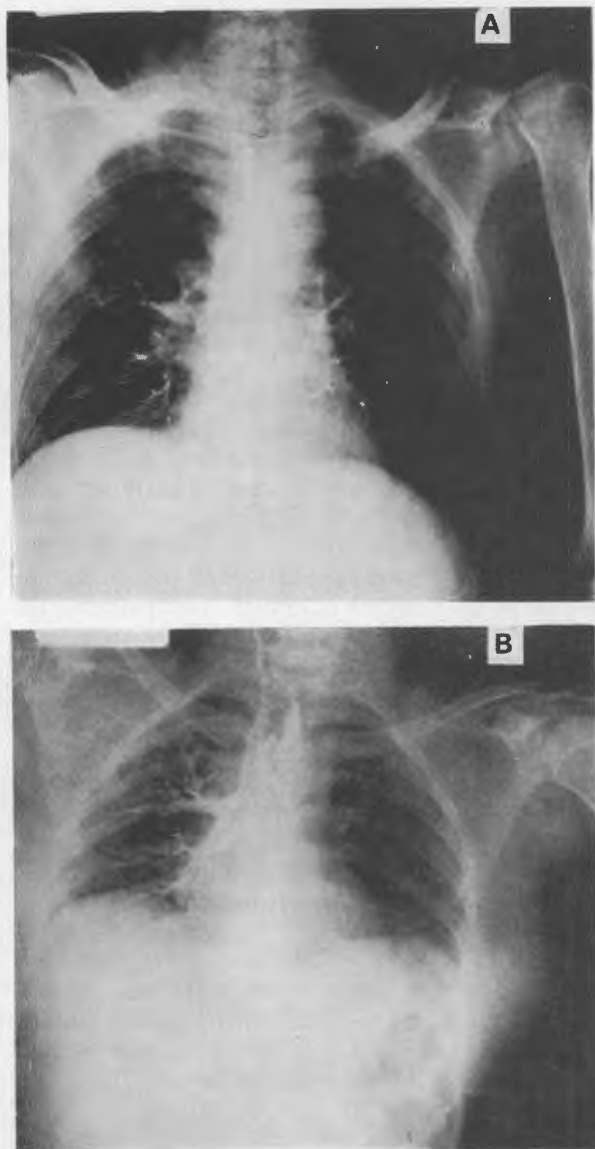


FIG. 1. Two examples of chest radiographs exhibiting evidence of aspiration of Dionosil in amounts sufficient to outline the bronchi.

(1968); Tomlin, Howarth and Robinson, 1968; Wise et al., 1969; Healey, Robinson and Vickers, 1970). Furthermore, Prout and Metreweli (1972) found that pulmonary aspiration occurred in 24% of patients undergoing fibre-endoscopy of the upper gastrointestinal tract under diazepam or chlormethiazole sedation and topical pharyngeal analgesia. Pontoppidan and Beecher (1960) demonstrated progressive loss of the protective reflexes with advancing age, and

concluded that depressant drugs should be used with great caution in the elderly.

Our study suggests that the method of neuroleptanalgesia, which we adopted, does not differ from the more popular general anaesthetic techniques in respect of the suppression of pharyngeal and protective laryngeal reflexes. The results indicate that neuroleptanalgesia should be accompanied by endotracheal intubation with a cuffed tube—perhaps especially during labour or in the semi-conscious patient undergoing neuroradiological investigation.

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INSUFFISANCE LARYNGIENNE PENDANT UNE NEUROLEPTANALGESIE EN COMBINAISON AVEC LE DIAZEPAM

RESUME

Après une angiographie de la carotide sous neuroleptanalgesie, on a instillé dans le pharynx de huit patients un colorant opaque aux rayons X. On a radiographié la poitrine de ces patients 15 min plus tard et remarqué qu'ils avaient tous aspiré le colorant. La technique de neuroleptanalgesie décrite dans cette communication ne doit pas être utilisée sans protection des passages d'air des patients qui sont susceptibles de régurgiter et d'aspirer le contenu gastrique.

LARYNXVERSAGEN WÄHREND NEURO-
LEPTISCHER NARKOSE IN VERBINDUNG MIT
DIAZEPAM

ZUSAMMENFASSUNG

Bei acht Patienten wurde unter neuroleptischer Narkose Karotid-Angiographie durchgeführt. Daraufgehend wurde ein undurchsichtiger Farbstoff in den Pharynx geleitet. Thoraxroentgenaufnahmen wurden 15 Minuten später gemacht. Es ergab sich, dass sämtliche acht Patienten den Farbstoff eingeatmet hatten. Das beschriebene Verfahren soll nicht benutzt werden, wenn keine Sicherheit besteht, dass die Luftwege genügend vor dem etwaigen Rückfluss und Inhalation des Mageninhalts geschützt werden können.

INCOMPETENCIA LARINGEA DURANTE
NEUROLEPTANALGESIA EN COMBINACION
CON DIAZEPAM

SUMARIO

Se instiló un medio de contraste radiopaco en la faringe de ocho pacientes, tras angiografía de la carótida bajo neurolepsia con analgesia (neuroleptanalgesia). A los 15 min se radiografió el tórax, observándose que los ocho pacientes habían aspirado el medio de contraste. La técnica neuroleptanalgesica descrita no debiera usarse sin salvaguardar la vía aérea en pacientes expuestos a regurgitación e inhalación del contenido gástrico.

LARYNGEAL INCOMPETENCE DURING EXPERIMENTAL "RELATIVE ANALGESIA" USING 50% NITROUS OXIDE IN OXYGEN

A preliminary report

J. RUBIN, J. G. BROCK-UTNE, M. GREENBERG, J. BORTZ AND J. W. DOWNING

SUMMARY

Ten healthy adult volunteers inhaled 50% nitrous oxide in oxygen while dental treatment was simulated for a period of 30 min. During this time 15 ml of radio-opaque dye was placed at the back of the tongue. A similar control study was performed 1 week later, the subjects inhaling pure oxygen without nitrous oxide. X-ray examination revealed that two of the 10 volunteers had aspirated dye while breathing nitrous oxide and oxygen, but no aspiration was apparent in the control study.

Regurgitation and inhalation of acid gastric content remains a common cause of death during anaesthesia (Harrison, 1968). The inhalation of 50% nitrous oxide in oxygen for induction of anaesthesia in the poor risk patient is often preferred to other induction techniques. The administration of nitrous oxide in oxygen in dentistry is a fashionable and popular technique with a high degree of patient acceptance because of the pleasant euphoria and relaxation produced (Clement, 1951). Inhalation of premixed nitrous oxide in oxygen (Entonox) for pain relief in labour occurs commonly. Pleasants (1971) challenged the safety of the latter technique, suggesting that the pharyngeal protective reflexes might be obtunded.

The purpose of this study was to assess the efficiency of laryngeal closure during the administration of 50% nitrous oxide in oxygen, employing the Quantiflex nitrous oxide/oxygen anaesthetic machine, an apparatus used commonly by the dental surgeon (Allen, 1972).

PATIENTS AND METHODS

Ten healthy non-pregnant adult female volunteers, aged 18-21 yr, gave informed consent for the study. After an overnight fast a control chest x-ray was taken before the study commenced.

Each volunteer reclined in the dental chair for 30 min, during which time she inhaled a mixture of 50% nitrous oxide in oxygen from a Quantiflex apparatus ("relative analgesia"). The inspired concentration of gas was monitored throughout using an Airco Ohio Model 600 oxygen monitor. Subjects breathed through a nasal mask for a period of 10 min until they were comfortable and equilibration with the inspired gas mixture could be assumed. The pulse was monitored continuously using a photoelectric pulse transducer (Sanei II Pulsemeter) attached to the thumb. All the necessary facilities for resuscitation were readily available. Volunteers with previous history of allergy or sensitivity to iodine were excluded from the study.

At intervals of 1½ min, 8-10 ml of water was sprayed into the mouth around the teeth with a dental drill. Adequate suction was applied to remove the water from the mouth.

Fifteen millilitres of radio-opaque liquid "Dionosil" was then placed on the back of the tongue with a soft-tipped plastic catheter over a period of 2 min, during which time most of the volunteers swallowed the dye. Intermittently, water from the dental drill was squirted into the mouth and suction was applied to the pharynx for a further 20 min, simulating drilling and filling of the teeth. Inhalation of the nitrous oxide in oxygen mixture continued throughout this time. Pure oxygen was then administered for 6 min at the end of the investigation, to wash out residual nitrous oxide from the lungs. At the end of the procedure, the x-ray examination was repeated to determine the fate of the dye.

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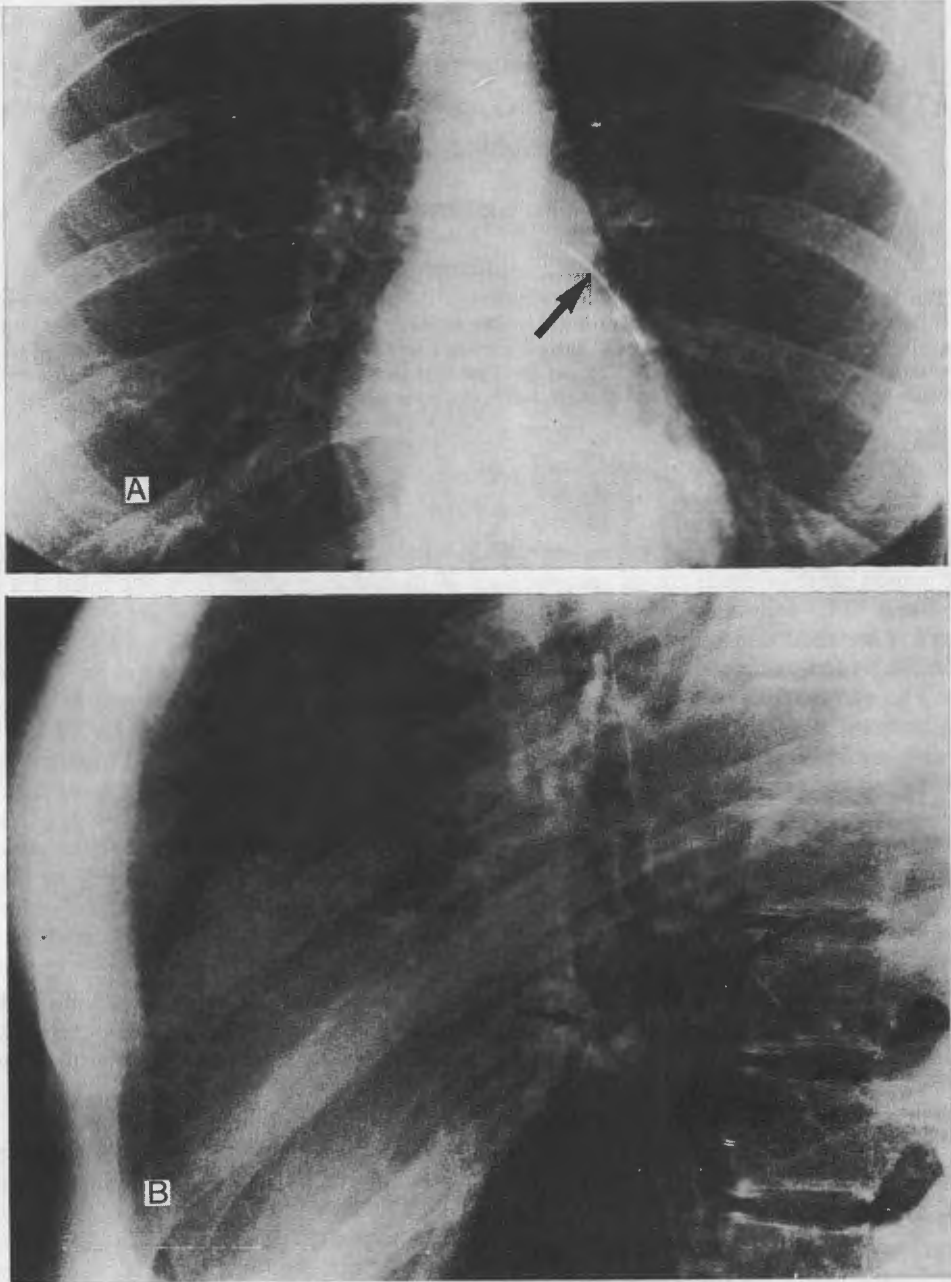


FIG. 1. Dye soiling left bronchus (A) and trachea and bronchi (B).

One week later, a similar study on the same volunteer was performed except that nitrous oxide was not included in the inspired gases. All the x-ray films were viewed independently by a radiologist (J. B.), who was unaware of the method of management on the day of the study.

RESULTS

In all subjects, the presence of dye in the stomach could be identified on screening after the procedure. No evidence of aspiration of dye was detected in the control study, but two of the 10 volunteers showed clear signs of pulmonary aspiration of dye on x-ray

examination after the inhalation of the nitrous oxide in oxygen mixture (fig. 1) (χ^2 test corrected for discontinuity: $0.4 < P < 0.5$).

DISCUSSION

Several investigators have shown that reflex laryngeal closure is depressed under general anaesthesia and following i.v. sedation with methohexitone, diazepam, ketamine and neurolept analgesia (Wise et al., 1969; Healy, Robinson and Vickers, 1970; Taylor and Towey, 1971; Brock-Utne et al., 1976).

Taylor and Towey (1971) failed to demonstrate radiological evidence of pulmonary aspiration of dye in conscious volunteers lying supine and premedicated with hyoscine. Prout and Metreweli (1972) found evidence of pulmonary aspiration in 24 patients undergoing fibroptic endoscopy of the upper gastrointestinal tract while sedated with diazepam or chlormethiazole and topical pharyngeal analgesia. Protective reflexes are compromised with advancing age, and depressant drugs should be used with great care in the elderly (Pontoppidan and Beecher, 1960). Pleasants (1971) has also expressed doubt as to the effects of relative analgesia on the laryngeal response during dental procedures, but his view has been refuted by Cleaton-Jones (1976).

Our study suggests that the inhalation of 50% nitrous oxide in oxygen differs little from other commonly used anaesthetic techniques with respect to suppression of pharyngeal and laryngeal reflexes. This study can be regarded as a pilot investigation only. The treatments were not allocated randomly and the difference between the treatments in respect of the main finding was not significant. We make this preliminary report in view of a recent communication advocating the safety of "relative analgesia" (Cleaton-Jones, 1976). However, in the latter study, conducted at an altitude of 1800 m, 50% nitrous oxide in oxygen was administered for only 5 min before challenging laryngeal competence. Under these circumstances there may have been less depression than in our study.

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INSUFFISANCE LARYNGIENNE AU COURS
D'UNE "ANESTHESIE RELATIVE"
EXPERIMENTALE A L'AIDE D'UN MELANGE
A 50% DE PROTOXYDE D'AZOTE ET
D'OXYGENE

RESUME

Dix adultes volontaires en bonne santé ont inspiré un mélange à 50% de protoxyde d'azote et d'oxygène au cours d'un traitement dentaire simulé d'une durée de 30 min. Pendant cette période, on a placé 15 ml d'un colorant opaque aux rayons X sur l'arrière de la langue. On a effectué une semaine plus tard une étude de contrôle similaire tandis que les sujets inspiraient de l'oxygène pur sans protoxyde d'azote. L'examen aux rayons X a révélé que deux volontaires sur les dix avaient inspiré le colorant alors qu'ils respiraient le mélange de protoxyde d'azote/oxygène, mais aucune aspiration de ce genre ne s'est apparemment produite pendant l'étude de contrôle.

KEHLKOPF-VERSAGEN WÄHREND "RELATIVER
ANALGESIE" MITTELS 50% STICKOXYD
IN SAUERSTOFF

Ein Vorläufiger Bericht

ZUSAMMENFASSUNG

Zehn gesunde, erwachsene Freiwillige atmeten 50% Stickoxyd in Sauerstoff ein, während 30 min lang eine Zahnbehandlung simuliert wurde. Während dieser Zeit wurden 15 ml einer radiopaqenen Farbe auf den hinteren Teil der Zunge gelegt. Eine ähnliche Kontrollstudie wurde 1 Woche später durchgeführt, wobei die Versuchspersonen reinen Sauerstoff ohne Stickoxyd einatmeten. Roentgenuntersuchungen zeigten, dass zwei der 10 Freiwilligen beim Atmen Farbe angesaugt hatten, während dies bei der Kontrollgruppe nicht der Fall war.

INCOMPETENCIA DE LARINGE DURANTE
"ANALGESIA RELATIVA" EXPERIMENTAL
EMPLEANDO 50% OXIDO NITROSO
EN OXIGENO

Un informe preliminar

SUMARIO

Diez voluntarios adultos saludables inhalaron 50% oxido nitroso en oxígeno mientras se simulaba tratamiento dental durante un período de 30 min. Durante este tiempo se colocaron 15 ml de tintura radio-opaca en la parte posterior de la lengua. Una semana más tarde se realizó una prueba de control similar, con los individuos inhalando oxígeno sin oxido nitroso. Un examen por rayos-X indicó que dos de los 10 voluntarios habían aspirado tintura mientras respiraban oxido nitroso con oxígeno, pero la aspiración no fué aparente durante la prueba de control.