Dexmedetomidine:

a phase I study to evaluate the pharmacokinetics and pharmacodynamics in paediatric patients

Thesis submitted for the Master in Medicine (Anaesthesia) degree, University of Cape Town

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DECLARATION

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Chapter One

Dexmedetomidine

Dexmedetomidine is a potent α_2-adrenergic agonist. The drug was registered early in the 2000's in the United States of America as *Precedex®*, for use as a sedative and analgesic agent in the intensive care unit setting.

The α_2 agonists were first developed for use as nasal decongestants.[4] As antihypertensives these drugs have been in use for more than 30 years.[20] Veterinary anaesthetists recognised the α_2 agonists' usefulness as sedative and analgesic adjuncts during the 1960's. In humans these drugs have not found common use apart from clonidine which has entrenched itself as an adjunct in regional anaesthesia. Clonidine's use as antihypertensive has declined due to adverse effects during use, and the rebound hypertension or hypotensive crises seen on sudden withdrawal.

As a group, the α_2-adrenergic agonists have diverse responses. As mentioned, they have been used as nasal decongestants and antihypertensives. Other effects include anxiolysis, sedation, analgesia and sympatholysis. This would indicate that the mode of action of this group of drugs is due to a whole host of effector mechanisms.

Dexmedetomidine is the pharmacologically active dextro-isomer of medetomidine and has a six to eight times higher affinity for the α_2-adrenoceptor than clonidine.[8] (Table 1)

Table 1 : Relative selectivity of α-adrenoceptor agonists

Dexmedetomidine (1300:1)	$\alpha 2$
Mivazerol (450:1)	▲
Guanabenz	▲
Guanfacine	▲
Clonidine (220:1)	▲
Xylazine	▲
Dopamine	▲
a-methylnorepinephrine	▲
Epinephrine	▲
Norepinephrine	▲
Phenylephrine	▲
Methoxamine	$\alpha 1$

Numbers in brackets indicate $\alpha 2$:$\alpha 1$ ratio

The mode of action of dexmedetomidine is at least partially mediated through post-synaptic α_2-adrenoceptors which, in turn, activate pertussis toxin-sensitive G-proteins. This leads to the inhibition of adenylyl cyclase, which results in the decreased formation of 3'5'-cyclic adenosine monophosphate

(c-AMP). A decrease in c-AMP is seen with almost all the α_2-adrenergic agonists, but this does not explain all of the drugs' effects.[20]

An alternative mechanism that has been proposed is a G-protein mediated alteration in ion exchange. The firing rate of excitable neuronal cells may be reduced by hyperpolarisation of the cell membrane through changes in potassium ion conductance. Neurotransmitter release may be decreased due to decreases in calcium ion conductance. A change in the sodium-hydrogen-ion exchange may cause alkalinisation of the interior of platelets, stimulating an increase in phospholipase A_2 activity. This, in turn, may be the explanation for the increase in thromboxane A_2 seen after α_2-adrenoceptor stimulation.[20]

As all clinically available α_2-agonists have an imidazole ring in their structure, it is at least possible that some of the effects of the α_2-agonists are mediated by the stimulation of the imidazoline receptor. This was thought to partially explain the central hypotensive and anti-arrhythmogenic actions of the α_2-agonists. Studies on genetically engineered mice have, however, shown that only the enhanced vagal tone seen after administration of α_2-agonists are due to the stimulation on the imidazoline receptor. The other cardiovascular effects of the α_2-agonists are thus probably mediated through the α_2-receptor.[19]

The three types of α_2-adrenoceptors known are named simply as α_{2A}, α_{2B}, α_{2C}. Stimulation of presynaptic α_2-receptors in sympathetic nerve endings and noradrenergic neurones in the central nervous system inhibits the release of noradrenaline. Postsynaptic α_2-receptors are distributed widely throughout the body.[20] Areas of particular interest will be noted in the discussion on the pharmacodynamics of dexmedetomidine.

Physical properties of Dexmedetomidine

Dexmedetomidine Hydrochloride is supplied in aqueous solution for infusion after dilution. In its pure physical form, it is an almost white powder, which is then combined with water (as the vehicle) and sodium chloride (to produce an isotonic solution). The final, sterile product is packaged in glass vials in a concentration of 100mcg/ml, and remains stable at a temperature of 25°C for three years. Some natural rubber products may absorb dexmedetomidine, and it is therefore advisable to use infusion sets manufactured from synthetic materials. (Abbott Investigator's brochure: Dexmedetomidine Hydrochloride)

Pharmacokinetics of Dexmedetomidine in adults

Intravenously administered dexmedetomidine has a short distribution half-life of 6-9 minutes and an elimination half-life of 2 hours. Dexmedetomidine exhibits a concentration-dependent non-linear pharmacokinetic profile.[20] The volume of distribution at steady state is 1.33L/kg and the clearance of the drug is 0.495L/h/kg.[3] Following an intravenous bolus though,

dexmedetomidine's volume of distribution and clearance decreases due to the vasoconstrictive action of the drug at high concentrations.[9]

The context-sensitive half-life of dexmedetomidine is said to be similar to that of fentanyl, but the authors[20] do not give their source and give no further data in this regard. Fentanyl is not an 'ideal' drug for long-term infusion compared to other drugs (e.g. remifentanyl) with more favourable context-sensitive half-lives. If dexmedetomidine does compare to fentanyl in this regard, one would have to take this into account during prolonged infusions of the drug. However, the data from a study on 10 intensive care patients who received dexmedetomidine (for a maximum of 16 hours) seem to indicate that the time from cessation of sedation to extubation had no relevance to the length of the infusion.[32] This may suggest a more favourable context-sensitive half-life for dexmedetomidine.

Dexmedetomidine is usually administered as a slow intravenous bolus (over 10 minutes) of 1mcg/kg, followed by a constant infusion of 0.2-0.7mcg/kg/h.

The intramuscular route has been investigated, and gives a reasonably rapid onset, with peak plasma concentrations at 15 minutes. The short elimination half-life of the drug makes it unlikely that this route will be accepted into clinical practice.

Dexmedetomidine is 94% bound to serum albumin and α_1-glycoprotein.[3] The drug is extensively metabolised by the liver to glucoronide- and methyl conjugates, which are eliminated mainly (95%) via renal excretion. It follows that patients with hepatic insufficiency will have markedly altered pharmacokinetics. A study in 5 patients with severe hepatic failure showed significantly increased volume of distribution (3.2L/kg) and elimination half-life (7.5 hours). Clearance in these patients was decreased at 0.32L/h/kg.[6]

In patients with severe renal disease, dexmedetomidine's volume of distribution at steady state and clearance were no different from the healthy control patients in the same study.[7] Patients with renal disease did, however, have a significantly shorter elimination half-life (113.4±11.3 vs 136.5±13.0 minutes). The patients with renal disease were sedated for a longer period (up to 60 minutes) than the control group (up to 35 minutes), but the authors unfortunately did not make any statistical comparison between the two groups in this regard. They commented that the decreased plasma protein binding in renal disease probably resulted in the more profound central nervous system effects, as dexmedetomidine has no known pharmacologically active metabolites which could be implied.

The pharmacokinetics of dexmedetomidine in intensive care patients has been investigated in a study on 10 patients who were electively admitted to the intensive care unit (ICU) after major abdominal or pelvic surgery.[32] All participants were expected to require a minimum of 6 hours post-operative ventilation. They received a loading dose of 2.5mcg/kg/h for 10minutes – a

dose equivalent to about 0.4mcg/kg – followed by an infusion of 0.7mcg/kg/h. Distribution half-life was similar to healthy volunteers at eight minutes but elimination half-life was prolonged (3.14 hours). Volume of distribution at steady state (V_{ss})(2.33L/kg) and clearance (0.65L/h/kg) were increased compared to the data published for healthy volunteers. The authors, however, compared their data with various sets of measurements supplied in the product leaflet for the drug. They concluded that there were no significant differences between their data and 'at least one set of measurements' in the product leaflet except for V_{ss} at steady state. They comment that the increased V_{ss} may be due to increased oedema formation as a result of the systemic inflammatory response.

Their conclusions must be read with caution, and may not hold true for all ICU patients. The study population were all elective admissions who needed a maximum of 16 hours of ventilation. Only patients with normal renal and hepatic function were included. None of the patients were reported to require any inotropic support, and none were septic. Comparison between 'some subjects' in their study and 'some subjects' reported in the product leaflet and proclaiming no difference between the two groups (except for V_{ss}) seems unscientific.

There has been concern that dexmedetomidine may inhibit the cytochrome P450 enzyme system, as *in vitro* studies suggest.[21,24,25] The clinical significance of this still seems unclear, as dexmedetomidine displayed reversible mixed (competitive/noncompetitive) P450 inhibitor activity, and was a less potent inhibitor than quinidine.[2]

An antagonist for dexmedetomidine, atipamezole, dose-dependently reverses sedative and sympatholytic effects of dexmedetomidine, with the further advantage that the two drugs have similar elimination half-lives.[26]

Pharmacodynamics of Dexmedetomidine

Although registered only for sedation and analgesia in the intensive care setting, dexmedetomidine exhibits a host of other clinically significant and possibly significant effects.

A. Central Nervous System

i)Sedation

Dexmedetomidine stimulates the α_{2A} receptors in the locus coeruleus of the brain stem, causing sedation. The drug has been used for over a decade in the pre-operative setting and to decrease intra-operative anaesthetic requirements. Renewed interest in the drug in recent years led to further investigation into its use as a sedative, with particular reference to use in the intensive care setting.[19]

In a study involving 7 healthy volunteers who received either placebo, or dexmedetomidine at an initial dose 6mcg/kg/h for 10minutes, followed by a 50minute infusion of either 0.2 or 0.6mcg/kg/h, dexmedetomidine caused significant sedation. Sedation was measured by bispectral index, visual analogue scale for sedation, and assessment by an observer. Analgesia was assessed with the cold pressor test and cognition tested with digit substitution and memory recall tests.[13]

In this study dexmedetomidine caused significant sedation in all subjects, but interestingly the degree of sedation did not differ significantly between the 0.2 and 0.6mcg/kg/h groups. At the end of the infusion period bispectral analysis scores decreased by 31% and 36% respectively compared to baseline scores. Also of interest is the finding that subjects' alertness "returned to baseline levels" when they were verbally or physically stimulated at the end of the infusion period.

Venn et al supported this latter finding regarding the quality of sedation noting that "patients are calmly and easily roused from sleep to allow excellent communication and co-operation while intubated and ventilated, and then similarly quickly return to sleep."[29]

In a much earlier study, Belleville et al reported no significant difference in sedation scores in patients who received either 1 or 2mcg/kg intravenously over a period of 2 minutes. They commented that sleep followed in most undisturbed subjects after a dose of 1mcg/kg. The sedative effect did however last longer in the patients who received 2mcg/kg, with the visual analogue scale for sedation in this group significantly higher at 195minutes.[2]

It is possible that the quality of sedation is linked to the modulation of spatial working memory via the α_{2A} adrenoceptor. Studies on rhesus monkeys have shown that α_2-agonists improve cognition via actions at post-synaptic α_2-receptors.[12] The Critical Flicker Fusion Test is a test of attentiveness, in which a (human) subject is asked to observe when a flickering light of increasing frequency becomes a fused line. In this test, no difference was found between dexmedetomidine and placebo treated subjects.[19,22] Unfortunately the authors of the latter articles do not quote their source, and it is not known at what plasma concentration level of dexmedetomidine this test was performed.

This scenario does not necessarily hold true in the clinical setting. A study on the effects of increasing dexmedetomidine concentrations in healthy volunteers[10] reported that patients with a dexmedetomidine concentration of 0.8ng/ml and higher lost their recall of a picture shown to them before the dexmedetomidine was administered. (The accepted loading dose of 1mcg/kg would result in a concentration level of 0.9ng/ml.)

Bustillo et al reported a small series of 5 patients undergoing endovascular embolization of cerebral arteriovenous malformations. All the patients were

given a dexmedetomidine infusion (either 1mcg/kg loading dose followed by an infusion of 0.2-0.6mcg/kg/h [2 patients], or 0.2-0.7mcg/kg/h infusion only [3 patients]) for the procedure and were 'comfortably sedated and breathing spontaneously'.[5] Although they were able to follow simple commands 10 minutes after the infusion was stopped, they could not undergo cognitive testing even at 45 minutes post-infusion. This contrasted sharply with patients who received propofol in the same setting – these patients were able to undergo cognitive testing 10 minutes after their infusion was stopped.

This small study is flawed in at least two ways though:

1) They administered fentanyl and midazolam to all the patients 'at the beginning of the case', with one patient receiving 300mcg of fentanyl and 6mg of midazolam, and all patients receiving *at least* 1mg of midazolam and 100mcg of fentanyl;
2) They compare the dexmedetomidine infusion to that of propofol, claiming that they could test the propofol patients cognitively, but do not give any further information regarding the propofol patients, and do not mention whether the propofol patients also received fentanyl and midazolam. If they did, then perhaps the study has some value in comparing propofol to dexmedetomidine as sedative drugs for invasive neurological procedures.

The claims of improved cognitive function – if they are true – thus still need to be proven. The study on recall in healthy volunteers implies that dexmedetomidine causes retrograde amnesia.

ii) Anxiolysis

The anxiolytic effect of dexmedetomidine is thought to be mediated through the α_{2C} adrenoceptor. Dexmedetomidine has been used as (intramuscular) premedication and to provide anxiolysis during regional procedures.[8]

Experimental work on mice with targeted inactivation of the α_{2C} adrenoceptor showed these animals to have an enhanced startle response and shortened attack latency in the isolation-aggression test. Conversely, if the genetic engineering brought about an overexpression of the gene that codes for the α_{2C} adrenoceptor, the mice showed opposite behavioural effects.

It follows that drugs acting via the α_{2C} adrenoceptor may be of therapeutic value in treating disorders associated with enhanced startle responses, for example attention deficit hyperactivity disorder, posttraumatic stress disorder, drug withdrawal states and schizophrenia.

iii) Reduction of agitation

Emergence agitation is a common side-effect of sevoflurane anaesthesia in children. Midazolam, fentanyl and ketorolac have been used in an attempt to diminish the agitation, but none consistently accomplished this. In a recent, non-blinded study 90 children randomly received either placebo, dexmedetomidine 0.15mcg/kg or dexmedetomidine 0.3mcg/kg intravenously after sevoflurane induction. [18] The authors showed a significant decrease in emergence agitation in the latter group receiving the higher dose of dexmedetomidine. The time to emergence from sevoflurane anaesthesia was slightly longer in the dexmedetomidine groups, but not statistically significantly so.

Dexmedetomidine has been used successfully in a patient with Acute Respiratory Distress Syndrome who required long-term sedation with lorazepam and fentanyl.[23] He developed withdrawal symptoms, characterised by a hypernoradrenergic state, when attempts were made to taper these drugs. Dexmedetomidine was added to his treatment regime on the grounds that it would lower sympathetic outflow. The patient was successfully weaned from his ventilator, and the fentanyl and lorazepam 5 days after initiating the dexmedetomidine infusion.

iv) Analgesia

The principle site for the analgesic action of dexmedetomidine is probably in the spinal cord, modulated via the α_{2A} adrenoceptor. There is, however, evidence of action at supraspinal and peripheral sites as well.

In ICU patients, a placebo-controlled, randomised, double blind study showed a 50% decrease morphine use in the post-surgical ventilated patients who received dexmedetomidine.[29] The patients received either placebo or a dexmedetomidine bolus of 1mcg/kg over 10minutes, followed by an infusion of 0.2-0.7mcg/kg/h to maintain a Ramsay score of greater than 2. In a separate study comparing propofol and dexmedetomidine for sedation if patients in the ICU, the propofol group needed three times more alfentanil than the dexmedetomidine group, while sedation scores for the two groups were equivalent.[31]

In an open-label study conducted in 25 centres in the United States of America and Canada on 295 patients after coronary artery bypass graft surgery, patients were randomized to receive either propofol or dexmedetomidine for sedation.[16] Only 28% of the dexmedetomidine patients required morphine for analgesia while ventilated versus 69% of patients receiving propofol ($p < 0.001$).

Alpha-2-agonists may have a role in neuropathic pain – their effect in this case may in fact be peripheral and not central, which opens the door to finding an α_2 agonist which does not cross the blood-brain barrier.

Analgesia after thermal injury remains a challenge. Clonidine has been shown to decrease fentanyl requirements in burns patients, but similar studies with dexmedetomidine have not been performed.

B. Respiratory System

Dexmedetomidine has been hailed as a sedative drug with "absence of respiratory depression".[8] It is, however, not entirely devoid of respiratory depressant effects.

In one of the earlier human studies – double blind and placebo-controlled - 37 healthy male volunteers received *either* placebo *or* 0.25, 0.5, 1.0 or 2.0mcg/kg over two minutes.[2] Effects on the respiratory system were measured by changes in p_aO_2, p_aCO_2, pulse oximetry, tidal volume and respiratory rate, and hypercapnic response.

Reporting the results of the respiratory parameters, the first comment made by the authors was that "immediately after the infusion there was a tendency for irregular breathing with short episodes of apnoea in some subjects." This event occurred in 7 out of 10 subjects in the 2mcg/kg group, and in 5 out of 6 subjects in the 1mcg/kg group. The apnoea was obstructive in nature in all subjects.

Interestingly, the greatest decrease in oxygen-haemoglobin saturation in the 1mcg/kg group occurred at 10 minutes after infusion, but only at 60 minutes after infusion in the 2mcg/kg group. Saturation levels decreased significantly from 98.5 ± 0.7% to 96.2 ± 1.3% in the 1mcg/kg group and from 98.3 ± 0.8% to 95.4 ± 1.2% in the 2mcg/kg group ($p<0.05$ for both groups). Four subjects were noted to have a saturation level of <94%, and the lowest saturation level measured was 91%. It was not noted how many of the 4 subjects reached this lowest level.

In the 2mcg/kg group the saturation levels remained significantly lower ($p<0.05$) until 150 minutes after the infusion, only returning to baseline levels at about 240 minutes after the infusion. Similar data for the 1mcg/kg group was not reported.

Resting minute ventilation decreased, with the maximum decrease in the 2mcg/kg group once again occurring at 60 minutes after infusion, corresponding with the timing of the maximum decrease in saturation levels in this group. At this time, resting minute ventilation decreased from a baseline of 8.73 ± 0.71 to 6.28 ± 1.49 l/min ($p<0.05$). Only after about 285 minutes after infusion did the resting minute ventilation in this group return to near baseline values.

In all groups, the decrease in resting minute ventilation predominantly reflected a reduction in tidal volume, with the respiratory rate only decreasing significantly in the 2mcg/kg group (from 17 ± 3.5 to 14.2 ± 2.1, $p<.05$)

End-tidal CO_2 increased statistically significantly (although probably not clinically significantly) in the 2mcg/kg group until 105 minutes after the infusion, with the maximum change at 10 minutes. Baseline $PaCO_2$ was 41.9±2.3mmHg, increasing to 46.1±5mmHg at 10minutes ($p<0.05$). In the 1mcg/kg group the change was also significant, but only up to 60 minutes after the infusion.

The slope of the response curve to increasing CO_2 (range 50-60mmHg end-tidal CO_2) was depressed in all groups. In the 2mcg/kg group this slope remained depressed even after 330 minutes, with a significant depression noted up to the measurements taken at 285 minutes.

In the previously quoted study by Hall et al none of the 7 subjects' saturation levels decreased below 95% in any of the dose groups, but there was a "statistically, but not clinically significant decrease" in the 0.2mcg group. Interestingly, this significance was not found for the 0.6mcg group. Respiratory rate was maintained in all groups. In the discussion on cardiorespiratory function, the end-tidal CO_2 was reported to have shown no dose effect. Unfortunately the individual data was not given, while the graph supplied suggests a definite difference in the drug groups as compared to the placebo group. The graph also suggests that the maximal change in end-tidal CO_2 occurred later in the higher dosage group compared to the lower dosage group.

The study by Ebert et al on increasing dexmedetomidine concentrations in 10 healthy volunteers reported their respiratory findings during the study in more detail.[10] They reported that the respiratory system remained relatively uncompromised, even at high doses. Their second (of seven) target was 0.8mcg/kg - equivalent to a dose just under 1mcg/kg – and their aim was 10 times that at 8mcg/kg, although only 2 out of the 10 volunteers reached this level. Measured PaO_2 remained at baseline (92±2mmHg) or higher for all the groups up to a dexmedetomidine concentration of 3.2ng/ml. (Seven out of the ten participants reached this level.) At a concentration of 5ng/ml, the PaO_2 of the 4 remaining participants dropped to 87±3mmHg, but then inexplicably increased to 100±21mmHg in the last 2 participants at a dexmedetomidine concentration of 8ng/ml (equivalent to a dexmedetomidine dose of 10mcg/kg).

The measured $PaCO_2$ increased statistically significantly in a stepwise fashion, but the increase was clinically rather insignificant. Baseline $PaCO_2$ was 43±1mmHg, increasing to 46±1mmHg at a concentration of 2ng/ml (9 participants) and 47±0 mmHg at the highest concentration. Respiratory rate increased (also in a stepwise fashion) from 14±1/minute at baseline to 25/min at the highest concentration.

In an ICU study in 33 postsurgical patients, patients who were expected to need at least 6 hours of post-operative ventilation were randomised to receive either dexmedetomidine or placebo.[30] All patients received a loading dose of the study drug, followed by a variable infusion to maintain a Ramsay Sedation score of 3 or more. Oxygen therapy was adjusted in the intubated and extubated patients to maintain 'satisfactory gas exchange'. Rescue medication consisted of midazolam and morphine during the intubated period, and paracetamol and midazolam after extubation.

Morphine requirements in the intubated patients were reduced by half in those receiving dexmedetomidine. This reduction was even more marked once the patients were extubated (0.003 ± 0.004 vs 0.008 ± 0.006mg/kg/hour; p=0.040) As the oxygen therapy was adjustable, it comes as no surprise that there was no difference in oxygen saturation levels between the two groups. No differences in respiratory rate or $PaCO_2$ were seen between the groups despite the marked difference in morphine requirements. However, if one calculates even the highest hourly morphine dose after extubation, it amounted to only 0.98mg/hour for a 70kg patient during the first 24 hours post-operatively. The authors comment that extubated patients were only sedated to a Ramsay Sedation score of 2 (awake, co-operative, orientated and tranquil) and that it would be ethically and practically difficult to gather data on more heavily sedated patients in the ICU setting. They state that we still do not have a clear dose-response curve for ill patients.

Of note was the significant difference in PaO_2:FiO_2 ratios between the 2 groups, with the dexmedetomidine group showing higher ratios for the intubated (p=0.037) and extubated (p=0.036) periods. The authors speculate about possible causes for this change, but conclude that – since this variable was not a primary outcome variable for the study – further investigation is needed in this regard.

C. Cardiovascular system

The dominant action of the α_2 agonists on the heart is mediated through blockade of the cardio-accelerator nerve and via a vagomimetic action.[19] Both would result in a slower heart rate, though not necessary in clinical bradycardia.

In the peripheral vasculature, α_2 adrenergic receptors mediate both vasoconstriction and vasodilatation. The vasodilatory actions are due to sympatholysis, mediated by the α_{2A} adrenergic receptor which inhibits firing of the locus coeruleus and decreases noradrenaline release. Inhibition of ganglionic transmission may further augment the sympatholytic effects. The vasodilatory effects usually occur at lower doses of the α_2 agonists.

Vasoconstriction is mediated through α_{2B} adrenergic receptors in the smooth muscle cells themselves, and is usually seen at higher α_2 agonists doses.[19] (There is some suggestion that the α_{2B} adrenergic receptors may be involved in the pathogenesis of essential hypertension.)

It follows that α_2 agonists can cause either hypotension or hypertension, and a biphasic response may be seen during intravenous administration.

Bloor et al published the cardiovascular data from the same double-blinded and placebo controlled study from which Belleville published the respiratory data (quoted previously).[4] In all dose groups, the heart rate decreased significantly within 1 minute of the start of infusion. In the 1 and 2 mcg/kg groups, this decrease remained statistically significant until the end of the study period at 330minutes after infusion (62 ± 9 vs 56 ± 9 and 57 ± 9 vs 53 ± 10 respectively.)

Mean Arterial Blood Pressure (MAP) decreased in the lower 2 dosage groups with the change becoming statistically significant at 10 minutes after the infusion (baseline MAP 96±10mmHg, decreasing at ten minutes to 85±15mmHg and 85±6mmHg for the 0.25mcg/kg and 0.5mcg/kg groups respectively). In the 0.25mcg/kg group the decreased MAP remained significant until 150min after the infusion, while in the 0.5mcg/kg group this period was 240minutes.

In the two higher dosage groups, a biphasic response was seen. MAP increased significantly at one minute post-infusion in the 1 and 2 mcg/kg groups, after which it decreased significantly. This decrease remained significant for the full period of study. In the 2mcg/kg group the baseline MAP was 95±11mmHg, at 1minute post-infusion the MAP was 118±12mmHg, and at 60 minutes 72±8mmHg. At 330 minutes the MAP was 82±8mmHg. The authors note that the peak of the increase in MAP occurred at 3 minutes post-infusion, but the exact values at this time are only displayed in graph format. The increases in MAP were therefore higher than reported above. The hypertensive response tapered off gradually, returning to baseline at 11±3 minutes in the highest dosage group.

Except for the 0.25mcg/kg group, cardiac output decreased significantly after dexmedetomidine infusion. The reduction was dose-dependent, reaching a maximum at 3 minutes after the start of the 2-minute infusion. The systemic vascular resistance at this time was double that at baseline.

In these 3 groups cardiac output increased after the 3-minute mark, with especially the highest dosage group showing a sharp increase in cardiac output from 3 – 5 minutes after the start of the infusion. Cardiac output remained significantly decreased in the 1mcg/kg group until the end of the study period, but for the 0.5 and 2mcg/kg groups the decrease remained for this time without being statistically significant.

Noradrenaline levels were measured on the arterial samples and were significantly lower than baseline in all groups. In the 3 highest groups, this change remained significant for the entire study period of 330 minutes. For the 0.25mcg/kg group the decrease remained significant until 285 minutes after infusion.

Three patients in the 2mcg/kg group had ECG abnormalities during the period of study. One subject had a R-R interval of 2.4seconds, although it is not noted for how many beats this persisted. Two subjects had episodes of junctional escape rhythm. The authors note that no medical intervention was required, that all three of these events occurred within minutes of the start of the infusion and were associated with an increase in blood pressure and decrease in heart rate.

In a study on the effects of increasing dexmedetomidine concentrations, Ebert et al showed similar changes in blood pressure as found in the previous study.[10] (Apart from an arterial line (used for measurement and sampling) participants had a pulmonary artery catheter inserted via their right internal jugular vein.) The lower dosage groups (dexmedetomidine concentrations of 0.5 and 0.8ng/ml) showed a 13% lower MAP than baseline, while the higher dosage groups' MAP increased by an average of 12%. Heart rate and cardiac output decreased in all groups by an average of 29% and 35% respectively. Central venous pressure (195%), pulmonary capillary wedge pressure (89%), mean pulmonary artery pressure (44%) and calculated pulmonary (155%) and systemic (67%) vascular resistance increased significantly at concentration levels above 1.9ng/ml (average individual maximum percent increases in brackets). Stroke volume only decreased at concentration levels above 5ng/ml.

Plasma noradrenaline and adrenaline levels decreased significantly at all drug concentration levels, and remained 60-85% lower than baseline for the entire study period. No mention was made regarding any ECG abnormalities. Baroreceptor sensitivity was tested by the response to a bolus dose of 100mcg sodium nitroprusside followed by a 200mcg dose of phenylephrine 1 minute later. The dexmedetomidine groups showed no change in baroreceptor sensitivity (as compared to their baseline reaction) during the hypotensive phase, but there was a significant potentiation of the response to phenylephrine.

In a clinical study by Talke et al using peri-operative dexmedetomidine infusions in patients undergoing vascular surgery, the authors reported a decrease in heart rate and blood pressure in all 3 dose groups compared to the placebo group.[27] This decrease continued through to the post-operative period. Intra-operatively, however, the dexmedetomidine group required more intervention to maintain haemodynamic parameters within predetermined levels.

In a different study Talke et al assessed the influence of dexmedetomidine on the response to emergence from anaesthesia.[28] The authors concluded that the drug attenuates increases in heart rate and systolic blood pressure during emergence.

The decrease in heart rate and sympatholysis may be beneficial in patients with myocardial ischaemia. Hynenen eg al enrolled 80 patients scheduled for elective coronary artery bypass surgery in a study to assess the influence of dexmedetomidine on perioperative haemodynamics and catecholamine levels.[17] The authors found greater blood pressure variability in patients receiving placebo, and a significant (and predictable) lower perioperative systolic blood pressure and heart rate in the dexmedetomidine group. They mentioned that the decreased pressure may in fact be detrimental, and that the significantly lower noradrenaline levels in the dexmedetomidine group have not been proven to change outcome.

In the same group of 80 patients Heikkila et al reported no difference in myocardial infarctions between the two groups, but noted that dexmedetomidine "tended to decrease the severity of ischaemia".[14] The dexmedetomidine group required less supplemental fentanyl, vasodilators and B-blockers, but more fluids and vasopressors to control hypotension. Interestingly, six patients in *both* groups required glycopyrrolate for bradycardia.

Dexmedetomidine clearly has significant cardiovascular effects, but whether and how this should be employed in the clinical setting remains to be proven.

D. Gastro-intestinal system

Dexmedetomidine reduces salivary secretions and causes xerostomia.[3,19] Nausea has been reported, but to date no significance difference between dexmedetomidine and placebo has been shown.[3]

An *in vitro* study on guinea pig ileum showed that dexmedetomidine potently inhibits peristalsis on the basis of its interaction with the α_2-adrenoceptor.[15] To date, no reports of this potentially problematic side-effect have been made in humans.

E. Renal

Stimulation of α_2 adrenoreceptors causes a decrease in the secretion of vasopressin and antagonises its effect on renal tubules. It may inhibit the release of renin and increase the production of atrial natriuretic factor, but the diuretic action is reported to be mild.[20]

F. Post-operative shivering

Post-operative shivering was reduced in patients scheduled for elective abdominal hysterectomy who received intramuscular dexmedetomidine as premedication, as compared to the group who received midazolam.[11]

G. Placental transfer

Dexmedetomidine crosses the placenta, but not to the same degree as clonidine.[1] Effects on the foetus and use during pregnancy have not been studied to date.

Drug Registration

As in the United States of America, Dexmedetomidine is registered in South Africa as Precedex®. In the USA, it is registered for ICU sedation for 24 hours, while in South Africa it is registered only for use in ICU patients who had coronary artery bypass grafts. Precedex® will be launched in South Africa in March or April 2004 at an estimated cost of R500 per 200mcg ampoule. Packaging will be in 5x2ml ampoules.

In summary, dexmedetomidine is a potent α_2-adrenergic agonist with sedative and analgesic effects. It causes minimal respiratory depression. Its haemodynamic effects are variable, and it may cause hypo- or hypertension and bradycardia, while it has little effects on other organ systems. Dexmedetomidine's characteristics make it a good addition to the selection of sedative drugs available for use in the intensive care setting.

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Chapter 2

Sedation in the intensive care unit

The hospital environment is a stressful one. Patients find themselves there in a state of uncertainty and fear, anxious about the procedures planned, about possible complications, about pain which may be inflicted on them, and about the unexpected and unknown. They are faced with their own mortality.

In the intensive care unit (ICU), these fears escalate. Emotionally, the mortality they faced when entering the hospital is now a very real entity – the ICU is a 'last bastion' in the hospital environment. In addition, patients are subjected to tubes or probes inserted into various orifices, to cannulation of veins and arteries, to procedures such as tracheal and bronchial suctioning with or without physiotherapy, and to artificial ventilation.

Sedation is administered to patients to reduce this emotional trauma and the stress response to the various interventions, to improve tolerance of mechanical ventilation, and to facilitate nursing care. Given the frequency with which sedative drugs are administered in the ICU, one would expect intensive care units to have set measurements of sedation and regimens according to which a particular drug or drugs would be administered. Unfortunately, the literature tells a different story of random usage, of poor ability to assess sedation, of lack of evidence for the superiority of any specific drug, and of cost implications which could render any such evidence, had it existed, practically useless. In addition, no drug is without side-effects, and this is certainly also true of sedatives administered to already critically ill patients.

The ideal scenario would be one where the various components of sedation are easily and meaningfully assessed in order to administer a drug specific to the patient's needs. This drug should have rapid onset of action, should be titratable, provide predictable and effective sedation which will wear off rapidly once administration of the drug is discontinued, have few or no adverse effects or drug-interactions, and be cheap.[53]

As with so much in medicine, this ideal scenario is far from the reality in the ICU. This chapter will aim to explain some of the difficulties in assessing sedation and will look at the various drugs at our disposal, their advantages and disadvantages and the problems in comparing the different drugs in the ICU environment.

Assessing sedation in the intensive care unit

In an editorial in Critical Care Medicine in 1999, Lieberman and Tremper noted that "If you do not know where you are going, any road will get you there." [43] They pointed out the inadequacy of currently used sedation scales – some of which will be discussed below. A possible reason for this problem may be that sedation is not a number as in respiratory rate or mean blood pressure. Rather, sedation is a state of mind of which an assessor can but provide an impression.

Probably the most widely quoted sedation scale is that which Ramsay published in 1974 (Table 1).[60] This sedation scale was developed for use in a trial assessing sedation with alphaxolone-alphadolone (Althesin) – a drug no longer in use due to the high incidence of anaphylactoid reactions associated with its use.

Table 1 - The Ramsay sedation scale

	score	Description
Awake levels	1	Patient anxious and agitated or restless or both
	2	Patient cooperative, oriented and tranquil
	3	Patient responds to commands only
Asleep levels	4	Brisk response to a light glabellar tap or loud auditory stimulus
	5	Sluggish response to a light glabellar tap or loud auditory stimulus
	6	No response to a light glabellar tap or loud auditory stimulus

The scale seems easy to use, with only 6 possible categories into which a patient may fit. This probably accounts for its widespread use despite the fact that it has never been validated.[29] Anyone who has assessed sedation according to this scale, will understand that the descriptions are rather vague and that scoring would be difficult to accurately replicate. Some patients would be difficult to score according to the simple structure – how would one score a patient who required a glabellar tap or loud auditory stimulus to wake up, but then became anxious and agitated? If a patient responded to commands only, could he or she not be seen as cooperative, oriented and tranquil too? How loud is a loud auditory stimulus? Considering this, it would be difficult or even impossible to validate this easy-to-use score. In an editorial, Shapiro suggested that any score requiring patient stimulation would be inherently inconsistent.[72] While this may seem harsh criticism, it is correct on a purely objective basis. The only exception may be standardised stimuli like that used in auditory evoked potentials.

Harris developed a scale for use in a trial using propofol for sedation.[30] (Table 2) This scale is only applicable to ventilated patients and requires assessment of 3 different categories, each having between 4 and 6 possible variables – a total of 14 different descriptions to be remembered by the assessor. It seems to be, however, a more accurate way of describing the quality of an ICU patient's sedation, exactly because it uses more variables. As with the Ramsay sedation

score, the Harris sedation score has not been validated. Similar objections raised with regard the Ramsay scale's vague descriptions may be brought against the Harris scale's descriptions: how rapid is a rapid recovery (with regards category C), when is a patient fighting the ventilator and when is one unable to ventilate the patient (category B)?

Table 2 – the Harris Sedation Scale

A.	General condition	
	1	Confused and uncontrollable
	2	Anxious and agitated
	3	Conscious, oriented, calm
	4	Asleep but rousable to speech, obeys commands
	5	Asleep but responds to loud auditory stimulus or sternal pressure
	6	Unrousable
B.	Compliance with mechanical ventilation	
	1	Unable to control ventilation
	2	Distressed, fighting ventilator
	3	Coughing when moved but tolerating ventilation for most of the time
	4	Tolerating movement
C.	Response to endotracheal suctioning	
	1	Agitation, distress, prolonged coughing
	2	Coughs, distressed, rapid recovery
	3	Coughs, not distressed
	4	No cough

The "COMFORT" scale was developed specifically for use in paediatric intensive care patients. This complex scale rates eight dimensions, each on a 5-point scale, thus giving a possible total of 40 points.[6,17] (Table 3) Adequately sedated patients would have a score of between 17 and 26. The scale cannot be used on head injury patients and patients receiving neuromuscular blockers. An advantage is that repeated disturbance of the patient is not required in the recommended 2-minute assessment period. The scale is also one of the few to have been validated.[47]

Table 3: The Comfort Scale's Parameters

1. Alertness	5. Blood pressure
2. Calmness/Agitation	6. Heart rate
3. Respiratory Response	7. Muscle Tone
4. Physical Movement	8. Facial Tension

In 1994, the "Sedation-Agitation Scale" for adult patients in the ICU was published.[64] The authors felt that agitation was a specific problem in the ICU which had not been included for evaluation in any other sedation scale. They devised a 7-point scale (Table 4) which they initially applied to patients in a haloperidol study. They then revised the scale and tested it for interrater reliability, comparing it to the Ramsay and Harris scales.[65] The revision involved eight experienced ICU nursing staff members who, together with a physician,

jointly assessed patients' sedation. By discussing their disagreements, they fine-tuned the descriptions in the various categories.

Table 4 – the Sedation-Agitation Scale (revised)

7	Dangerous Agitation	Pulling at ET tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing side-to-side
6	Very Agitated	Does not calm, despite frequent verbal reminding of limits; requires physical restraints, biting ET tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
4	Calm and Cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very Sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unrousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

In the actual assessment part of the study, 45 patients were simultaneously assessed 69 times by pairs of the 9 evaluators, resulting in 138 (69x2) observations. The 9 evaluators had not been part of the group who refined the scale. The pairs of evaluators assessed each patient according to the Ramsay, Harris and Sedation-Agitation Scale (SAS). The authors found that the SAS correlated with the other two scales and concluded that the SAS scale was both reliable and valid, and – in addition – provided clearer details regarding the state of agitation of the patients.

In their editorial comment on this study, Lieberman and Tremper noted that the SAS failed to discriminate between ventilated and unventilated patients.[43] They felt that this would be the most obvious way of grouping ICU patients, before one even started the sedation assessment, as the goals and risks of sedation in each of these patient groups differed.

In 1999 a Belgian group – feeling the need for a simple-to-use scale - developed the Brussels Sedation Scale.[20] (Table 5) Levels 1 and 2 were considered as 'oversedation', levels 3 and 4 as 'correct sedation', and level 5 as 'undersedation'. They evaluated the "clinical usefulness" of the scale with emphasis on whether it would modify the management of sedation and avoid excessive or insufficient sedation. The study was done in two phases on ventilated patients only, while comatose patients and those requiring deep levels of sedation were excluded.

In the first phase, the principal investigator independently estimated the level of sedation of 31 patients using the Brussels scale. This was done while the ICU

team continued to sedate the patients "as normal" although the team knew that a sedation study was in progress. In this ICU's case "as normal" meant that patients were sedated "based on clinical evaluation" (no further details supplied). The second phase took place after the ICU team was trained in the use of the Brussels sedation scale and asked to manage sedation accordingly. The principal investigator once again estimated the level of sedation of each of the 24 patients, having no access to the sedation sheets used by the ICU team.

Table 5 – the Brussels sedation scale

Level	Description
1	Unrousable
2	Responds to pain stimulation (trapezius muscle pinching, but not auditory stimulus
3	Responds to auditory stimulus
4	Awake and calm
5	Agitated

For each patient included in the study, the lowest, highest and mean sedation levels were determined on a daily basis. The authors reported no significant differences in mean or highest level in patients between the two phases, but showed a significant decrease in patients sedated to the lowest level in the second group (this was incorrectly reported in the summary as an increase). They interpreted this as an indication that using the Brussels scale significantly reduced the number of patients who were excessively sedated.

This study only incorporated ventilated patients, and has not been tested on unventilated ones. Interrater variability has also not been tested. Furthermore, the same difficulties noted with the Ramsay scale (to which it is rather similar) may be experienced when using the Brussels score.

In their editorial on the measurement of sedation in the ICU, Rosser and Bion commented on the Brussels scale, noting that the application of a simple scoring system may be helpful in changing the management of sedation.[67] They emphasise that it is not so much the scoring system that is important, but rather the "translation from measurement to effective action which counts". They also criticise the notion that sedation is needed for all ventilated patients and note that not all 'comfort care' is drug related. They comment that the assumption that ventilated patients need sedation is a major contributor to the oversedation of ICU patients.

It is not clear from their comments whether they would necessarily agree or disagree with Lieberman and Tremper's statement that sedation score studies should discriminate between ventilated and unventilated patients. The two

groups of editorial authors certainly do agree on one aspect – the need to show that assessing sedation has a significant impact on patient management.

In this regard, the UK Intensive Care Society's guideline on sedation has been shown to have a significant effect on total sedative use. Saitch et al audited sedative use and cost over a period of 3 months in 3 intensive care units after the introduction of the society's guideline. They compared this period with the same 3 months in the 2 preceding years, and found that the sedative cost per ICU bed after the guideline introduction was significantly decreased.[68]

Patient outcome seems more difficult to link directly to the use of a single score or guideline, and – until a few years ago – there was little data on this issue. Reasons for this probably include the issues with sedation scores that have already been highlighted. Furthermore, the difficulty of performing studies in a clinically stressful environment on potentially unstable patients presents both practical and ethical obstacles, even when using simple scales. The ICU population is a relatively small one, and this further complicates the gathering of statistically meaningful data.

In recent years, however, studies to determine the impact of sedation assessment in ICU patients on outcome have found both clinical and financial benefits. Burns et al reported a statistically significant decrease in ventilator duration, length of ICU and hospital stay and mortality rate after the implementation of sedation and weaning guidelines and sedation assessment. They claimed that the implementation of the guidelines resulted in a total saving of $3million in 510 patients over a period of 12 months.[13] Brook et al reported statistically significant reductions in ventilator time (28%), ICU stay (30%) and tracheostomies (53%) after the implementation of a protocol for sedation.[10]

It seems from these studies that the implementation of a protocol for assessment of sedation and thus the use of sedatives indeed influence patient outcome. Unless evidence to the contrary is found, it would be considered mandatory to monitor sedation in all ICU patients. Whether the specific sedation scale used is of importance remains to be seen.

Some authors have proclaimed the Bispectral Index (BIS) Monitor as a valuable tool in assessing sedation in the ICU.[7,73] The Bispectral Index was derived from the bifrontal electro-encephalogram collected from more than 5000 patients undergoing anaesthesia.[52] The data was converted into a linear numeric index with 0 representing an iso-electric EEG and 100 representing a fully awake patient. Although this monitor assesses level of consciousness without the intervention of the caregiver (i.e. no stimulus needs to be applied), its value as an ICU sedation monitor has been questioned.

The revised Sedation-Agitation scale (SAS) was compared to BIS monitoring in 63 adult patients who were selected at the investigators' convenience.[73] The authors, Simmons et al, concluded that the 'average BIS values correlated well with SAS', but that the correlation between subjective and objective scales were better for trauma patients than for patients who underwent general or cardiac surgery. The latter finding could not be explained.

Another study, also on a convenience sample of 20 ICU patients, found that the correlation between the SAS and BIS scores was 'suboptimal and inconsistent'.[52] The authors were critical of the conclusions in the study by Simmons et al, noting that the Simmons data actually showed even poorer correlation between the two scores than that found in their own study.

A study in the paediatric ICU population by Berkenbosch et al[7] compared three different sedation scales to the BIS score. They classified patients into three categories - inadequately, adequately or over-sedated - according to the sedation scales, and compared the scores within these categories to the BIS score. They found that the BIS score reliably differentiated between the inadequately and adequately sedated groups, but that it failed as a measure between the adequately sedated and over-sedated groups.

Another study in the paediatric ICU by Courtman et al compared BIS scores to the Comfort Score.[17] They found moderate correlation between the two scores, also noting that BIS was able to discriminate between light and deep levels of sedation, but not between deep and very deep levels. This finding seems similar to that of Berkenbosch et al.

Courtman points out that the BIS monitor was not designed for children, and that the EEG in children changes over the first 15 years of life, when the central nervous system reaches maturity. There are a number of studies which show that the BIS monitor is difficult to use as an indicator of clinical end points in anaesthesia in the paediatric population, especially in infants.[5,15,18]

A further finding in the Courtman study was the absence of a specific BIS value at which tracheal suctioning would not result in an unpleasant stimulus for patients. Tracheal suctioning is a painful and stimulating procedure, and such procedures were singled out as the events resulting in the most frequent negative recollections of children treated in the ICU.[58]

Overall, the BIS monitor does not seem to be the answer to scoring sedation in the ICU, except maybe for the group of patients who require neuromuscular blockade.[66] The clinical sedation scores are useless in these patients, and – as up to 36% of them have recall of this time – it seems prudent to attempt to sedate them according to another measurement. The BIS monitor seems to be that monitor, at least for the time being.

One may expect more studies in this regard in the near future for two reasons: 1) The issue of objectively monitoring sedation in the ICU, and the question surrounding the influence of sedation on the outcome of ICU patients need to be clarified, and (2) since it would make economic sense for the manufacturers of the BIS monitors to have these monitors installed in more intensive care units, they will no doubt support further studies.

Sedatives in the intensive care unit

Although one could be tempted to reach for the closest ampoule when standing next to the bed of an obviously anxious ICU patient, it has to be emphasised that pharmacological means of sedation is not 'first line-treatment'. Various aspects of patient comfort need to be addressed first, and good communication with patients is vital. The ICU team need to attempt to understand the reason for the discomfort – is it pain, is it something as simple as a wet sheet or is it anxiety? A patient-friendly environment (this includes keeping noise levels to a minimum and attempting to keep a normal day-night rhythm) with caring and efficient staff members is indispensable in keeping patients calm and comfortable.

In reaching for the closest ampoule, the next question should be what it is that needs to be treated. This is a question the authors of the COMFORT scale tried to address by scoring pain, sedation and agitation (or delirium) separately. Each of these problems should be addressed separately with an appropriate drug. There may be some overlap between drug classes, in that both opiates and antipsychotics provide some degree of sedation, and – as such – all three classes will be discussed in the following section. A drug that would probably fall into both the sedative and analgesic classes, dexmedetomidine, was discussed in the previous chapter.

Sedatives and anxiolytics

A. Benzodiazepines

The benzodiazepines act on their own receptors, which in turn act on the gamma-aminobutyric acid (GABA) receptors in the central nervous system.[84] This increases neuronal chloride conductance which results in hyperpolarization. Benzodiazepines also act via glycine-mimetic effects in the spinal cord and brainstem. As GABA receptor occupancy increases, the effects range from anxiolysis, sedation and elevation of seizure threshold, and hypnosis. Other effects of benzodiazepines include anterograde amnesia, muscle relaxation,

respiratory and cardiovascular depression and a decrease in cerebral metabolic rate. Importantly, benzodiazepines have no analgesic action.

Benzodiazepines are generally classified according to the duration of their action (Table 6). It should be kept in mind though that other factors, e.g. co-administration of other sedatives or opiates, or impaired metabolism as would occur in the elderly or in those with organ failure, could significantly prolong their effects.

Table 6 – Classification of benzodiazepines

Duration of action	**Examples of Benzodiazepines**
Ultra short	Midazolam, triazolam
Short	Oxazepam, temazepam, loprazolam, lormetazepam
Intermediate	Alprazolam, bromazepam, lorazepam
Long	Diazepam, flunitrazepam, nitrazepam, clobazam

A limited number of benzodiazepines are available in injectable form – in South Africa these are diazepam, lorazepam and midazolam. This obviously limits the choice in those ICU patients who cannot absorb from their gastro-intestinal tract. In those whose digestive tracts function, the oral form should always be considered, at least to provide baseline levels of sedation, as it is considerably cheaper than the intravenous form.

Diazepam

Diazepam is a long-acting benzodiazepine which is highly lipophilic, and therefore requires solvents as vehicle for the intravenous form.[85] The solvents may be the cause of the local complications like pain on injection, thrombophlebitis and venous thrombosis. It is not suitable for intramuscular use, as intramuscular injection is very painful, and the absorption from this site is erratic and unreliable. The oral form is well absorbed, reaching peak concentrations within 2 hours.

After intravenous administration, the distribution half-life is around 30-40 minutes, but the elimination half-life is prolonged at 20-100 hours.[4] The elimination half-life of desmethyldiazepam, the major active metabolite of diazepam formed by demethylation in the liver, is in the order of 100-200 hours.[85] Hydroxylation of diazepam forms N-Methyloxazepam, which in turn is demethylated to oxazepam. Oxazepam has a much shorter half-life of 6-20 hours.

The long half-life of diazepam and desmethyldiazepam leads to accumulation after repeated doses. As such, it is not an ideal drug for sedation in the ICU, but

is still used, as it is cheap. It may also be used where patients have become tolerant of shorter-acting benzodiazepines. It is administered as boluses, and not as an infusion. Diazepam is highly protein bound (98%) and causes no hepatic enzyme induction.[84] Drug-interactions occur with other central nervous system depressant, like alcohol, where a synergistic effect should be expected. Opiates, in particular, should be used with great care when administered together with benzodiazepines, as the resultant respiratory and cardiovascular depression may be sudden and marked.

The already long half-life of diazepam and desmethyldiazepam may be prolonged even further in the elderly and in patients with liver disease. In this regard, it is important to note that diazepam's metabolism occurs by microsomal oxidation, a process which is easily depressed by factors such as age, cirrhosis and liver enzyme inhibition.

Cimetidine and disulfiram inhibit hepatic enzymes and thus prolong the elimination half-life of diazepam and desmethyldiazepam. Tolerance and dependence occur with chronic use of diazepam, as with all benzodiazepines.

Lorazepam

The pharmacodynamics of lorazepam is similar to that of diazepam, but pharmacokinetically there are a few differences of note.

At about 3 minutes, lorazepam's distribution half-life is shorter than that of diazepam or midazolam. This is probably a reflection of its lower lipid solubility, being less lipophilic than the other two benzodiazepines.[45] It also has the lowest protein binding of the three, at about 90%. Its terminal half-life is in the order of 10-18 hours.[4]

Lorazepam is metabolised in the liver by glucoronide conjugation, a process much less sensitive to liver disease and age than oxidation. The inactive metabolite is excreted renally.[2] As such, it is the safer drug to administer to the elderly and to patients with liver disease.

Onset of action after intravenous administration of lorazepam is very slow at 20-40 minutes, although other sources state this time to be closer to 2 minutes[62] or 10-20 minutes.[14] (It is for this reason that Lorazepam cannot be used as anaesthetic induction agent.) Similarly, peak levels after oral administration (despite good absorption from the gastro-intestinal tract) are only reached within 3 hours. Lorazepam is better absorbed after intramuscular administration than diazepam, but is still painful, and should be avoided. The drug is also available for sublingual administration.

Midazolam

Midazolam is a water-soluble benzodiazepine with an imidazole ring. In vivo, however, it is highly lipid soluble. These seemingly contradictory characteristics are the result of the benzodiazepine ring of midazolam which opens at pH values of less than 4, and closes in less acidic surroundings. The open-ring structure is hydrophilic, the closed-ring structure lipophilic.[22]

Midazolam is formulated in the aqueous form, buffered to a pH of 3.5 and without the need for solvents. At physiological pH, the benzodiazepine ring closes, and the drug becomes highly lipid-soluble – more lipid-soluble than diazepam. As a result, a bolus dose crosses the blood-brain-barrier very rapidly, causing sedation within 1-2 minutes. Distribution half-life is 6-30 minutes and elimination half-life 1-4 hours.[45]

The pharmakokinetics of midazolam in critically ill patients is different from that in healthy patients though, with the elimination half-life and volume of distribution considerably increased.[21,46] This is particularly true in septic patients with impaired liver blood flow.

Intramuscular administration is possible and is less painful than the other two benzodiazepines mentioned here. Oral absorption is hampered by substantial first-pass hepatic extraction, and so the oral dose is considerably higher than the intravenous dose. Effect after oral absorption is nevertheless good, and it is often the oral sedative of choice in children, where clinical effect is seen within about 20 minutes. The oral midazolam dose for sedation in children is generally given as 0.5mg/kg, but is inversely related to age, so that the dose is usually decreased slightly for older children.[35]

Midazolam undergoes oxidation-reduction reactions in the liver, making it sensitive to factors like age and liver disease. The fused imidazole ring is oxidised very rapidly by the liver, and this leads to very rapid clearance when compared to diazepam and lorazepam (which have diazepine rings). The metabolites, 1- and 4-hydroxy-midazolam, have some pharmacological activity but this is clinically not significant. The two metabolites are conjugated and excreted in the urine.

Midazolam's effects on the cardiovascular system seem to be slightly greater than that of diazepam and lorazepam. Blood pressure changes are reported to be 'minimal' and are equated with that of thiopentone.[42]

Respiratory depression after midazolam administration seems to be more marked than that seen with diazepam. The depression is dose-dependent, and there is

synergism with the opiates. The combination of opiates with midazolam may produce particularly rapid-onset apnoea.

B. Propofol

Despite having been in use for more than 15 years, propofol (2,6-di-isopropylphenol) remains the youngest member of the anaesthetic induction and sedative agent family.[41] It is highly lipid-soluble, and is formulated in soybean oil, glycerol and purified egg phosphatide.[49]

It is only available for intravenous use. After an intravenous bolus, the peak effect is at about 90 seconds. Propofol is rapidly distributed to the brain and other tissues, with a distribution half-life of 2-8 minutes.[45] Volume of distribution is high at 1.84-11.9 L/kg during steady-state, as is clearance at 18-28ml/kg/min.[76] The clearance exceeds hepatic blood flow, and extrahepatic metabolism has been demonstrated during the anhepatic phase of liver transplants.[40] It has been suggested that propofol is partially metabolised by non-specific esterases. The elimination half-life of propofol, when using a two-compartment model, is about 1-3 hours, but this increases to 3-6 hours (some sources say 4-23.5 hours) when a three-compartment model is used. This longer elimination half-life reflects the elimination of propofol from the deep, highly lipophilic compartment with limited perfusion.[76]

Pharmacokinetic studies in children have found the elimination half-life of propofol to be 209min, the volume of distribution at steady-state between 5 and 10 L/kg and the clearance between 30 and 40ml/min/kg.[34,36,69] Studies in critically ill children have found that infants have an increased volume of distribution due to a larger deep compartment, but that propofol pharmacokinetics varied greatly between the paediatric subjects.[61,63]

The context-sensitive half-life of propofol is favourable to its use for continuous infusion. After a prolonged infusion, the context-sensitive half-life in adults is about 50 minutes.[76] In children, the context-sensitive half-life of propofol has been shown to be shorter in infants than in older children.[63] Rigby-Jones et al showed that infants awakened sooner than their older counterparts, but took longer to recover completely. They attributed this latter effect to slow redistribution from the relatively larger deep compartment of the infants.

Metabolism in the liver occurs by glucuronidation and sulfation, with the resultant water-soluble metabolites being excreted in the urine. As such, hepatic or renal disease does not influence the pharmacokinetics of propofol much. Renal disease seems to have no influence,[38] whereas liver disease results in an increased distribution volume, unchanged clearance and a slightly prolonged elimination

half-life.[71] The elderly do require dosage reductions, as volume of distribution and clearance are reduced in this patient group.[37] The studies on the effect of fentanyl on propofol pharmacokinetics are conflicting – some show a decrease in volume of distribution and clearance of propofol, some show a reduction in propofol's half-life, and others show no effect.

Considering the extent of use of propofol for sedation in intensive care units – 35% of European intensive care units preferred this agent[77] - there are surprisingly few studies on the pharmacokinetics of propofol in critically ill patients. McMurray et al showed that patients who were admitted to the ICU following cardiopulmonary bypass had a prolonged elimination half-life for and reduced clearance of propofol.[50] Similarly, Albanese et al reported a prolonged elimination half-life and found that the volume of distribution of propofol was increased in intensive care patients.[1] They commented that the clearance of propofol was high in this group, but quote a clearance value of 1.57±0.56L/min, which is similar to that in healthy volunteers.

Concern has been expressed about the high lipid load received by patients sedated by long-term infusions of propofol. Lipid tolerance may be impaired in these patients, and – if they receive fat emulsions in their parenteral nutrition as well – the fat load may exceed their capacity to metabolise the fat load. Close monitoring of serum triglyceride concentration is therefore recommended.[3,44]

Propofol is a hypnotic which probably acts via facilitation of inhibitory neurotransmission mediated by GABA.[45] It has no analgesic properties, but – in subhypnotic doses - has antiemetic, antipruritic and anxiolytic effects.[11] It has been used in the treatment of epilepsy and tetanus, the former despite initial reports of proconvulsant effects.

Propofol decreases systemic vascular resistance due to inhibition of sympathetic vasoconstrictor activity and causes myocardial depression.[25] The resulting hypotension is more than that seen with thiopentone. In addition, the heart rate does not increase significantly in response to the hypotension, as propofol impairs the baroreflex response. The combination of a drop in systemic vascular resistance and a (relatively) slow heart rate may lead to a marked drop in cardiac output, particularly in the elderly.

Respiratory depressant effects of propofol are evident even in subanaesthetic doses. It inhibits both the hypoxic and hypercarbic ventilatory drives. Induction doses give rise to apnoea, with the reported incidence of apnoea varying between 25 and 100%. Maintenance doses of propofol (100mcg/kg/min) depresses tidal volume by 40% and increases respiratory frequency by 20%, but the resulting change in minute ventilation is reported to be unpredictable. Doubling this infusion rate caused a further moderate change in tidal volume,

with no further change in respiratory rate.[26] The depression in the carbon dioxide response curve during the same maintenance dose is equivalent to that of 1 MAC of halothane. Propofol depresses laryngeal reflexes, reducing the incidence of post-induction laryngospasm and assisting with the insertion of a laryngeal mask.

Current formulations contain disodium edetate or sodium metabisulfite which retard the growth of micro-organisms. These substances do not, however, comply with United States Pharmacopeia standards regarding microbial inhibitors,[75] and ampoules should be discarded within 6 hours of opening. Aseptic techniques should be employed when opening glass ampoules, or when aspirating the drug though the rubber stopper of the larger vials.

Allergic reactions may occur, but are rare. Most of the reactions occur in individuals with multiple drug allergies. The reactions may be triggered by either the propofol itself, or by the carrier/lipid emulsion. Contrary to some teachings, patients with allergies to egg usually have no reaction to propofol. This may be explained by the fact that egg allergy is usually against the egg albumin, whilst the egg lecithin in propofol is extracted from egg yolk.

Propofol causes pain on injection in a large percentage of patients. It may be diminished by injecting into a large vein, by injecting slowly, and by mixing lignocaine with the propofol before injecting it.

The controversy surrounding the use of propofol for sedation in children is addressed in the section "Sedation in the Paediatric Intensive Care Unit"(p19).

C. Isoflurane

This volatile anaesthetic agent may be delivered to ventilated patients. It has a MAC of about 1.2%, but concentrations of 0.25-0.5% have been used to provide satisfactory sedation to ICU patients. As it is only minimally metabolised and elimination occurs mainly via exhalation, hepatic and renal disease has no influence on its pharmacokinetics. Although there is some concern as fluoride levels do rise after 24hours, clinical trials have shown no evidence of renal impairment.[78]

D. Ketamine

This anaesthetic agent, which may be administered via various routes, provides dissociative anaesthesia as well as analgesia. It has been used in low doses, together with either midazolam or propofol, to facilitate painful procedures in the ICU (for instance a change of dressings in burns patients.) The hallucinations

and emergence phenomena seen with ketamine may be reduced by the concomitant use of benzodiazepines, but probably still precludes its long-term use as a sedative drug of choice in the ICU.

Other drugs with sedative and anxiolytic properties

Chloral hydrate is available for oral administration only, and has been used extensively as sedative in children younger than 3 years. It is unreliable in older children, and its long half-life of 10 hours (18 hours in term infants) precludes its long-term use and its use in day-case procedures.[9] It is metabolised in the liver to the active substance trichlorethenol, which in turn is metabolised to the acetate and glucoronide. Both these latter substances will accumulate in renal dysfunction.[8]

Many of the **antihistamines** have pronounced sedative effects. **Trimeprazine** (also known as alimemazine) is a phenothiazine derivative which has been used extensively as oral premedication for children. It's onset takes 60-90 minutes, with the recommended dose 1-2mg/kg. It has a long half-life of 6.8 hours[79] and is generally prescribed as a once-off dose only.

Clonidine, an alpha2-agonist drug, has been used as adjunct in sedation in the ICU. The alpha2-agonist drugs were discussed in the previous chapter.

Many of the **anticonvulsants** have sedative properties, but they are not used as chief sedative agents in the ICU. Similarly, some of the older **antidepressants** have sedative properties, but these drugs are only used as adjuncts in the management of ICU patients.

Analgesic agents

A. Opiates

Good analgesia forms one of the cornerstones of any ICU sedation regimen, and it may often be the only 'sedative' needed to keep a patient content. Although the opiates have some sedative effects, they are primarily analgesic agents, and good ones at that.

The delta, kappa and mu opioid receptors have recently been renamed as OP1 (delta), OP2 (kappa) and OP3 (mu), and the probability of a specific morphine-6-glucoronide (an active morphine metabolite) receptor exists.[74] These receptors are found at supraspinal, spinal and peripheral sites, with the OP3 (mu) receptor being the main receptor involved in analgesia. Mechanisms of action at a cellular

level are complex, and involve both inhibitory and stimulatory effects (the latter being the poorer understood.)

Most of the available opiates have been used in the ICU for both analgesia and sedation. With the exception of remifentanil, all the opiates tend to either accumulate due to active metabolites and altered pharmacokinetics in the critically ill or have extended context-sensitive half-lives after prolonged infusion.

All the opiates cause respiratory depression and decrease the sensitivity of the respiratory centre to CO_2 and as well as the hypoxic drive. The CO_2 response curve is not only depressed (as is the case with the benzodiazepines), but also shifted to the right.

Muscle rigidity may be seen with all the opiates, but may be particularly problematic with remifentanil. Opiates cause delayed gastric emptying, ileus and constipation and – with the exception of pethidine (which is a smooth muscle relaxant) – causes spasm of the sphincter of Oddi. It increases ureteric, detrusor muscle and vesicular sphincter tone. Opiates stimulate the chemoreceptor trigger zone and activate the vomiting centre.

Effects on the cardiovascular system include decreased sympathetic outflow and vagomimetic effects, but – with the exception of pethidine and morphine – the opiates' depressant effect is usually only seen at doses much higher than that used clinically.

Morphine

Despite all the semi-synthetic opiate derivatives that are available, morphine remains the gold standard against which other drugs are measured. It also remains the drug of choice in many instances due to its good, predictable effect and low cost.

Morphine is a natural alkaloid present in opium and the prototype mu-agonist. Due to its low lipophilicity, it is relatively slow to cross the blood-brain-barrier.[83] A high hepatic extraction ratio results in low oral availability, but oral administration is nevertheless still useful, particularly in the management of terminal disease pain. Morphine may be used in neuraxial blocks, either on its own or in conjunction with local anaesthetic drugs.

In the liver, morphine is conjugated to morphine-6-glucoronide and morphine-3-glucoronide, and demethylated to normorphine.[12] Morphine-6-glucoronide is pharmacologically active with a higher potency than morphine. It is thought to contribute significantly to the respiratory depression caused by morphine.

Morphine-6-glucoronide is excreted renally and thus accumulates in patients with renal dysfunction.

In the elderly, volume of distribution is about half that in young adults and clearance is reduced, resulting in higher plasma concentrations. As the main metabolic process is conjugation, hepatic disease does not impair morphine's metabolism much.

Fentanyl, Sufentanil and Alfentanil

Although there are marked differences in pharmacokinetics between these three synthetic opiates, they are all metabolised in the liver to inactive metabolites. They have all been used for long-term infusions in ICU patients, but their context-sensitive half-life is not as favourable as remifentanil's. Fentanyl has the least favourable context-sensitive halftime, and patients may take a considerable time to recover after a prolonged infusion.

Remifentanil

As the youngest member of the synthetic opiate family, remifentanil has some unique properties. The formulation contains glycine, an inhibitory neurotransmitter, and is unsuitable for neuraxial use.

Remifentanil has an ester structure, which makes it susceptible to very rapid ester hydrolysis by non-specific esterases in red cells and tissue.[56] This results in rapid elimination, and the drug has a terminal elimination half-life of only 10minutes. Its context-sensitive half-life is about 3-4 minutes, regardless of the duration of the infusion.[23,51] Metabolism is unchanged in patients with end-stage renal and hepatic disease. These pharmacokinetic properties make remifentanil ideal for long-term infusion for analgesic purposes. It has little sedative action.

It has a narrow therapeutic index, and should be administered by infusion after the initial loading dose. Muscle rigidity seems to be particularly problematic with remifentanil, and respiratory arrest may occur very suddenly. A dose-dependent decrease in heart rate and arterial blood pressure occurs at infusion rates up to 1mcg/kg/min, where after no further depression occurs.

Other opiates

Pethidine is not very popular for use as long-term infusion, partly because it has active metabolites, norpethidine and pethidinic acid. It is, however, still

popular as an analgesic agent, particularly where its smooth muscle relaxant effects are desirable, as in patients with renal or biliary colic.

Tilidine is a very popular drug for use in particularly the South African paediatric population. It is a prodrug, with its metabolite, nortilidine, being responsible for its analgesic activity.[27] It is only available for oral administration in South Africa.

Tramadol exerts its analgesic actions by (weakly) acting on mu-receptors and by inhibiting the reuptake of noradrenaline and serotonin in the spinal cord.[70] It has active metabolites, and is not generally used for long-term infusions.[19]

B. Regional Blockade

Whilst providing excellent analgesia, regional blockade is often not a practical solution in the ICU. ICU patients often have multiple sources of pain or discomfort,[8] they may have coagulation deficiencies which preclude the placement of an epidural catheter, or they may be cardiovascularly unstable. In addition, epidural catheters are generally only left in situ for 72 hours, due to the risk of sepsis. Where epidural analgesia may be employed, it often allows for earlier extubation in patients who had upper abdominal surgery.

C. Non-steroidal anti-inflammatory drugs

These drugs are usually used with great caution in the ICU, as patients often have renal dysfunction and because gastric ulceration is a very real problem in this patient group. They should be reserved for the more stable patients.

An exception may be **paracetamol**, particularly in the paediatric population. Given in proper and adequate doses of 90mg/kg/day (60mg/kg/day in neonates), paracetamol is an excellent adjunct to analgesia and sedation which causes no gastric irritation. It should, however, be used with caution (and reduced doses) in patients with hepatic impairment.

Antipsychotic agents

Delirium is characterised by acute mental confusion with a sudden onset. Confusional states in the ICU may be caused by cerebral ischaemia, organic brain lesions, infection and septicaemia, drug withdrawal states or metabolic disturbances.[80] It may also occur idiosyncratically.

While the diagnosis and management of delirium in the ICU falls outside the scope of this discussion, treatment needs to be initiated in the ICU to facilitate management of the patient. As mentioned before, it is important - but not always easy - to differentiate between anxiety (treated with the benzodiazepines) and delirium, which should be treated with an antipsychotic drug.[24] The antipsychotic used most commonly in the ICU is haloperidol.[64] In drug-withdrawal states, clonidine has proved of benefit (together with benzodiazepines) in the treatment of delirium tremens.

Chlorpromazine is widely used as an antipsychotic agent, but in the ICU the hypotension caused by its alpha-adrenoceptor blocking effect may be particularly problematic. It may also prolong the QT interval[86] and cause serious ventricular dysrhythmias or aggravation of existing heart block.[39]

Haloperidol may also cause hypotension but this is generally less severe than that seen with chlorpromazine. It has greater potential, however, to cause extrapyramidal effects like dystonic reactions and akathisia.

The Neuroleptic Malignant Syndrome is a rare complication of antipsychotic treatment, but may be life-threatening when it does occur. It is characterised by fever, muscle rigidity, rhabdomyolysis, autonomic instability and altered consciousness. Creatine kinase levels are often elevated. Treatment is by stopping the antipsychotic immediately, resuscitation with fluids and management of electrolyte disorders and active cooling. Dantrolene 2mg/kg intravenously 6 hourly has been used, but reports on its efficacy in this syndrome vary. Bromocriptine has also been used with some success, but in South Africa this is only available for oral administration. Benzodiazepines may offer some symptomatic relief. Symptoms may last for 7 days after discontinuation of the causative drug.

Sedation in the Paediatric Intensive Care Unit

This paediatric population presents the intensivist with unique challenges. Children have been called 'pharmacological orphans' with reference to the fact that the pharmacokinetic and pharmacodynamic properties of drugs used in paediatric patients are often poorly researched. In addition, variations in these pharmacological parameters may be huge, as neonates differ from infants who differ from older children. In their comparison between propofol and other sedative drugs used in paediatric intensive care units in the United Kingdom, Pepperman and Macrae noted that "there is limited experience in the correct dose, method of administration and potential adverse effects of many sedatives, including propofol, used for sedation in the paediatric intensive care patients."[57]

A recently published study by Playfor et al[59] reported on the current practice in paediatric intensive care units in the United Kingdom. Sedation was formally assessed in 40% of the units questioned, with most of the units using locally devised sedation scales. The most commonly used sedative agents were midazolam combined with morphine. Enteral sedation was introduced early in 68% of units and 25% of units rotated drug regimes in an effort to minimise the development of tolerance. The rate of neuromuscular blockade was high – 31% of paediatric ICU patients received these drugs at some time during their ICU stay. No questions regarding procedural sedation and analgesia were included in the study.

Although a figure is not given, this study showed that many PICUs used propofol for sedation, particularly in head-injured children. Propofol use in the paediatric population received a share of bad press in the early 1990's, with cautionary reports issued by Scandinavian authorities as well as the manufacturers, and in a report in the British Medical Journal.[55] The cautionary reports related to incidents of metabolic acidosis, myocardial failure, lipaemia, rhabdomyolysis and hypoxia.

Subsequent investigation has shown that propofol may be used safely, provided the infusion rate is kept below 4mg/kg/h.[16] In a retrospective study of 198 patients, Pepperman and Macrae found no difference in adverse events or mortality between patients sedated with propofol and those sedated using other drugs.[57] The mean infusion rate of propofol used in their study was 3.39mg/kg/h.

Comparing sedative agents for use in the intensive care unit

A plethora of studies comparing various ICU sedation regimes may be found in the literature, but – despite this – there is little consensus on the correct regime or the 'ideal' drug. Studies are often difficult or impossible to compare, as there is no standardisation in sedation assessment, drug usage or study design.

Cultural differences seem to apply, even amongst very westernised countries.[77] Soliman et al studied the sedative and analgesic practice in a European survey, and reported that 75% of ventilated patients in the United Kingdom were likely to receive sedation, whilst their Italian counterparts only received sedation in 30% of cases. Sedation scores were utilised in only 18% of Austrian units, compared to 49% in German units and 61% in Danish units. Some, like the French and Norwegian units, used midazolam almost exclusively (as opposed to propofol), while others used both these drugs.

In his editorial comment on this study, Park notes that midazolam and propofol are not different versions of the same drug, but that propofol is better at

inducing sleep, while midazolam is the better anxiolytic and amnesic.[54] He also makes the point that not all drugs commonly used in one country are necessarily available in another.

Equipotent doses of the study drugs are not always easily or scientifically calculated. The study protocol may allow for relatively high doses of one drug, but only moderate doses of another. Loading doses are used in some studies, but not in others.

Hall et al compared propofol and midazolam for sedation in the ICU.[28] He concluded that the two drugs either did not differ in time to tracheal extubation or ICU discharge, or that propofol was associated with earlier extubation, but longer time to discharge. Patients treated with propofol spent more time at target Ramsay score level than the patients treated with midazolam. A cost analysis between the two groups was not done.

Weinbroum et al made similar findings after comparing propofol and midazolam treated ICU patients, while their cost comparison showed a five times higher cost for the propofol group.[82]

McCollam et al compared midazolam, propofol and lorazepam in ICU patients, and concluded that lorazepam was a cost-effective choice for sedation.[48] Patients sedated with lorazepam, however, tended towards oversedation. The long duration of lorazepam's effect may also be of concern after long-term sedation. Despite this, they noted that lorazepam might be the sedative of choice in critically ill patients.

Lorazepam is also the drug of choice for long-term sedation according to the American Society of Critical Care's Medicine Guidelines. Propofol is the preferred sedative when rapid awakening (e.g., for neurologic assessment or extubation) is important, while midazolam is recommended for short-term use only, as it produces unpredictable awakening and time to extubation when infusions continue longer than 48–72 hours.[33]

Three systematic reviews of the literature [32,53,84] in recent years (2 published in 2000, one in 2002) failed to show the superiority of any one drug. All three groups commented that more research was needed into sedation to better define effectiveness of available drugs. Young et al advocated an individualised approach to sedation, based on our knowledge of drug pharmacology.

Dexmedetomidine, the new kid on the block, now adds a new dimension to ICU sedation studies. To date, only a few comparative studies have been published. Venn and Grounds compared dexmedetomidine to propofol in patients who required ventilation after major abdominal or pelvic surgery.[81] They found no

difference in sedations levels, arterial pressures or extubation times. Predictably, the propofol group required significantly more opiates (alfentanil) for analgesia. The dexmedetomidine group had significantly lower heart rates compared with the propofol group, and the authors comment that this may protect against myocardial ischaemia.

Herr et al studied dexmedetomidine and propofol sedation regimes in patients who were admitted to the ICU after coronary artery bypass graft surgery.[31] As before, and predictably, the propofol group required more opiates (morphine) for analgesia. There was no difference between the groups in sedation levels, time to weaning and extubation, or respiratory rate and SpO_2 after extubation. Due to the study design, hypotension or hypertension could not be compared between the two groups. No ventricular tachycardia occurred in the dexmedetomidine group, compared to a significantly higher incidence (7/147 or 5%) in the propofol group. Significantly fewer patients required beta-blockers, 'high-dose diuretics' (defined just as furosemide), non-steroidal drugs or adrenaline in the dexmedetomidine group. Considering the antiemetic effects of propofol, it is interesting to note that 6 out of 147 patients in the propofol group (but none in the dexmedetomidine group) required antiemetic drugs.

In summary, considering the studies showing the advantages of monitoring sedation and implementing sedation guidelines, it seems mandatory to sedate patients in response to a clinically determined score. There are no clear indicators of superiority of any one drug, and the choice of drug should probably hinge on individual patient pathology and pharmacology. Cost limitation is a reality in medical care worldwide, and should be taken into account.

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Chapter Three

Dexmedetomidine – evaluating the pharmacokinetics and pharmacodymanics in paediatric patients

Objective, Study Design and Methods

Objectives

The primary objective of this study was to evaluate the pharmacokinetics and safety of a single, intravenous dose of dexmedetomidine in paediatric patients. The secondary objectives were to evaluate the level of sedation caused by dexmedetomidine and to assess the haemodynamic and respiratory effects of the drug.

Study design

The open-label study was performed in two centres – at Red Cross Children's Hospital in Cape Town, South Africa, and at the Hospital for Sick Children in Toronto, Canada. Ethics approval was obtained from the relevant ethics committees. Each unit enrolled 18 patients between the ages of 2 and 12 years. Although the study design for the two centres was similar, further comments in this section pertain only to the work done at Red Cross Children's Hospital.

Patients were screened pre-operatively. This had to be done within 3 days of the planned surgery, but in most cases took place the day before surgery. Patients who required surgery for which a general anaesthesia combined with an epidural was indicated, and who had to remain in hospital for at least an overnight stay were screened. Patients were only included if they met none of the exclusion criteria, if there was no suspicion of altered pharmacokinetics as in children with renal or hepatic compromise, and if the parents or guardians gave full consent. A record was kept of all patients screened.

Exclusion criteria were:

1) Subject had serious CNS trauma that had a potential to affect level of consciousness.
2) Subject had undergone or required intracranial surgery during current hospitalisation.
3) Subject required premedication (i.e. midazolam). This excluded the need for the sevoflurane used for the insertion of the intravenous catheters.

4) Subject in whom propofol was contraindicated, or had known or suspected serious allergy to any medication that might have been administered during the course of the study.
5) Subject grossly obese (body weight greater that 50% above ideal body weight for height) or markedly underweight (under the 3rd percentile for age).
6) Subject currently using enzyme-inducing drugs.
7) Subjects in whom alpha-2 antagonists of alpha-2 agonists were contraindicated.
8) Subject currently being treated or treated within last 30 days with alpha-2 agonists or antagonists.
9) Subject had participated in a trial with any experimental drug within 30 days prior to the start of the study.
10) Subject previously exposed to dexmedetomidine
11) Subject terminally ill
12) Subject had bleeding tendencies
13) Subject had unstable or uncontrolled diabetes
14) Subject had received antihistamines or other sedative medication within 12 hours prior to the planned administration of the study drug (sevoflurane for insertion of intravenous catheters excluded)
15) Any other condition which, in the opinion of the investigator, may increase the risk to the patient or may influence the study data.

With regard the consent, the investigator would approach the parents or guardians, explaining that the reason for the visit was possible inclusion in the trial. It was made clear that refusal to partake in the trial would in no way compromise the care the child would receive. An information booklet in either English, Afrikaans of Xhosa was given to the parents to peruse in their own time before signing the consent.

Once all the criteria for inclusion were met, the patient was once again examined physically. Height and weight was determined, routine laboratory blood samples taken for a Full Blood Count, serum electrolytes, urea and creatinine and liver function tests and a urine sample collected for routine urinalysis. A standard 12-lead ECG was performed.

Children included in the study were assigned to receiving either the drug or act as control. In each of the three groups of six patients each (see below), the first and second, and fourth and fifth patients received the study drug, while the third and sixth patients acted as controls.

The study started with the lowest dosing group (Group I), in which patients received 2mcg/kg/h intravenously for 10 minutes. Following a safety assessment after this initial part of the study, the study continued with the second group who

received 4mcg/kg/h (Group II). Another safety analysis followed, after which the final and third group of patients received 6mcg/kg/h (Group III). These dosing schedules translated to slow bolus infusions of 0.33, 0.66 and 1mcg/kg, respectively.

On the day of surgery, the enrolled patient was taken to the dedicated induction room in theatre where standard monitoring consisting of an ECG, oximeter and non-invasive blood pressure cuff was applied. The patient was given Sevoflurane in oxygen by mask and Aires-T-piece until sufficiently asleep to insert a peripheral venous catheter (all patients) and a femoral venous catheter (excluding the control patients). The sevoflurane was allowed for a maximum of 15 minutes. The peripheral catheter was to be used for drug infusion, while the femoral catheter was meant for blood sampling.

After insertion of the catheter(s), the Sevoflurane anaesthetic was terminated, and the patient recovered from the anaesthesia with ongoing standard monitoring. A minimum period of thirty minutes after the sevoflurane was stopped was allowed for recovery from this short general anaesthetic. During this time, the calculated fluid deficit (using the standard '4-2-1' formula) of the (starved) patient was infused using Ringer's Lactate.

The study drug was supplied in 2ml glass ampoules containing 100mcg/ml dexmedetomidine. The drug was diluted with normal saline to either 2mcg/ml or 4 mcg/ml in a 50ml syringe. (The higher concentration was needed for some of the bigger patients, as the syringe driver had a maximum infusion rate of 99ml/h.) The ampoules were kept in the hospital pharmacy and released in batches of 5 to theatre, where it was kept in the locked drug cupboard. Each ampoule was labelled with a two-part perforated label so that the tear-off portion could be affixed to the case report form. Any leftover drug in either the ampoule or 50ml syringe was discarded after completion of the drug infusion. A drug register was kept for all ampoules released to theatre, and was filled in by the investigator.

Once the allocated recovery time had been completed, and 5 minutes before the planned start of drug infusion, a 4ml baseline blood sample was taken from the femoral line. This sample was for analysis of plasma proteins.

Infusion of the study drug started at "zero time", and this time was used for all further calculations of time in the 24-hour study period. The study drug infusion was calculated according to 2, 4 or 6 mcg/kg/hour, depending on the relevant dosing group. Infusion start and stop times were noted. The study drug was infused into the distal port of the peripheral line, so that dead space was limited to less than 1ml.

Blood samples from the femoral line were taken after aspirating a sufficient amount of blood to ensure a fresh sample of whole blood. This aspirate was returned to the patient after the sample was taken to avoid unnecessary blood loss. The femoral line was then 'heparin locked' with normal saline containing 1unit of unfractionated heparin/ml.

Blood samples of 3ml each were taken at zero time, immediately before the end of the 10-minute infusion, and then at 15, 30, 45, 60 and 75 minutes, 2 hours, 2 ½, 4, 6, 12 and 24 hours. (The Canadian site did not take the sample at 2 hours.) The sedation level of the patient, the non-invasive blood pressure, heart rate, oxygen-haemoglobin saturation (SpO_2) and respiratory rate were noted at baseline, zero time, 10, 15, 30, 45, 60 and 120minutes and then at 4-hourly intervals until study completion. Temperature measurement (either tympanic or axillary) was done at baseline, at the end of the drug infusion period, at 12 and at 24 hours. The site of temperature measurement was noted. In addition to these observations, continuous SpO2 and ECG monitoring was done during the 24 hour study period and any event which the investigator deemed to be clinically significant, for example a drop in SpO2 or changes in blood pressure, was reported. All observations in the induction room and in theatre were done by the investigator.

Sedation was assessed according to a scale prescribed by the study protocol:

0. Appropriately asleep
1. Awake and alert
2. Drowsy but responds to stimulation
3. Very sedated

"Appropriately asleep" was defined as an asleep patient who was easily aroused by calling his or her name, or by a light glabellar tap. Category 2 was used when a patient needed more stimulation, for instance pressure behind the angle of the jaw or a loud verbal stimulus, to be aroused. Category 3 was used when even more stimuli was needed for a response from the patient.

The blood samples were collected in heparinized tubes. At an appropriate time, and once a few samples had been collected, the samples were centrifuged until separation between cells and plasma took place. Using a clean plastic pipette for each tube, the plasma was removed from the tubes, transferred to clean tubes, and placed in a freezer. The samples for each patient were later collected by the laboratory staff, placed in dry ice, and shipped to the Abbott Laboratories in Illinois, United States of America. This laboratory conducted the relevant studies to obtain the pharmacokinetic data using a non-compartmental model. (See below)

Surgery was timed to start after two hours from zero time. During these two hours, the calculated maintenance fluid per hour was given using Ringer's Lactate. Further fluid management was done at the investigator's discretion. Once the operating theatre was ready to accept the patient, the patient was transferred from the induction room to theatre. Once the monitors had been reconnected, general anaesthesia was induced using propofol. If muscle relaxation were indicated, this would be done with vecuronium (although rocuronium was also allowed). Anaesthesia was maintained with isoflurane in oxygen with air or nitrous oxide as deemed appropriate by the investigator.

For analgesia, a lumbar epidural catheter was placed using standard equipment and techniques. Bupivacaine (without adrenaline) in concentrations of 0.2-0.25% was injected into the epidural. Appropriate bolus doses were used while in theatre, while a continuous infusion of 0.2% at 0.1-0.2ml/kg/hour was used during the post-operative period.

All sedative drugs were avoided during the post-operative period, although intravenous morphine was allowed as rescue drug in case of insufficient analgesia. Ondansetron was to be given if the need for an anti-emetic arose.

Any intervention needed for clinically significant events was done at the discretion of the investigator and was noted. Fluid resuscitation was recommended for persistent hypotension. If significant hypotension or bradycardia persisted during the infusion period, the investigator should determine whether the study drug should be discontinued.

Adverse events were defined as any event considered to be an undesirable occurrence, whether or not it was considered to be related to the study drug. The period for which these adverse events were to be reported was set at 30 days. All adverse events were noted in the case report form. Adverse events were rated as mild, moderate or severe, where 'mild' denoted an adverse event that was transient and easily tolerated and severe defined as causing considerable interference with the subject's activities. The relationship of an adverse event to the study drug was indicated as 'probable', 'possible', 'probably not' or 'not related'.

Adverse events were, in addition, rated as a "serious adverse event" if it resulted in:

1) Death
2) Life-threatening situation
3) Prolonged hospitalisation
4) Persistent or significant disability or incapacity
5) Other medically important events

Serious adverse events were reported on a special, dedicated form and the events reported to the clinical research associate of Abbott within 24 hours.

After completion of the surgical procedure, the patient was transferred to the high care area of the surgical ward. ECG and SpO_2 monitoring was continued for the full study period, and non-invasive blood pressures were performed according to the protocol. For the rest of the 24-hour period a registered paediatric nursing sister dedicated to the sole care of the patient observed the patient.

Control patients were treated and observed according to the same protocol as patients receiving the study drug, the only difference being that they did not receive the drug, did not need a femoral catheter placed, and did not have pharmacokinetic blood samples taken.

At the end of the 24-hour study period, the patient was examined physically and a 12-lead ECG was done. Blood samples were collected for a full blood count and blood chemistry (the same tests as were done on the pre-study blood sample.) A urine sample was collected for urinalysis. The femoral line (if present) and peripheral cannula were removed unless needed for further management.

All protocol deviations were noted – these were categorised as either an event timing deviation, event omission or administration of disallowed medication.

Case report forms were completed in quadruplicate. Abbott Laboratories conducted a Quality Assurance clinical audit on site from 19-20 March 2001.

Pharmacokinetic analysis

A validated Gas Chromatography/Mass Spectrometry (GC/MS) method was used for the analysis of dexmedetomidine in plasma. The lower limit of detection of dexmedetomidine in plasma was 10 pg/ml (0.010 ng/ml).

The calibration curve for the dexmedetomidine plasma concentration contained five standards that ranged between 10.0 and 1500 pg/ml. The correlation values for all calibration curves were greater than 0.996. Samples quantified below the lowest standard were reported as zero. In-study quality control samples, supplemented with concentrations of 20, 600 and 1200 pg/ml of dexmedetomidine were analyzed with the unknowns. The coefficient of variation for the analyses ranged between 7.1 and 11.7%.

The *in vitro* protein binding for [^{3}H] dexmedetomidine was determined in the baseline plasma samples obtained from eleven of the children using an ultrafiltration technique.

Values for the pharmacokinetic parameters of dexmedetomidine were obtained using noncompartmental methods.

1) The maximum observed plasma concentration (C_{max}) and the time to the maximum observed concentration (peak time, T_{max}) were obtained from the plasma concentration-time data.
2) The terminal elimination rate constant (β) was determined from the slope of the least squares linear regression of the terminal log-linear plasma concentration-time profile. The terminal log-linear phase was identified using WinNonlin-Pro™, Version 3.2 (Pharsight Corporation, Cary, North Carolina) and visual inspection. A minimum of three concentration-time data points was used to determine terminal elimination rate constant (β). The terminal elimination half-life ($t_{½\beta}$) was calculated as ln(2)/ β.
3) The area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration (AUC_t) was calculated by the linear trapezoidal method. The AUC was extrapolated to infinite time (AUC_{ext}) by dividing the last measurable plasma concentration (C_t) by β. Thus, the area under the plasma concentration-time curve from time 0 to infinite time (AUC_∞) was calculated as: $AUC_\infty = AUC_t + AUC_{ext}$.
4) The total plasma clearance was the administered dose divided by the AUC_∞.
5) The mean residence time (MRT) was the area under the first moment of the plasma concentration-time curve (AUMC) divided by AUC_∞ minus the mean drug administration input time.
6) The steady-state volume of distribution (V_{ss}) was the calculated by multiplying MRT by clearance.

Pharmacodynamic analysis

The changes in HR, SBP, DBP, RR, and SpO_2 from baseline were compared over time and among the dosing groups using Repeated measures ANCOVA, adjusting for baseline values. Main and interaction effects were identified. Sedation scores were analysed using non-parametric techniques. $P<0.05$ was accepted as the threshold for statistical significance.

Chapter 4

Dexmedetomidine in children – pharmacokinetic and pharmacodynamic results

Demographic detail

A total of 36 subjects were enrolled at the two sites (18 at each) – 26 males and 10 females. Sixteen subjects were White, four Black, one Asian, one Hispanic, and 14 were classified as "Coloured", "Cape Coloured, or "Cape Malay".

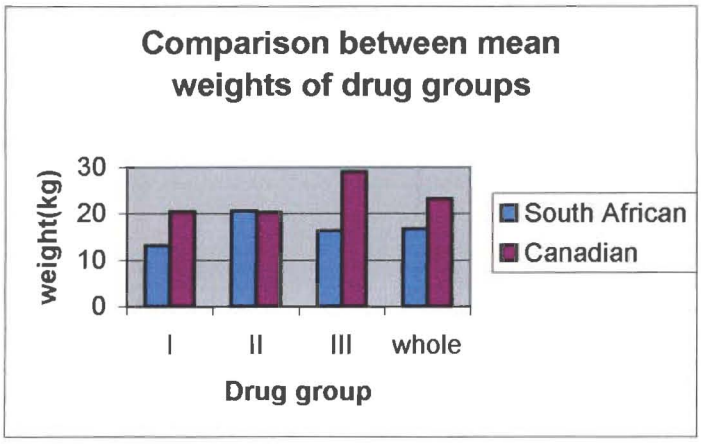
All the subjects were between 2 and12 years old. A comparison between age, weight and length for the different groups is tabled below:

Table 1: A comparison between age, height and weight for the different groups

	Group I		**Group II**		**Group III**	
	Control n=4	**Dex 2mcg/kg/h** n=8	**Control** n=4	**Dex 4mcg/kg/h** n=8	**Control** n=4	**Dex 6mcg/kg/h** n=8
Age (yrs)						
Mean(STD)	8.8(2.1)	4.1(2.4)	5.3(4.3)	6.4(2.7)	6.5(5.3)	6.3(2.8)
Range	6-11	2-8	2-11	3-11	2-12	3-11
Height(cm)						
Mean(STD)	136.5(16.9)	104.4(15.3)	111.8(26.7)	115.6(18.1)	102.0(28.6)	114.4(15.5)
Range	115-154	84-124	89-143	90-143	84-135	91-138
Weight(kg)						
Mean(STD)	33.1(10.5)	16.8(5.2)	22.0(10.4)	20.5(6.8)	20.9(10.7)	22.7(9.3)
Range	22-47	10-26	12-35	14-33	12-31	12-42

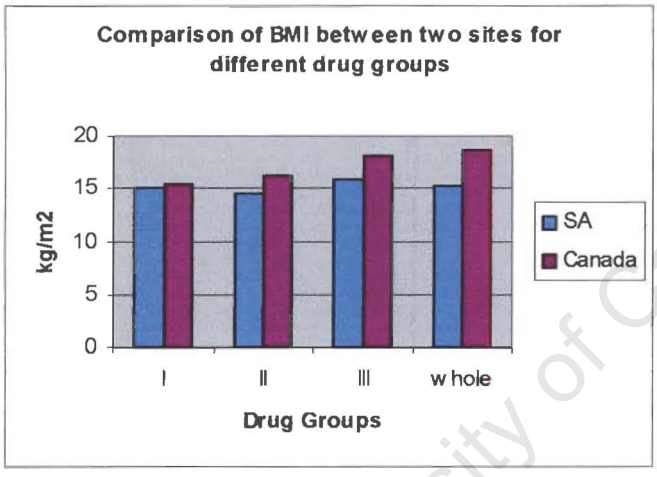
Comparing the subjects who received the study drug from the two sites, the Canadian subjects were generally heavier and had a higher body mass index (BMI) than the South African subjects. (Figures 1 and 2)

Figure 1



(Control subjects excluded)

Figure 2



(Control subjects excluded)

Since body surface area (BSA) may play a role in the pharmacokinetics the BSA for the different groups was also compared. (Figure 3) The Canadian subjects had larger BSA's in groups I and III, but in group II the BSA's for the two sites were similar. (Weight in the three groups showed the same distribution.)
A comparison of the ages of drug recipients at the two sites revealed that the subjects in Group I and III in Canada were older than their South African counterparts, but that the ages in Group II were similar. (Table 2)

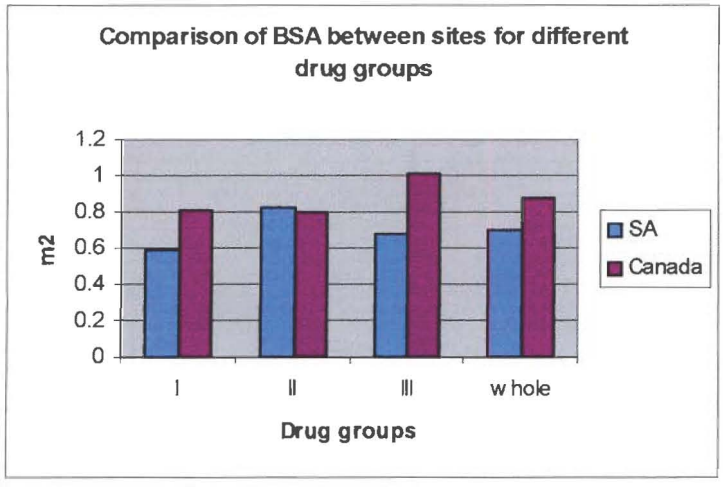
Table 2: Comparison of ages of drug recipients

	South Africa	Canada
Group I	2.5	5.7
Group II	6.75	6.05
Group III	4	8.6

Mean age given in years

All 36 enrolled subjects completed the study.

Figure 3



(Control subjects excluded)

Pharmacokinetic results

Plasma concentrations of dexmedetomidine were determined from each of the blood samples taken for this purpose. The pharmacokinetic parameters for each of the three groups are shown in table 3. Plasma concentrations for subject 4 (South African site) could not be determined, as the blood samples had haemolysed.

Table 3

Pharmacokinetics of Dexmedetomidine per dose group (mean±SD)			
Pharmacokinetic Parameter	Group I 2mcg/kg/h	Group II 4mcg/kg/h	Group III 6mcg/kg/h
C_{max} (ng/ml)	0.298±0.168	0.623±0.312	1.150±0.633
$t_{½\beta}$ (h)	2.18±0.46	2.12±0.77	1.61±0.28
V_{ss} (L/kg)	2.33±0.57	2.13±0.32	1.65±0.43
Cl (L/h/kg)	0.894±0.231	0.835±0.296	0.848±0.223
T_{max} (h)	0.186±0.045	0.223±0.116	0.187±0.040

See text for explanation of abbreviations

The maximum plasma concentration (C_{max}) and the time to the maximum concentration (T_{max}) were read directly from the plasma-concentration data. The other values were calculated using methods described in the previous chapter.

In all three dosage groups, clearance (Cl) was higher (see table) in this paediatric study group than in adults (0.495L/h/kg). Volume of distribution (V_{ss}) was higher for all dosage groups than for adults (1.33L/kg), with a marked difference in the 2 and 4mcg/kg/h groups. The terminal elimination half-life ($t_{½\beta}$)

of dexmedetomidine in this paediatric study group was similar to that of adults for the 2 and 4mcg/kg/h groups, but considerably shorter for the children in the 6mcg/kg/h group. The plasma protein binding of dexmedetomidine in this paediatric study group was 92.64%, which is similar to the value of 94% reported in adults.

C_{max} for the 6mcg/kg/h group is almost twice as high as that of the 4mcg/kg/h group despite only a 50% increase in dose/kg. The $t_{½\beta}$ and V_{ss} for this group is also lower than that of the other two groups. The smaller volume of distribution could explain the high C_{max} for this group.

It is known that, following an intravenous bolus, dexmedetomidine's volume of distribution **and** clearance decreases due to the vasoconstrictive action of the drug at high concentrations (see chapter one), and this may be the reason for the higher C_{max} in the highest drug dose group.

The difference in V_{ss} between the first two groups and the third group cannot be explained in the same way though, as this parameter refers to steady state. The vasoconstrictive effects should only occur in the initial phase of infusion and while the dexmedetomidine concentration is high. As the concentration decreases, the vasodilatory effects of dexmedetomidine should step in.

With clearance remaining similar in all drug groups, the change in $t_{½\beta}$ in group III would be ascribed to the change in V_{ss}, as $t_{½\beta} \approx V_{ss}/Cl$.

With reference to the vasoconstrictive effects of dexmedetomidine at high concentration, one would have expected an increase in blood pressure at the time of C_{max}, but the corresponding blood pressures were lower than at baseline. Interestingly, the maximum decrease in heart rate occurred at approximately the same time as C_{max} for the 6mcg/kg/h group (but not for the other two groups – see data below). This decrease is then probably due to the vagomimetic effect of the drug, and not to a baroreceptor reflex.

It is interesting to note that the maximum plasma levels in the Canadian group all occurred at 10 minutes after the start of the infusion. The South African subjects' maximum plasma levels were much more scattered, and is shown with the bold figures in table 4.

This difference in the South African group can probably be explained by the timing of the so-called '10 minute'-sample. This sample was actually taken at 9 minutes, as the protocol instructed that it should be taken 'just before the end of the infusion.' It would therefore reflect a lower plasma level than if the sample were taken at the end of the infusion period. It is assumed that the Canadian site interpreted this part of the protocol differently, and took the sample at the end of the infusion period.

The maximum plasma concentration at 30 minutes for the South African subject 11 cannot be explained in the same way, and it has to be questioned whether this was due to a sampling or measuring error. The 12-hour sample of Canadian subject 102 showed a dexmedetomidine level more than three times the level at 6 hours, and it is most probable that this was due to measuring error.

Also of interest is the markedly higher maximum plasma levels (Cmax) in the Canadian group, particularly obvious at 10 minutes after the start of the infusion. (Figure 4) At 15 minutes this marked difference is not apparent in groups I and II anymore, with the difference in group III remaining obvious until the 30 minute values.

Table 4: Individual dexmedetomidine concentrations in ng/ml

			Minutes after starting drug infusion			
Subject	**Site**	**Dose***	**10**	**15**	**30**	**75**
1	SA	2	0.136	**0.166**	0.129	0.09
2	SA	2	0.113	**0.116**	0.078	0.059
5	SA	2	**0.217**	0.213	0.162	0.093
101	C	2	0.231	0.168	0.131	0.083
102	C	2	0.571	0.28	0.171	0.083
104	C	2	0.306	0.262	0.158	0.068
105	C	2	0.479	0.26	0.144	0.08
7	SA	4	**0.431**	0.429	0.275	0.161
8	SA	4	**0.528**	0.425	0.322	0.165
10	SA	4	0.303	**0.408**	0.294	0.245
11	SA	4	0.093	0.187	**0.377**	0.158
107	C	4	0.708	0.526	0.295	0.161
108	C	4	1.341	0.583	0.318	0.165
110	C	4	0.637	0.296	0.209	0.245
112	C	4	0.555	0.361	0.31	0.158
13	SA	6	**0.619**	0.595	0.366	0.24
14	SA	6	0.589	**0.629**	0.452	0.257
16	SA	6	**0.544**	0.541	0.386	0.236
17	SA	6	0.551	**0.587**	0.418	0.261
114	C	6	1.69	0.797	0.4	0.258
115	C	6	1.696	1.103	0.554	0.277
117	C	6	1.308	0.558	0.385	0.173
118	C	6	2.127	1.066	0.622	0.385

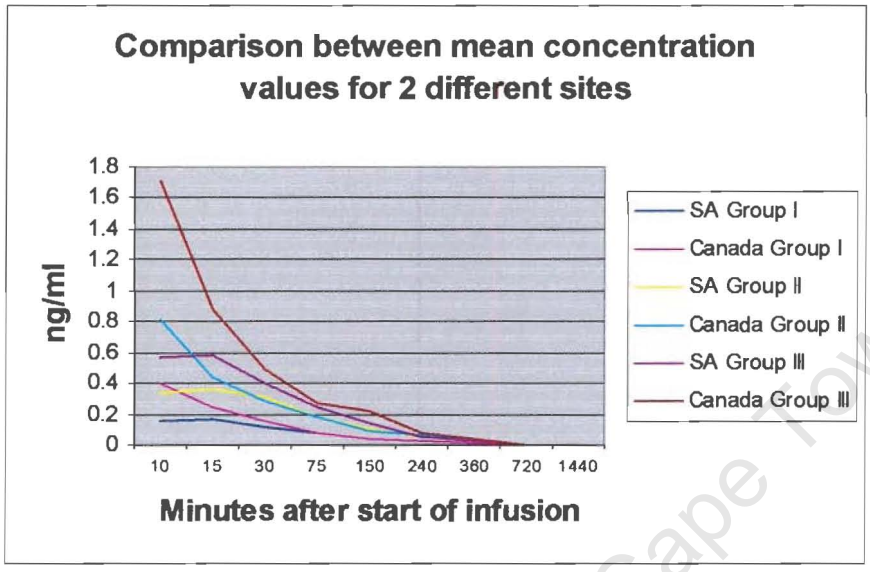
Bold figures in blue indicate maximum concentration levels in the SA group
* - dexmedetomidine dose in mcg/kg/h
Site – SA = South Africa, C = Canada
Subject 4 in SA group excluded as samples haemolysed

Since the dosage was adjusted to the weight of each subject, the reason for the higher levels in the Canadian group must be sought elsewhere. If one assumes that dexmedetomidine is *not* a highly fat-soluble drug (this information has never been published to my knowledge), the higher weight and BMI in the Canadians for groups I and III may explain their higher Cmax. All group II's comparisons for weight, BMI and BSA are similar between the two sites, and this argument therefore does not hold true. Altering dosing schedules to BSA, which may be a more accurate way of calculating dose, would not have altered the dose

administered, at least not for group II, and thus cannot account for the higher peak concentration levels.

This difference is intriguing, but – unless there was an unknown or unspoken difference in protocol interpretation between the two sites, the explanation remains out of reach.

Figure 4



Pharmacodynamic data

Sedation

The sample size was too small to draw exact conclusions regarding the sedative properties of the study drug or its dose-response relationship, but the figures indicate that the subjects who received the study drug were more sedated than the control subjects. Sedation also increased with increasing dexmedetomidine dose. Since the Canadian data for this parameter is not complete, only the South African data is reported here. (figures 5-8)

For the sake of clarity, the term 'drowsy but responds to stimulation' (as explained in the previous chapter), which refers to a deeper state of sedation than 'appropriately asleep', has been shown as 'deeper sedation' in the figures. No subject was noted to be in the deepest sedation category (category 3) at any stage.

The number of subjects (y-axis) in each sedation category at each time interval (x-axis) after the start of the infusion is indicated for the three drug groups (4 subjects per group) as well as for the combined control group (6 subjects).

Figure 5

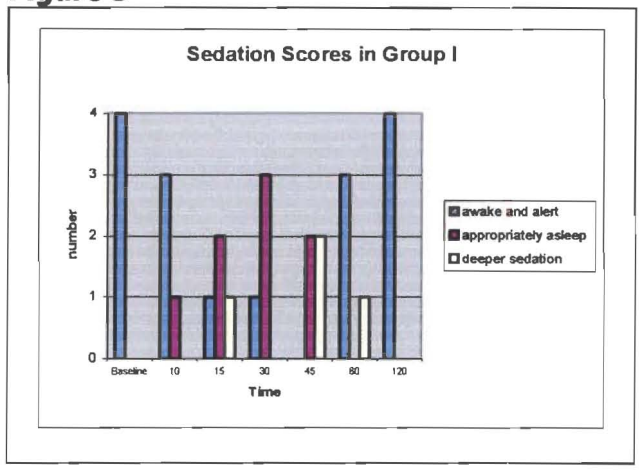


Figure 6

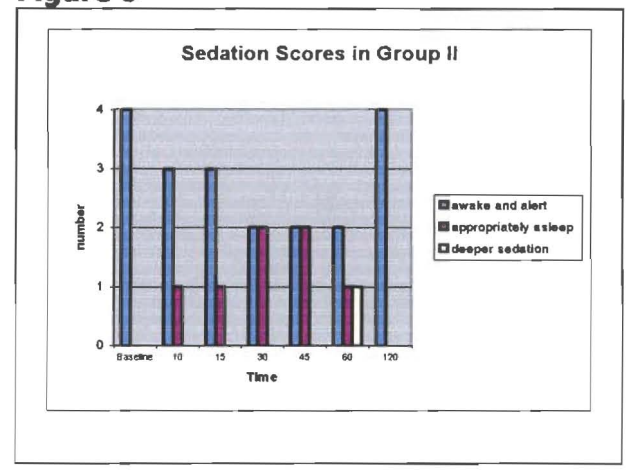


Figure 7

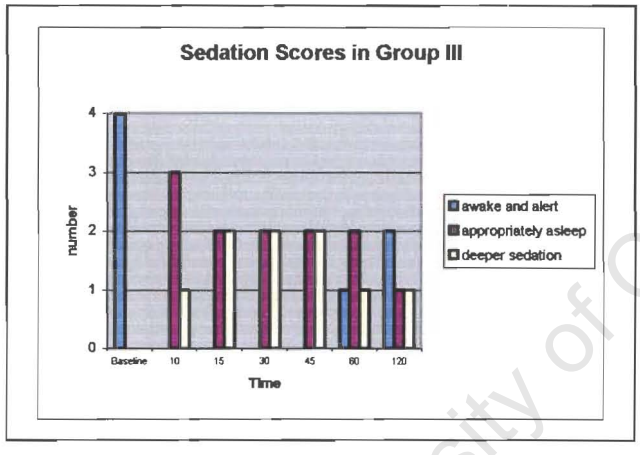
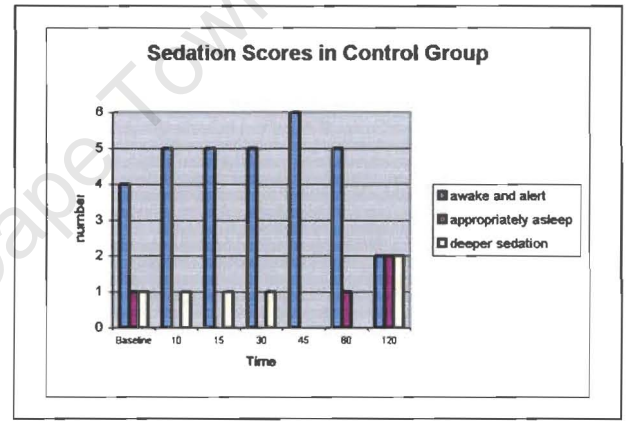


Figure 8



Blood pressure and heart rate

Reductions in systolic and diastolic blood pressure, and heart rate were seen in the study drug group compared to the control group (Table 5), although the small numbers in each group preclude statistically correct conclusions. (Data presented here reflect both sites' subjects.) The drop in blood pressure (systolic and diastolic) in all three dosage groups was most marked at 30, 45 and 60 minutes, with the maximum decrease (in the order of 20%) occurring in the 6mcg/kg/h dosage group. In this latter group, the heart rate decreased notably more than in the other groups, starting earlier than the drop in blood pressure. The maximum decrease in heart rate in this group occurred early, at ten minutes after the start of the infusion, with the order of change around 23%.

Table 5: Mean changes in Blood pressure and heart rate

		Group I		Group II		Group III	
		Control	Dex2	Control	Dex4	Control	Dex6
		n=4	n=8	n=4	n=7	n=3	n=8
Baseline	SBP	112	104.4	95	105.1	108.7	115.4
	DBP	66.3	59.3	52	59.4	62.3	69.3
	Pulse	85.3	103.5	89.3	97.4	109.3	98.5
		n=4	n=8	n=4	n=7	n=3	n=8
10min	SBP	-1	0.8	8.8	-2.9	11.7	-5.1
	DBP	-2	-0.3	15.3	3.9	8	-4.9
	Pulse	3	-3	-2.8	-5.1	6	-23.6
		n=4	n=8	n=4	n=7	n=2	n=8
15min	SBP	-1	-1.4	2.5	-3.3	6	-9.9
	DBP	-0.3	3.3	5.3	0.9	0	-10.5
	Pulse	3	-5.6	6.5	-3.3	4	-20.8
		n=4	n=8	n=4	n=7	n=4	n=8
30min	SBP	-6	-6.5	3.3	-8.7	3.5	-14.3
	DBP	-1.5	-2.6	-0.3	-4	3.3	-13.5
	Pulse	5.8	-8.1	15.5	-16.8	22.5	-20
		n=4	n=8	n=3	n=5	n=4	n=8
45min	SBP	-0.8	-5.4	-4	-14.4	0.3	-22.4
	DBP	0.8	-3.1	-2	-8.4	-0.3	-19.1
	Pulse	0.5	-5.1	12	-17.6	13	-17.4
		n=3	n=7	n=3	n=6	n=4	n=8
60min	SBP	3.7	-7.3	1.3	-11.2	-4.5	-24.5
	DBP	7.7	-1.8	-0.3	-11.7	-0.5	-26.4
	Pulse	-2.3	0.1	5	-9.1	10.8	-17.8

Mean SBP and DBP given in mmHg; Mean heart rate in beats/minute

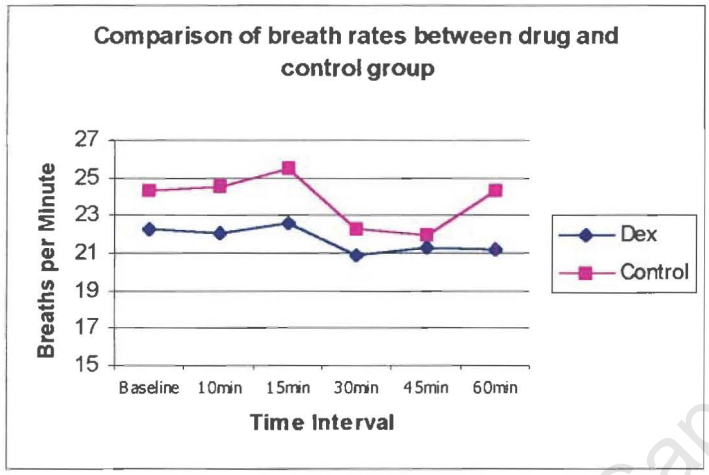
The ten-minute infusion of 6mcg/kg/h correlates with a loading dose of 1mcg/kg, and it would seem from the data that this dose (or a higher dose) should be given with great caution until the dose-response curve relative to the bradycardia is clear. Bradycardia may be dangerous in particularly the younger paediatric patient who is dependent on heart rate for cardiac output.

No comparison between the timing of maximum changes in sedation and cardiovascular parameters is possible, but it should probably be noted that the maximum changes in blood pressure occurred about 50 minutes after the infusion was stopped. Continuous monitoring should thus be advised for at least 1 hour (and probably longer, depending on further studies) after administration of dexmedetomidine.

Respiratory parameters

The Canadian data for these parameters were not available. Amongst the South African subjects, no respiratory effect of dexmedetomidine could be shown, probably because of the small sample size. Apart from the subjects who developed hypoxia in the initial period after drug infusion (discussed under adverse events), no other subjects showed a change in their oxygen-haemoglobin saturations after drug infusion.

Figure 9



Drug dose/concentration relationship to response

The relationship between drug dose (or plasma concentration), and combined sedation and vital sign changes was not assessed. From the previous discussion it seems obvious that the highest drug group showed the biggest drop in blood pressure and heart rate. The differences between sedation scores in the three groups show that the subjects were more sedated the higher drug dose they received. The absence of influence of the drug on respiratory parameters corresponds with the known effects of the drug, as discussed in chapter one.

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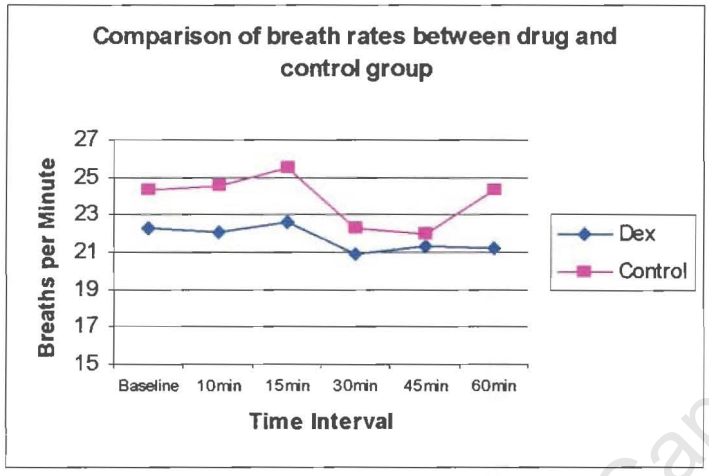

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Adverse events in the 24-hour study period

Three subjects (all from the Cape Town group) had adverse effects reported between the start of the study drug infusion and the start of surgery.

Table 6: Adverse events in the initial period after drug infusion

Subject	Dosage group #	Age(yrs)/ gender	Adverse event	Time*	Severity	Relationship to drug
2	2	2/M	Hypertension	0:15	Moderate	Probably not
5	2	4/M	Hypoxia**	0:05	Moderate	Possible
16	6	4/M	Hypoxia**	0:09	Moderate	Probable

dexmedetomidine in mcg/kg/h
* time from start of infusion
** Hypoxia defined as SpO_2<95%

The hypertension in subject 2 may have been due to emotional disturbance, as the subject was crying at the time of this specific measurement. However, this subject's blood pressure at baseline was 131/80mmHg, and his blood pressures (apart from the anaesthetised period) were all relatively high. For instance, his blood pressure at 20 hours post-infusion, which was at 04h50, with the subject 'appropriately asleep' according to the sedation scale, was 156/87mmHg. Blood pressures at 30, 45 and 60 minutes in this subject varied between 91/53 and 107/67mmHg.

The lowest recorded SpO_2 was 94%, and subject 5's SpO_2 levels improved after encouragement to cough out oral secretions. The relationship to the drug was thus noted as possible, as upper airway obstruction due to secretions was the likely cause. Subject 16's hypoxia was probably due to the respiratory depressant effects of the study drug.

Most subjects had at least one adverse event (AE) in the 24-hour study period. The most common AE was vomiting, with a 50% incidence in group II and III each, and a 33% incidence in group I. In addition, one subject in group I and two in group III reported nausea. Overall, 19 out of the 36 subjects reported either nausea or vomiting – an incidence of almost 52.8%.

One other subject in group I had hypertension. It is not noted in the study results when or in which subject this occurred, or what the possible relationship to the drug may have been.

Although it is often difficult to differentiate between pain and anxiety in children, the number of patients who were reported as experiencing pain (14/36) is disconcerting. All drugs with sedative action had to be avoided in the study period, although morphine was allowed as 'rescue' medication. From personal experience with other paediatric patients, almost all post-operative children need additional analgesia despite receiving an epidural infusion. One is faced with a

possible ethical dilemma here: Since sedation assessment was only a secondary aim of this study, and only of real importance in the first two hours after infusion, should the use of analgesics not have been allowed more freely? Did any child perhaps suffer pain because he or she was an enrolled subject?

From personal experience while observing some of the study subjects, this was probably not the case. The study allowed the subjects to have an epidural infusion post-operatively, since it provided for a dedicated, paediatrically trained nursing sister to observe them. This would not have been possible if that child had not been an enrolled subject, as shortages in nursing staff at Red Cross Children's Hospital did not allow for the necessary care of such patients. Even though no formal comparison was made, the study subjects seemed to have better pain control than other post-operative children in the same ward. Still, one has to ask whether it is possible to honestly state that the administration of morphine was absolutely not influenced by the fact that the subject had been enrolled in the study.

Two patients who received 2mcg/kg/h dexmedetomidine complained of dry mouth. The only other AE noted specifically was fever, which is usually a normal post-operative occurrence secondary to chemical mediator release. The numbers are too small to comment on, but it was noted that no control patients developed fever.

Adverse events after the 24-hour study period

Seven subjects had events reported as 'serious adverse events' according to the definitions explained in the study methods. (Table 7) None of the events were considered by the investigators to be related to the study drug.

There were no deaths, and no premature discontinuations due to adverse events and the incidence of serious adverse events were not considered to be unusual or unexpected for this population.

Table 7: Serious Adverse Events after the 24hour study period

Subject number	Treatment group	Adverse event	Onset day	Result
14	6mcg/kg/h	Infection	12	Prolonged hospitalisation
104	2mcg/kg/h	Anaemia	3	Blood transfusion
107	4mcg/kg/h	Infection, Hydronephrosis, Abnormal kidney function	6 8 13	Prolonged hospitalisation, Antibiotics, Surgery
110	4mcg/kg/h	Diarrhoea & fever, dehydration	8 13	Hospitalisation
113	Control	Cellulitis	3	Prolonged hospitalisation
116	Control	Right bundle branch block	2	ECG 3 hrs later normal No intervention needed
117	6mcg/kg/h	Haematoma	7	Resolved spontaneously

Abnormal laboratory results

Although changes in laboratory values were noted after the 24-hour study period, none of these values were unexpected in the post-operative patient. The incidence of these changes was similar between treatment groups.

In summary, protein binding of dexmedetomidine in children is similar to that of adults. Clearance is higher and volume of distribution larger. The terminal elimination half-life in the highest dosage group was shorter than that of adults, but the other two dosage groups showed similar values to adults.

Children treated with dexmedetomidine were generally more sedated than control patients. The highest dosage group (who received the 'normal' loading dose of 1mcg/kg as used in adults) showed a marked decrease in heart rate soon after the drug infusion, with decreases in blood pressure becoming more notable at about an hour after infusion. Two patients had incidents of hypoxia soon after the infusion: in one the study drug was thought to be the probable cause, and in the other the relationship was more difficult to determine.

It could be said that dexmedetomidine was generally well tolerated, but that the necessary caution (similar to when any sedative drug is administered) should be exercised when administering the drug.