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COST-EFFECTIVENESS OF NEBULISED IPRATROPIUM AS ADJUNCTIVE THERAPY IN ACUTE ASTHMA.

A G PARRISH

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Abstract:

Aim: To determine whether the addition of nebulised ipratropium to the therapy of acute asthma leads to a cost-effective reduction in the mean duration of admission and time to maximum peak expiratory flow rate (PEFR).

Method: Patients with an admission diagnosis of acute asthma were studied in a double-blind, placebo-controlled trial in which they received a standard therapeutic regimen of continuous intravenous aminophylline, 4-hourly fenoterol nebulisation, intravenous methylprednisolone 125mg 12-hourly, and, every four hours, either nebulised saline placebo or ipratropium bromide 500mcg in 3ml saline. Data on age, gender, initial and maximum PEFR, time to maximum PEFR, and duration of hospital stay was collected from the hospital record after discharge.

Statistical techniques: 2-way contingency tables for categorical variables, 1-way ANOVA for treatment effects, and life-table analysis of the time till discharge.

Results: Records of 279 of the 400 patients entered in the study were suitable for analysis after excluding re-admissions, non-asthmatics and incomplete records. Baseline comparisons of age and severity on presentation showed no significant differences. The trial group did not differ significantly from the control group with respect to either time to PEFR (respectively 21.11 hours (SD 14.3) versus 22.89 (SD 15.82)) or duration of admission (5.02 (SD 3.65) versus 5.38 (SD 3.13) 6-hour units). In a sub-group of patients

(n=155) demonstrating more than 100% improvement in PEFR, the time to maximum PEFR was significantly shorter in the ipratropium group (20.35 hours SD 12.4) versus 25.20 hours (SD 17.0); p= 0.045).

Conclusion: The addition of ipratropium bromide to a standard treatment regimen for acute asthma reduced the time to achieve maximum PEFR in a sub-group of patients with markedly reversible airflow limitation. Overall, however, the addition did not prove cost-effective.

CONTENTS

INTRODUCTION

Ipratropium has been shown to be effective in acute asthma[1,2,] and more recently it was demonstrated that this effect was additive to that of standard[67] asthma regimes[6,28,39.41]. However, a statistically significant difference in recovery rate is not necessarily clinically useful and it would thus seem appropriate to look at the cost-effectiveness of additive therapy in terms of a reduction in duration of hospital stay.

CONCEPTS

1.Cost-effectiveness

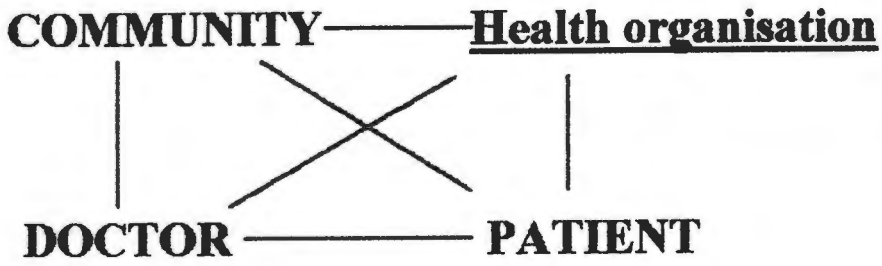
All decisions in medicine are ultimately related to evaluating the benefits and risks of a therapeutic intervention (or non-intervention) in relation to the expected outcome. Attempts to formalise this decision process are fraught with difficulty[12,38] but several concepts have been defined.

"Cost-effectiveness" compares the cost in financial terms of using a specific intervention with outcome measures which are translated into monetary values. An example would be comparing the cost of renal transplantation with that of long-term dialysis.

"Cost-benefit" does not translate outcome into financial terms, but rather uses other units such as quality adjusted life years (QALYs) or other quantifiable measures of benefit. While this has the advantages of seeming more easily clinically interpretable it is perhaps more open to inter-observer variation at the level of outcome assessment.

Traditionally, most medical decisions have been limited to assessing benefit to the individual patient, according to the Hippocratic principle of benificence. This viewpoint was reinforced in the past by the fact that the majority of therapeutic interventions were limited by biotechnology and not by cost. In the public health sector this situation is now changing[58], and if one takes the concept to its logical extreme, then the model of doctor - single patient is no longer viable in terms of health economics, and should be replaced by the tetrad of doctor - community - individual patient - health resources. By prescribing an expensive drug in the face of a limited drug budget, one may be "harming" another of one's

patients with a more readily curable disease if the treatment for that patient is no longer affordable.



Interactions to consider when assessing the aspect from which to evaluate a cost-effectiveness intervention.

At present there still seems to be ambiguity about the responsibility for resource allocation[48]. While health administrators stress global cost saving measures, it is important for clinicians to distinguish between strategies leading to suboptimal care and those where a less expensive treatment may be equally efficacious. It is in the light of this that any data which helps evaluate the cost-effectiveness (or otherwise) of a strategy should be regarded as being of value.[5,6]. However, as has been emphasized recently[27], there are potential hazards with studies of this type, such as:

1. Unstandardized methodology. As this is a relatively new field, some of the assumptions made by the investigators may not be clear to readers of the study, eg precise data on costing.

2. Negative results. Because economic analysis is sometimes regarded more as a marketing strategy than a research tool there may be some reluctance to publish negative results.[27].

3.Comparative agents. There may sometimes be inherent bias in that the agent under investigation may be compared with other agents with known efficacy but unfavourable cost profiles.

4.Frame of reference. As mentioned previously, the beneficiaries of the cost-effective strategy should be clearly defined, eg, hospital, patient or third party supplier.

ii Trial design and Type 2 errors

Many of the studies on the use of ipratropium in asthma are of relatively low power (small numbers of patients), as will be shown later. It has been pointed out that these studies are open to type 2 errors[68], where the finding of a negative result should be interpreted with caution (a clinically significant difference between groups may fail to achieve statistical significance if the groups are small).

Also, highly selected groups of subjects tend to be used in trials designed to assess the biological effect of an agent, eg when evaluating a new bronchodilator only young patients with previously defined highly reversible asthma might be studied. Strikingly different outcomes regarding both efficacy and adverse effects may, however, occur in clinical practice, a phenomenon best evaluated by post-marketing surveillance and other pharmaco-epidemiological methods.

For this reason it was decided that in this trial of cost-effectiveness an attempt would be made to recruit relatively large numbers of patients, unselected except for the fact that they were judged by casualty medical officers to have acute asthma requiring hospital admission.

iii. Historical background

The fact that anticholinergic medication has been used for asthma for many centuries[43,61] is a pointer to its therapeutic efficacy, but may also have something to do with the more ready bio-availability of atropine-like alkaloids in plants such as Datura strammonium and the lack of other remedies with consistent efficacy.

Ayurvedic texts discuss dosage[19]:

"When the chest, throat and head become light and the cough is reduced, one should regard it as the result of proper smoking. When the sound (?wheeze) is not clear, the throat is full of cough and the head is moist, one should know that smoking has been inadequate."

and side-effects:

"If one oversmokes, his palate, head and throat will be dried up and will be hot; he will suffer from thirst and be unconscious; there will be excessive flow of blood, his head will be dizzy, and he will be stupefied."[19]

Although probably not the earliest user in Britain, a surgeon called William English described the effects of Datura smoke in 1811:

"...the irritation and constant cough ceased, and I expectorated from the bronchia pieces of clear congealed phlegm, from half an inch to about an inch in length, and the thickness of a crow's quill, which enabled me to fill the chest with air"[19].

Even as late as 1959, smoke-borne anticholinergic therapy was still being advocated by Herxheimer[26] ("Atropine cigarettes in asthma and emphysema"), and studies from the mid-seventies demonstrated some benefit from the use of atropine nebulisation. However the narrow margin between efficacy and toxicity prevented atropine from finding much favour in clinical practice, and it was only with the synthesis of Sch 1000 (ipratropium) that anticholinergic therapy in asthma was once again popularised.[23,24,43,62,65].

iv. Nebulizer theory

The physics of particle deposition from nebulizer devices involves consideration of features such as the volume of solution used, the breathing pattern of the patient, and the type of airways disease. Particle deposition in a branching tubular system occurs by a combination of impaction and sedimentation, with the nett result that there are preferential sites for deposition of particles of different sizes. Broadly speaking, however, the following features are the most important.[8,50].

1. Volume of nebulizer solution. It appears that minimum volumes of 4-6 ml are required, as up to 50% of the solution may remain in the apparatus, even when the reservoir appears to be empty[49].

2. Flow rate of the driving gas. If jet nebulizers are operated at only 4 *l*/min, the aerosol particle size may lie outside the optimum range, and thus flow rates of 6-8 *l*/min have been recommended. The "ideal" particle size is difficult to determine because of confounding variables such as evaporation, hygroscopic growth, aggregation and the normal fairly wide range in particle size from a conventional system. Particles less than 1 *u*m in diameter tend to either get exhaled or settle in the alveoli, whilst particles bigger than 8 *u*m are usually trapped in the oropharynx. Particles ranging in size from 1-5 *u*m are likely to reach most parts of the lungs and thus a mass mean aerodynamic diameter (MMAD) of less than 5 *u*m with a geometric standard deviation of <2 has been recommended[8].

3.Drug dose. When determining the appropriate dose[46] it must be borne in mind that only about 10% or less of the dispensed amount will actually reach the lungs[8,50].

4.Pattern of inhalation. Published investigations on differences in particle deposition related to forced inspiration versus tidal breathing, and on the increased sedimentation related to inspiratory pauses mainly apply to metered dose inhalers. For jet nebulization therapy the avoidance of excessive oropharyngeal deposition due to too rapid inhalation is, however, probably advisable.

5.Airways disease. Patchy distribution of particle deposition in airways obstruction has been described[49].There also seems to be a more central deposition in these patients when compared to subjects without obstructive lung disease. Airways inflammation may enhance drug delivery to receptors due to increased vascularity and mucus production.

v. Airway innervation

Although more recent reviews[25,35,45] of the pathogenesis and treatment of asthma lay particular emphasis on the inflammatory nature[10,13,15,20,29,30,31,51] of the disease, the final common pathway is still bronchoconstriction,[33,34,56,72] and treatment directed at acute exacerbations must recognise this[21,34]. Airway tone is thought to be due to at least four factors:

1. Cholinergic neurones: Excitation of these neurones[3] leads to the endplate release of acetylcholine, the transmitter which causes the formation of excitatory postjunctional potentials leading to increased bronchomotor tone. Repetitive cholinergic stimulation may lead to the release of prostanoids and noradrenaline, which inhibit acetylcholine release, thus acting as a form of negative feedback. This pathway is central to the presumed mechanism of action of ipratropium.

2. Adrenergic mechanisms: Although there is probably no direct sympathetic innervation of the airways in humans, the fact that *B*-blockers may cause bronchoconstriction in asthmatics lends support to the theory that circulating catecholamines may inhibit cholinergic transmission either at a pre-junctional level or may act directly on B_2 receptors on bronchial smooth muscle.

3.NANC neurones: Non-adrenergic non-cholinergic effects are probably due to co-release of neuropeptides and other transmitters from "conventional" fibres, rather than there being a separate set of neurones[4]. Inhibitory non-adrenergic non-cholinergic (i-NANC)mechanisms lead to bronchodilatation, and although there is still debate about the neurotransmitters involved, vaso-active intestinal peptide (VIP) probably plays a part, as may nitric oxide (NO). In asthmatics, tryptase from mast cells may increase the rate of breakdown of VIP, and free radical release from other inflammatory cells may lead to the more rapid degradation of NO. When C-fibre sensory nerves are stimulated, there may also be retrograde release of neuropeptides - eg substance P and neurokinin A - leading to

bronchoconstriction (the so-called excitatory non-adrenergic non-cholinergic or e-NANC effect)[4]. This increased sensory output is speculated to be more likely in the setting of epithelial inflammation.

4."Mechanical" tone: this is thought to be due to the local release of endogenous prostanoids and possibly other mediators, and through release of calcium from intracellular stores leads to the generation of some intrinsic muscle tone that is not due to external neuronal input.

The basic contractile mechanism is fairly well established: neurotransmitter-receptor binding leads to the generation of increased myoplasmic calcium concentrations, the calcium binds to calmodulin, and this complex activates the enzyme myosin light chain kinase, which leads to the phosphorylation of the 20 000D myosin subunits, and subsequent mechanical activation of the actin-myosin complex with resultant shortening of the smooth muscle cell. Those actin-myosin bridges which are active towards the end of a contraction form and break less quickly and are thought to be involved more with force generation whereas earlier-forming bridges contribute more to shortening. The mechanism for this is far from clear, but it has been postulated either that there is progressive slowing of normal bridge cycling, or that permanent "latch bridges" impede the cycling rate of the other bridges.

Thus, studies on the neurophysiology of asthma are easier to perform on earlier (shortening) changes than the later (isometric) events, and it is unclear whether all the conclusions about smooth muscle behaviour in an in-vitro preparation are necessarily applicable to the state of affairs pertaining in the asthmatic's airways, where the extent of contraction may be closer to the isometric end of the spectrum[3]. Two other properties of smooth muscle deserve mention. The first is that of "supercontraction" - the fact that smooth muscle cells can contract to 10% of their optimum length explains in part the

observation that airways subjected to bronchoconstrictive stimuli can close almost completely. The second is the phenomenon of reduced activation at short muscle length: although fibres do have the potential to shorten by 90%, the ability to contract seems to be less the shorter the fibre[3]. The mechanism for this is not clear, although it has been suggested that the distortion of the T-tubules that occurs as the cells become thicker may lead to reduced excitation-contraction coupling.

Finally with relevance to asthma, it is found that "sensitized" muscle contracts more easily. The increase in myofibrillar ATPase may be due to altered ratios of myosin isoenzymes or to a change in light chain phosphorylation. There is also a reduction in the internal resistance to shortening which may be due to changes in some or all of the cytoskeletal proteins (desmin, vimentin, filamin, non-erythrocytic spectrin, titin and nebulin)[3].

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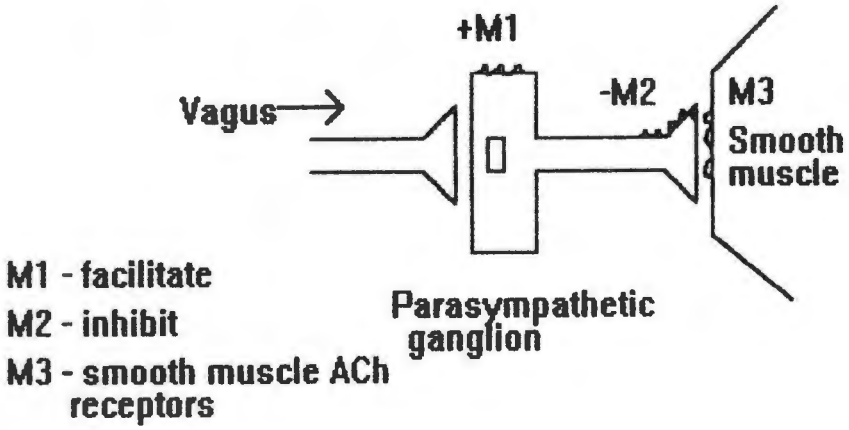
Cholinergic innervation of the bronchi.

The nerve supply to the lung is both afferent and efferent.[18,47,63,71]. The efferent side is both excitatory and inhibitory, and involves output to airways smooth muscle, blood vessels and secretory tissue (mucus production). The afferent side includes the bronchopulmonary stretch recepts in smooth muscle, and irritant and pulmonary J receptors on epithelium and in the alveolar walls. Muscle cells also are connected to each other via gap junctions, and axon reflexes may also play a role. (For example, antidromic conduction from sensory stretch receptor collaterals may lead directly to smooth muscle., although local neuropeptide release may subserve the same function.). In some afferent fibres, "co-transmission" of substance P, neurokinin A and calcitonin gene related peptide may occur[4]. Likewise, VIP is probably co-transmitted with acetylcholine. The simultaneous release of this potent vasodilator may help to increase the blood flow to contracting

muscle, but in vitro VIP is a bronchodilator, and thus may exert a braking effect on the bronchoconstriction mediated by acetylcholine.

There are at least three[4] muscarinic receptor subtypes in the lung: M_1 (excitatory) found in animal parasympathetic ganglia and blocked by pirenzepine which may also inhibit reflex bronchoconstriction in the human lung) and M_2 which are probably prejunctional inhibitors of acetylcholine release. M_3 receptors are found on smooth muscle, and their stimulation leads to contraction. The nomenclature of these receptors is still not completely uniform. Prejunctional muscarinic receptors on cholinergic nerves lead to reduced acetylcholine release when stimulated, and inflammatory mediators are thought to have an effect on these receptors as well as inhibiting sympathetic inhibition and modifying muscarinic receptor coupling.[4]



Sites of the various muscarinic receptor subtypes.

From the above diagram it can thus be seen that a non-selective pre- and post-junctional blocker such as atropine or ipratropium could theoretically cause paradoxical bronchoconstriction by excessive blockade of the M_2 inhibitory receptors. A similar sort of effect [4] has been demonstrated in guinea pigs infected with influenza virus where the viral

neuraminidase acts selectively on the sialic acid residues of the M_2 receptors, leading to increased bronchoconstriction.

Although the bronchodilator response to atropine of the normal airways implies the presence of basic resting vagal tone[66], there is little direct evidence to support the idea of increased cholinergic tone in asthma[3]. The mechanisms of the increased cholinergic effects in asthma are thought to include the following[3]:

1. Increased afferent discharge because of epithelial damage and the direct effects of inflammatory mediators.

2. Facilitation of neurotransmission by TXA (which probably also causes inhibition of sympathetic inhibition.)

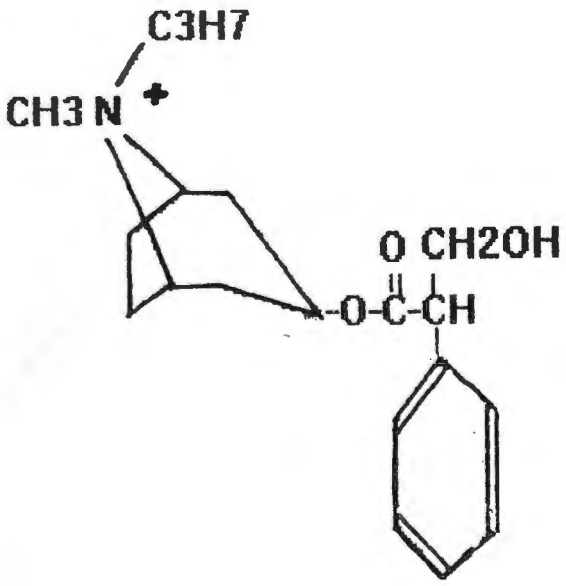
3. Inactivation of VIP by inflammatory cell enzymes. (Thus loss of the braking effect of VIP on cholinergic bronchoconstriction.)

4. An increase in the end-organ responsiveness to acetylcholine which may be mediated by an increase in receptor numbers, an increase in receptor affinity, a post-receptor mechanism, or some combination of these.

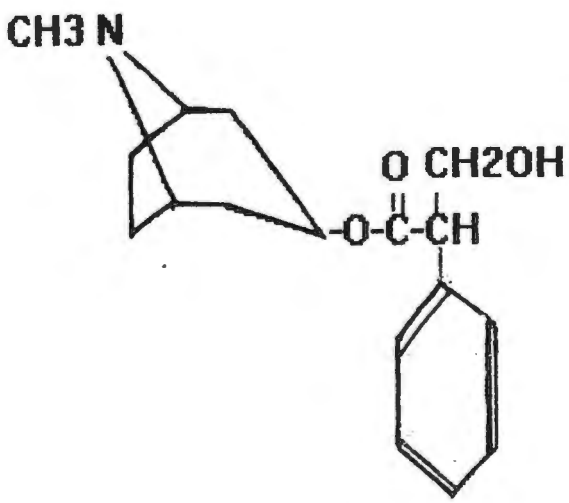
2. IPRATROPIUM.

Ipratropium is structurally very similar to atropine except that it is a quaternary ammonium compound (rather than tertiary)[23,53]. It is thus positively charged and poorly lipid soluble. This accounts for the major pharmacokinetic difference between the two compounds - whilst inhaled atropine is rapidly distributed throughout the whole body, including the brain, ipratropium, even after intravenous administration, only crosses very poorly into the central nervous system. After inhalation very little systemic absorption occurs[11,17], and in fact a large proportion is recovered in the faeces after having been swallowed. There also appears to be significant first pass metabolism, with 54% of the total urinary activity of radio-labelled drug being due to metabolites four hours after intravenous administration, as opposed to 76% after oral administration[53].When administered as an inhaler, the optimum dose is reported to be about 20 to 40 micrograms, but a higher dose of up to 500 micrograms is recommended when using a nebulizer[43,53].

STRUCTURE OF IPRATROPIUM



STRUCTURE OF ATROPINE



The time to maximum bronchodilating effect is $1^1/_2$-2 hours longer than that for B_2 stimulants, with a duration of effect of up to six hours[53] and this may obscure relative efficacy in clinical comparative trials of the two preparations. Reports of side-effects are accumulating slowly in the literature, and probably because of the minimal systemic absorption, are generally described as minor. The paradoxical bronchoconstriction induced by earlier hypertonic formulations appears to be rare with the present formulation.

Isolated side-effects reported with the use of ipratropium are remarkably few, but include the following:

1. Transient angle closure with narrow angle glaucoma when used at the same time as salbutamol[32]. This increase can be prevented by wearing swimming goggles during nebulisation.

2. Bladder outflow obstruction in the presence of prostatic hypertrophy.[42].

3. Irritant contact facial dermatitis[16], when used for prolonged periods in combination with terbutaline.

4. Paralytic ileus in a man with spastic diplegia[44].

5. Paradoxical bronchoconstriction[9]. It is unclear exactly which preparation this patient was using, but this effect, while theoretically explicable in terms of the anticholinergic effect itself, as discussed previously, is thought to be extremely rare with the newer formulation.[59].

6. Transient dry mouth.[53].

It must be emphasized, however, that the effects described above are mostly isolated case reports, and the drug is generally considered safe in glaucoma and the elderly[23]. It is also thought to have no significant effect on mucociliary clearance[23].

3. AN OVERVIEW OF RELATED TRIALS.

In general, whilst there have been a large number of trials looking at the effects of ipratropium in both patients with asthma and those with COPD[14,22,37,55,57], there is a much smaller group which have direct relevance to the issue of using nebulised ipratropium in the acute care situation. A brief overview of some of these is presented in *Chart 1*, and as can be seen, most of them reported a favourable result. The last trial in the table [28] was the only one of those included not to demonstrate definite improvement, and in this case there was only a small number of patients with a relatively short follow-up period. Another trial[54] (not included in the table because ipratropium was given as an inhaler with a spacer rather than by nebulisation) failed to demonstrate the maintenance of significant benefit beyond 24 hours, and the authors suggested that it could safely be discontinued beyond this period because of cost.

On reviewing the trials quoted in *Chart 1* several methodological difficulties become apparent:

1. most of the trials contained relatively small numbers of patients (which does not necessarily invalidate their conclusions).

2. Various dosage regimens of ipratropium were used. Although all except one[36] used a dose of 500 micrograms, the volume of solution in which this was nebulised was not always clearly stated, and when it was, varied from 2 to 4 millilitres. As has been discussed previously, this might have a significant effect on the amount of ipratropium being delivered to the airways. Not all the trials used multiple nebulisations - in three studies[52,60,64]only one dose of ipratropium was given. This complicates extrapolation of the data to the clinical setting, since most people requiring admission with acute bronchospasm would require more than one nebulisation prior to discharge.

Chart One: Selected Trials of Ipratropium in Acute Asthma

Ref. No.	No. of Pts	Trial Pts	Steroids	Ip. Dose	Neb. Vol	No. of Rxs	Conclusion	*Comment*
60	*199*	51	*13*	0.5	*4*	S	*Beneficial*	*Better starting PF*
41	*145*	50	*56*	0.5		M	*Beneficial*	*Follow-up 24 hrs*
70	*24*	11	*100*	0.5		M	*Beneficial*	*Follow-up < 5 hrs*
52	*103*	33	*40*	0.5	*2*	S	*Beneficial*	*Follow-up < 5 hrs*
64	*50*	25		0.5	*4*	S	*Beneficial*	*Follow-up < 5 hrs*
7	*28*	15	*0*	0.5	*3*	M	*Beneficial*	*FEV1 at 48hrs 2.1 vs 2.7*
69	*28*	22	*100*	0.5	*4*	M	*Beneficial*	*Crossover trial*
36	*12*	12	*33*	1	*2*	M	*Beneficial*	
28	*40*	21	*100*	0.5		M	*Not of value*	*Follow-up < 5 hrs*

Trial pts = number of asthmatics getting ipratropium
Ip dose = Ipratropium dose in milligrams
Neb vol = volume of nebuliser solution (millilitres)
No. of Rxs: S = single: M = multiple.
Steroids = percentage given corticosteroids

3. Few trials have reported on a longer than 24-hour follow-up, and thus while demonstrated improvements in peak flow are incontrovertible, it is far from clear that these changes translate into earlier discharge, or even necessarily quicker resolution of the initial "critical" clinical state - ie stabilisation.

4 AIM OF PRESENT STUDY.

The aim of this study was to determine whether nebulised ipratropium bromide, used as an adjunct to standard bronchodilator therapy in an acute asthma service, was cost-effective.

END-POINTS

1. **Primary:** Time in hours to maximum peak flow.

2. **Secondary**: Admission duration measured in units of six hours (as all routine discharges occurred on either the morning or afternoon ward round.)

The need for admission to either a conventional medical ward or the respiratory ICU was documented.

5. METHODS

A double-blind placebo controlled trial design was adopted.

1.**Patient selection**. All patients requiring admission to the Groote Schuur Hospital Emergency Unit's asthma room were entered in the trial after obtaining verbal informed consent. The study was continued until four hundred patients had been recruited. Although there were no formal guide-lines, medical officers admitting patients to the asthma room were expected to exclude those with end-stage chronic obstructive airways disease as judged by a history of minimal reversability and documented failure of peak expiratory flow rate to improve by at least fifty percent during previous admissions. However no formal selection criteria were imposed, as the aim of the trial was to assess the efficacy of the trial preparation in a functioning emergency room situation.

2.**Randomisation.** Identical trial medication bottles (labelled 1 to 400) were randomised by the suppliers of the nebuliser solution. Two millilitres of the trial solution (containing either 500 micrograms of ipratropium or placebo of normal saline) was nebulised with 3 millilitres of saline using a Hudson face-mask nebuliser driven by 100% oxygen at a flow rate of 6 litres/minute.

3.**Routine medication.** The standard asthma room protocol (Appendix II) which had been in place for the preceding six years was followed:

i) Patients were given four-hourly oxygen-nebulized fenoterol (1ml solution in 4ml saline) and the trial medication was alternated with this, also four-hourly, so that patients received a nebuliser every two hours.

ii)An aminophylline infusion ran constantly according to dosage tables (Appendix II) available in the asthma room designed to achieve a constant therapeutic level of aminophylline in the majority of cases.

iii)Corticosteroids (methylprednisolone 125mg 12 hourly IVI) were given in the majority of patients, being omitted only at the discretion of the admitting clinician.

iv)Also, where judged necessary by the asthma room medical officer, a salbutamol infusion was started. The ususal criterion was that the patient was seen not to be responding to the above therapy (For dose, see Appendix II).

4. Discharge criteria. An emergency room medical officer allocated for the day to the asthma room was responsible for all discharges. The person drawing up the duty roster had no connection with the trial. A patient was eligible for discharge if they satisfied all of the following: 1. No features of distress and able to walk to the toilet.

2. Patient feels able to cope at home

3. Peak expiratory flow rate shows an upward trend or has plateaued at >70% of best value in the past year (or >70% of predicted normal) AND morning dipping is not below 50% of best value in past year (or predicted normal)

5.Monitoring. This consisted of four-hourly peak flow measurements using a Wright's Mini Peak Flow Meter (done before and after fenoterol nebulization) and daily serum theophylline estimations. Other investigation were only done where clinically indicated according to the judgement of the asthma room medical officer.

6 Data collection. After discharge the hospital folder was examined by the investigators to obtain the following data which had been collected by the admitting medical officer and the nursing staff in the asthma room. The form (*Appendix 1*) was then completed for each patient entered in the trial. The following information was thus available:

1. Trial medication randomisation number.

2. Height in metres.

3. Weight in kilograms.

4. Year of birth.

5. Date of admission.

6. Time of admission.

7. Admission peak flow rate. (In litres/minute)

8. A second peak flow, (usually recorded after the first fenoterol nebulisation, at the end of the admitting officer's assessment, and prior to transfer to the asthma room.)

9. The peak flow 24 hours after admission.

10 The peak flow 48 hours after admission.

11 Whether or not the patient wason maintenance steroids prior to admission.

12. The maximum peak flow achieved.

13. The time (in hours) to maximum peak flow.

14. Whether the patient was given intravenous corticosteroids

15 Whether intravenous salbutamol was given.

16. The serum theophylline levels on the 1st, 2nd, and 3rd day after admission.

17. The discharge date.

18. The discharge time.

19. Whether the patient required ward or ICU admission.

6. STATISTICAL METHODS.

These included: 1. **2 x 2 contingency tables** comparing treatment and:

gender

prior corticosteroids

readmission pattern.

2. **One-way ANOVA tests** of the quantitative covariates to assess whether the treatment groups differed on any of these potentially confounding factors.

3. **One-way ANOVA tests** of the time to maximum peak flow and the number of six-hour admission units.

4. **Life-table analysis** of the distributions of the times to discharge.

7. RESULTS

Of the original 400 patients entered, 121 were omitted from the analysis for the reasons shown below. The exclusions appear evenly distributed between the trial and placebo groups, and were made before the trial code was broken.

Reason for exclusion	Ipratropium	Placebo	Total
No admission PEFR	1	3	4
Could not do PEFR	3	0	3
Left ventricular failure	1	1	2
Incomplete records	17	20	37
Medication not used	3	1	4
Nebuliser stopped early	0	2	2
Re-admissions	35	31	66
Clinical COPD	0	3	3
Total	**60**	**61**	**121**

The records of the remaining **279** patients were suitable for analysis.

1.Comparability.

The analysis was done in four stages, and figures on comparability are presented for each of the subgroups. The composition of the groups was as follows:

1. Phase 1 Group. This was the largest group (279 pts) and was unselected, representing the results of the data of allall analysable patients entered in the trial. It probably most closely reflects the group of interest, being all those patients requiring admission who presented with features of acute bronchospasm. It was made up as follows.

Standard therapy + ipratropium or placebo	249
No methylprednisolone + ipratropium /placebo	11
Salbutamol infusion + standard Rx* + ipratropium/placebo	18
No IV aminophylline + ipratropium/placebo	1

(*Rx=therapy)

2. Phase 2 Group. This sub-group excluded those who did not receive methylprednisolone and those who did receive a salbutamol infusion. It is thus the group which most closely follows the trial protocol, but it possibly selects out some patients with very reactive airways requiring salbutamol

Standard therapy + ipratropium/placebo	249

3.Phase 3 Group. This subgroup of the Phase 2 analysis group selected those patients who were shown to have significant reversibility, in that their PEFR increased by more than 50% during their hospital stay. (Of importance, this definition could only be applied retrospectively.)

Subgroup with >50% increase in PEFR	213

4.Phase 4 Group. A subgroup of the Phase 2 analysis group which showed >100% increase in PEFR during admission. (Again, note that this definition could only be applied retrospectively.)

Subgroup with >100% increase in PEFR	155

Tables 1 to 4 show that the base-line characteristics of the trial and placebo groups were very similar at all phases of the analysis, and formal statistical testing revealed no significant differences. The lack of complete congruity in the numbers in each group with regard to different variables (eg n=116 for height but n=118 for weight in the trial group in Phase One) reflects the retrospective nature of the data collection, with some missing data.

	IPRATROPIUM	PLACEBO	Total
Gender			
Male	**45**	**52**	**97**
Female	**95**	**87**	**182**
TOTAL	**140**	**139**	**279**
Prior Steroids			
Yes	**67**	**58**	**125**
No	**51**	**60**	**111**
Total	**118**	**118**	**236**

	Mean	n	SD	SEM	Mean	n	SD	SEM	Total
Age	**39.82**	140	**15.2**	1.29	**38.98**	139	**15.2**	1.26	**279**
Height	**161.8**	116	**8.83**	0.82	**161.3**	108	**16.2**	1.56	**224**
Weight	**66**	118	**16.6**	1.53	**67.6**	113	**16**	1.5	**231**
1st PF	**140.8**	136	**67.9**	5.82	**145.4**	135	**75.1**	6.51	**269**
2nd PF	**182.3**	135	**82.2**	7.08	**179.8**	133	**87.9**	7.62	**268**
Theo 1	**67.92**	103	**31.5**	3.1	**71.26**	103	**30.4**	3	**206**
Theo 2	**66.6**	30	**23.2**	4.23	**72.56**	39	**31.8**	5.09	**69**
Theo 3	**80.83**	6	**30.1**	12.3	**89.44**	9	**57.1**	19.03	**15**

Theo 1, 2, & 3 = Theophylline levels on 1st, 2nd, & 3rd days.

	IPRATROPIUM				PLACEBO				
									Total
Gender									
Male	43				44				87
Female	84				78				162
TOTAL	127				122				249
Prior Steroids									
Yes	64				53				117
No	45				54				99
Total	109				107				216
	Mean	**n**	**SD**	**SEM**	**Mean**	**n**	**SD**	**SEM**	**Total**
Age	**40.23**	127	**15**	1.33	**39.61**	122	**15.1**	**1.36**	**249**
Height	**161.3**	110	**8.77**	0.84	**162.5**	98	**3.39**	**0.85**	**208**
Weight	**66.31**	111	**16.8**	1.6	**67.47**	103	**16.3**	**1.6**	**204**
1st PF	**143.3**	127	**68.5**	6.08	**144.1**	122	**71.8**	**6.5**	**249**
2nd PF	**185.6**	127	**83.2**	7.38	**179.3**	122	**86.5**	**7.83**	**249**
Theo 1	**68.9**	95	**32.3**	3.31	**72.02**	95	**30.7**	**3.15**	**190**
Theo 2	**67.15**	26	**23.3**	4.57	**73.54**	35	**33.3**	**5.67**	**61**
Theo 3	**80.83**	6	**30.1**	12.3	**91.63**	8	**60.6**	**21.44**	**14**

Theo 1, 2, & 3 = Theophylline levels on 1st, 2nd & 3rd days.

CHARACTERISTICS OF PHASE THREE GROUP. 33

	IPRATROPIUM	PLACEBO	Total
Gender			
Male	**37**	**37**	**74**
Female	**73**	**66**	**139**
TOTAL	**110**	**103**	**213**
Prior Steroids			
Yes	**56**	**47**	**103**
No	**37**	**43**	**80**
Total	**93**	**90**	**183**

	Mean	n	SD	SEM	Mean	n	SD	SEM	Total
Age	**40.02**	111	**15.4**	1.46	**38.63**	102	**15.1**	1.5	**213**
Height	**162**	97	**8.84**	0.9	**160.9**	83	**18**	1.97	**180**
Weight	**66.42**	97	**17.5**	1.78	**67.28**	85	**16.8**	1.83	**182**
1st PF	**129.8**	111	**54.3**	5.16	**124**	102	**51.8**	5.13	**213**
2nd PF	**174.7**	111	**73.5**	7	**164.6**	102	**71.7**	7.1	**213**
Theo 1	**69.57**	83	**33.1**	3.64	**71.07**	82	**31.8**	3.51	**165**
Theo 2	**67.35**	23	**23.6**	4.93	**74.32**	31	**34.2**	6.15	**54**
Theo 3	**80.8**	5	**33.7**	15.1	**91.63**	8	**60.6**	21.44	**13**

Theo 1, 2, & 3 = Theophylline levels on 1st, 2nd and 3rd days.

	IPRATROPIUM	PLACEBO	Total
Gender			
Male	**23**	**26**	**49**
Female	**54**	**52**	**106**
TOTAL	**77**	**78**	**155**
Prior Steroids			
Yes	**38**	**33**	**71**
No	**27**	**34**	**61**
Total	**65**	**67**	**132**

	Mean	n	SD	SEM	Mean	n	SD	SEM	Total
Age	**39.64**	78	**15.9**	1.8	**37.22**	77	**14.4**	1.64	**155**
Height	**161.1**	67	**8.98**	1.1	**159.6**	64	**19.9**	2.48	**131**
Weight	**64.95**	68	**14.8**	1.8	**66.77**	67	**16.7**	2.04	**135**
1st PF	**110.6**	78	**45**	5.1	**105.8**	77	**40.4**	4.61	**155**
2nd PF	**163.2**	78	**71.8**	8.13	**157**	77	**68.3**	7.79	**155**
Theo 1	**68.36**	58	**33.6**	4.41	**69.4**	65	**31**	3.84	**123**
Theo 2	**69.72**	18	**25.4**	5.99	**71.89**	27	**34.3**	6.61	**45**
Theo 3	**93.67**	3	**40.4**	23.3	**91.63**	8	**60.6**	21.44	**11**

Theo 1, 2, & 3 = theophylline levels on 1st, 2nd & 3rd days

2. Outcome.

The endpoints of the study were the time taken to reach maximum peak flow (measured in hours) and the duration of admission, measured in units of 6 hours (as decisions about discharge, and thus ultimately the cost of the therapy, were not made more frequently than this). The results are shown in **Table Five**. (Next page.)As can be seen from the table, there were only minor differences at any phase of the analysis in the time taken to reach maximum peak expiratory flow, the maximum flow rate achieved, or the mean peak flow at either 24 or 48 hours. Formal statistical testing found that these differences were not significant. Likewise, the mean number of admission units in the two groups are shown not to differ significantly at the first threee phases of the analysis. In the fourth phase (those showing more than 100% increase in PEFR) this difference did reach statistical significance.(p=0,045)

Mean Admission Units

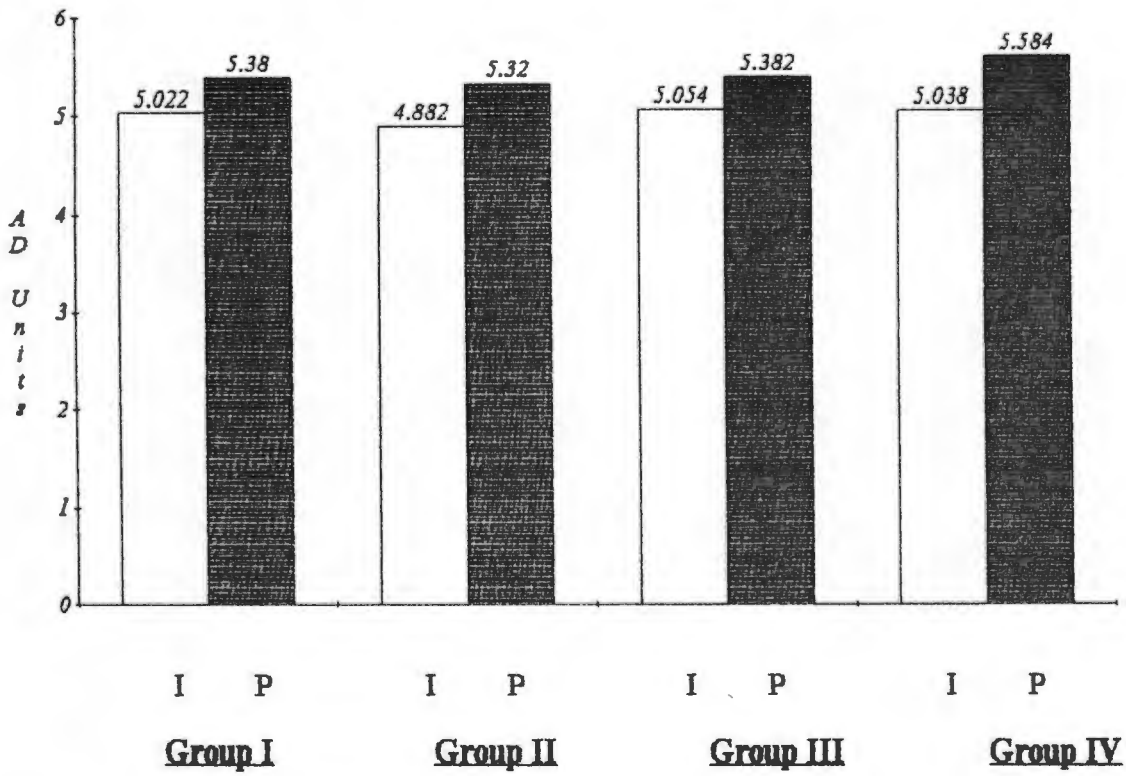


TABLE 5: Outcome measures in the four phases of the analysis.

	IPRATROPIUM				PLACEBO			
	Mean	SD	*SEM*	**n**	**Mean**	SD	*SEM*	**n**
GROUP 1								
PF max	**315.88**	86.75	*7.44*	**136**	**321.05**	82.8	*7.18*	**133**
T max	**21.11**	14.33	*1.23*	**136**	**22.89**	15.82	*1.37*	**133**
PF 24	**281.43**	87.45	*10.45*	**70**	**274.5**	91.74	*10.39*	**78**
PF 48	**254.21**	62.39	*14.31*	**19**	**300.48**	94.05	*20.52*	**21**
AD Units	**5.022**	3.65	*0.31*	**136**	**5.38**	3.13	*0.27*	**133**
Mantel Cox for Mean Ad Units Life Table analysis: p = 0.3479								
GROUP 2								
PF max	**315.83**	88.35	*7.84*	**127**	**319.92**	82.45	*7.46*	**122**
T max	**20.21**	13.64	*1.21*	**127**	**22.89**	15.42	*1.4*	**122**
PF 24	**285**	90.11	*11.44*	**62**	**276.4**	93.5	*11.02*	**72**
PF 48	**255.63**	67.82	*17*	**16**	**307.37**	94.08	*21.72*	**19**
AD Units	**4.882**	3.68	*0.33*	**127**	**5.32**	3.04	*0.28*	**122**
Mantel Cox for Mean Ad Units Life Table analysis: p = 0.2309								
GROUP 3								
PF max	**318.5**	85	*8.07*	**111**	**321.7**	79.7	*7.89*	**102**
T max	**21**	13.8	*1.31*	**111**	**23.9**	15.9	*1.57*	**102**
PF 24	**286**	92.1	*12.2*	**57**	**276.3**	86.1	*11*	**61**
PF 48	**250**	62.8	*17.4*	**13**	**302.5**	94	*23.5*	**16**
AD Units	**5.054**	3.73	*0.35*	**111**	**5.382**	3.04	*0.3*	**102**
Mantel Cox for Mean Ad Units Life Table analysis: p = 0.3213								
GROUP 4								
PF max	**324.5**	87.6	*9.9*	**78**	**324.5**	79.5	*9.1*	**77**
T max	**20.35**	12.4	*1.4*	**78**	**25.2**	17	*1.9*	**77**
PF 24	**286.8**	99.6	*15.6*	**41**	**278.8**	92.2	*13.2*	**49**
PF 48	**233.3**	62	*20.7*	**9**	**293.3**	89.6	*23.1*	**15**
AD Units	**5.038**	3.62	*0.41*	**78**	**5.584**	3.17	*0.36*	**77**
Mantel Cox for Mean Ad Units Life Table analysis: p = 0.2077								

PF max= maximum peak flow; Tmax = time to PFmax; AD Units = admission units

8. DISCUSSION

These results show that in a large group of patients presenting with acute wheeze, the addition of ipratropium to a standard asthma regime had little impact on either the time taken to reach maximum peak flow or the duration of hospitalisation. In both cases the difference between control and trial groups was of the order of 3 hours. As this trial was primarily designed to display cost-effectiveness, one can look at the results as follows:

1. Cost of nebulizers: These were being given every two hours. For Group One the cost is as follows:

	Ipratropium	***Placebo***
Number of admission units	5.02	5.38
Hours (AdUnits x 6)	30.12	32.28
Number of nebs ([hours/2]+1)	16	17
Number of fenoterol nebs*	8	9
Number of ipratropium nebs	8	8
Cost of fenoterol (one neb= R0.24)	R1.92	R2.16
Cost of ipratropium nebs (one neb = R1.17)	R9.36	R0.00
Total cost of nebuliser solutions	R11.28	R2.16.

(*The first nebuliser given was always fenoterol)

It would thus cost an average of R9.12 more per patient to add ipratropium to the current asthma room regimen, for a saving of (5.38-5.02) x 6 hours = 2.16 hours on the admission duration. If a patient were to be charged by the hour according to the "private" scale of fees, this would in fact be cost-effective treatment for the patient. (Cost per hour = R12.04; for 2.16 hours = R26.00.[Personal communication, Groote Schuur Hospital Superintendent's office, 1992]) In a public service hospital, however, the true cost of bed

occupancy is far more difficult to ascertain, and a two-hour difference in occupancy is of marginal significance. At present patients are discharged from the asthma room at two times: late morning and late afternoon. From a logistic point of view, having more than two times of discharge during the course of the day would make little difference to the cost of a hospital stay, and would considerably increase the doctor and nursing workload.

2. Cost of other medication: The theophylline infusions were made up to run over 6 hours, and the methylprednisolone was given every 12 hours. Thus the cost of neither of these would be influenced by a change in hospital stay of two or three hours.

3. Duration of hospitalisation: It could be argued that failure to demonstrate a significant difference between the durations of admission of the trial and placebo groups might be due to inefficiency of the discharge procedure.However the trial was designed to evaluate efficacy of the trial preparation in a busy emergency room setting where more frequent than twice daily evaluations for discharge would not be feasible. Also, the lack of a statistically significant difference in time to maximum peak flow would suggest that this was not the case in the first three groups analysed. Although the difference was statistically significant in the fourth group (Those with a more than 100% improvement in peak flow), this difference of five hours was still less than the minimum time between discharge rounds.

Thus at whatever level one examines the cost-effectiveness in this study, use of ipratropium nebulisation between standard B_2 adrenoreceptor agonist doses cannot be justified in financial terms in a state hospital. It is important to emphasize that this trial was not designed to look at the short term efficacy of ipratropium, and generalisations beyond its use in our specific hospital situation cannot be made It appears likely that if case selections were made on the basis of (a) severity of airflow obstruction on admission

and (b)known capacity to reverse obstruction (i.e. true acute severe asthma), the benefits of the addition of ipratropium to routine therapy might have been more stiking. It is possible that ipratropium might prove as effective as one or other components of the standard regimen if used as replacement rather than in addition. In particular, it would be interesting to consider substituting it for intravenous theophylline in this regimen, particularly in view of the current decline in the popularity of theophylline for acute asthma.[35].

9. CONCLUSION

The addition of ipratropium nebulisation to standard therapy in the management of acute severe asthma in a routine emergency unit setting was not found to be cost-effective in this trial. It should be noted, however, that the known beneficial effect of ipratropium bromide in acute asthma was almost certainly obscured in a trial which attempted to add further therapy to a recognized efficacious treatment regimen. The effectiveness of ipratropium may have been diluted further in this clinical setting by the fact that many patients had only mild to moderate (<50%) reversibility of airflow limitation.

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DATA SHEET
ACUTE SEVERE ASTHMA
ATROVENT IN ACUTE ASTHMA TRIAL

1 Trial No:

Height 2
Weight 3
4
Year of birth 5 19.....
Sex M 1 F 2 6

Admission data

Date 7 __/__/19__
Time 0-6 (1) | 6-12 (2) | 12-18 (3) | 18-24 (4) 8
Adm. PEFR 9
2nd Adm.PEFR 10
24h PEFR 11
48h PEFR 12
Maint Sterold Y 1 N 2 13

Asthma Room

Max.PEFR 14
Hrs.to max. 15
Ventolin Infusion Y 1 N 2 16
Theophylline levels Day 1 17
Day 2 18
Day 3 19

Discharge

Date 20 __/__/19__
Time 0-6 (1) | 6-12 (2) | 12-18 (3) | 18-24 (4) 21
Ward Adm. Y 1 N 2 22
ICU Adm. Y 1 N 2 23

Comments _____

APPENDIX II

ASTHMA ROOM PROTOCOLS

The following extract is from the Groote Schuur Hospital Asthma Room management guide-lines:

"THERAPY:

a. All patients receive fenoterol by nebuliser, 1:4 ml saline, 4-hourly: in more distressed patients this can be given 2-hourly.

b. Distressed asthmatics should be given oxygen by face-mask (40%) when they are not using the nebuliser.

c. Aminophyllin: This drug should be used with extreme caution in patients:

1. who have been using theophylline-containing preparations prior to presentation;

2. with impairment of liver function;

3. with heart failure, since toxicity frequently develops. The administration regimen of aminophyllin is described below.

d. Intravenous salbutamol should be used in the following cases:

1. where aminophyllin is contra-indicated;

2. patients who appear not to have responded to aminophyllin infusion after 6 hours - this might be due to the fact that therapeutic aminophyllin levels have not been achieved, but no scientific basis for increasing the dose without knowing the theophylline level exists, or the patient appears to be resistant to aminophylline.

The administration regimen for salbutamol is described below.

e. methylprednisolone should be used in the following cases:

1. all patients who required prednisone (or other corticosteroid) treatment in the preceding 3 months as part of their maintenance therapy.

2. all patients who have been in the asthma room during the preceding four weeks.

3. all patients who fail to show a satisfactory response to the treatment outlined above within the first ONE hour after admission. "Satisfactory response" may be defined as improvement with regard to general state of distress, reduction of tachycardia and pulsus paradoxus and improvement of PEFR by 50% or more.

4. patients who, on previous admissions to the asthma room showed a slow response curve or required i.v. corticosteroids."

The dose of methylprednisolone is 125mg i.v. 12-hourly.

"Administration regimen for aminophyllin.

A. Loading dose regimen: Give 6mg/kg (ideal body mass) over 45 min to patients who have not taken any thoephyllin-containing preparation during the past 24 hours.

e.g. 350mg (14ml) for 60 kg patient or
425mg (17ml) for 70 kg patient.

If a history of some theophyllin ingestion at home is obtained, but this is judged to have been inadequate to obtain therapeutic blood levels, then half of the above loading dose may be given. If in doubt, go straight to the maintenance dose described below.

B Maintenance dosage: To be given as a 6-hourly infusion according to the patient's lean body mass and adjusted after 12 hours. Since the rate of excretion is slower in patients who do not smoke, are elderly, have liver or cardiac failure, different infusion rates apply to each category of patient.

1 Young adult smokers (<60yrs old) Maintenance 1.18mg/kg/hr.

e.g. 60kg patient, give 425mg (17ml) 6-hrly
70kg: 500mg (20ml) 6-hrly.

for 12 hours (i.e. 2 doses) then 0.94 mg/kg/hr

e.g. 60kg : 325mg (13ml) 6 hrly.
70kg : 400mg (16ml) 6 hrly.

2. Young adult non-smokers: 0.82 mg/kg/hr for 12 hours, then 0.59 mg/kg/hr

3. Elderly patients or patients with cor pulmonale: 0.71 mg/kg/hr for 12 hours, then 0.35 mg/kg/hr

4. Patients with congestive cardiac failure or liver disease: 0.59 mg/kg/hr for 12 hours, then 0.18 mg/kg/hr".

"Administration regimen for salbutamol:

Put 10 mg salbutamol in 1 litre saline (=10 micrograms per 1 ml) and use a 60 dpm microdropper giving set.

Loading dose of salbutamol: 0.285 micrograms/kg/min over 15 mins.

e.g. **60kg patient give 1.7 ml/min for 15 mins (25ml total)**
70kg patient give 2 ml/min for 15 mins (30ml total)

Maintenance dose of salbutamol:

5 microgram/min i.e. 30 microdrops/min (0.5 ml/min)"