A Comparative Study Between Dexmedetomidine And Mixtures of Midazolam and Morphine For Postoperative Sedation In Intensive Care Unit

by:

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Dissertation Submitted In
Partial Fulfillment Of The
Requirements For The Degree Of
Master of Medicine (Anaesthesiology)

UNIVERSITI SAINS MALAYSIA
MAY 2005

ACKNOWLEDGEMENT

I would like to acknowledge the following for their guidance and assistance:

- Associate Professor Dr Nik Abdullah Nik Mohamad, Head Department of Anaesthesiology, USM and co-supervisor.
- Special thank to my supervisor, Dr Saedah Ali for her advice, guidance, patience at every stage of this dissertation preparation.
- Associate Professor Dr Syed Hatim Nor (Head of Biostatistic Unit of School Medical Science, USM) for invaluable guidance in the statistical analysis of this study.
- All participants of this study
- Staff Nurse Roslina (Acute Pain Service Nurse) and ICU & Operation Theatre staff nurses of HUSM.
- Academic staffs and colleagues.
- My husband and children for their support, patience and understanding in the completion of this dissertation.
- School of Medical Science, USM Health Campus

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LIST OF ABBREVIATION

CI	Confidence interval
HUSM	Hospital Universiti Sains Malaysia
SPSS	Statistical Packages for Social Science
s.d.	Standard deviation
IV	Intravenous
i.e.	*id est*, that is
et al.	*et alii*, and others
no.	number
fig.	Figure
GABA	Gamma-aminobenzoic acid
Kg	Kilogram
L	Litre
e.g.	*exempli grati*, for example
ICU	Intensive Care Unit
PCA	Patient Controlled Analgesia
mg	Miligram
mmHg	Milimeter Mercury
vs	Versus

ABSTRACT

Introduction: The α2 agonist dexmedetomidine is a new sedative and analgesic agent which is licensed in the USA for post-operative intensive care sedation. We compared dexmedetomidine with the mixture of midazolam and morphine for post-operative patient who required mechanical ventilation in intensive care unit (ICU).

Objective: To compare the effect of dexmedetomidine and midazolam-morphine mixture among post-operative patients in ICU; in term of the amount of analgesic (PCA morphine) requirement, sedation score, haemodynamic profiles and time of extubation.

Methodology: Prospective, double-blinded randomized controlled trial study design involved post-operative patients admitted to the Intensive Care Unit (ICU) of Hospital Universiti Sains Malaysia (HUSM) conducted from June 2003 to June 2004. Thirty-four mechanically ventilated post-operative patients were randomly assigned to receive short-term (minimum 4 hours) sedation with either continuous intravenous infusion of dexmedetomidine (group Dex, n=17) or midazolam-morphine mixture (group MM, n=17). Both groups received similar intraoperative anaesthetic regime. Patient controlled analgesia (PCA Morphine) was given to patient as rescue analgesic. Analgesic (PCA morphine) used (mg/hour), Ramsay sedation scoring, extubation time (minute), systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate were

Medical Sciences, Universiti Sains Malaysia had approved this study on 9th April 2003.

Result: Mean extubation time of dexmedetomidine group was significantly lower than midazolam and morphine mixture group [mean (s.d.): 40.3 ± 16.5 minutes versus 57.9 ± 17.7 minutes, p=0.05]. Within the first 4 hours drug infusion, mean systolic blood pressure [mean (s.d.): 105 ± 14 mmHg vs 127 ± 24 mmHg, (p=0.000)], mean diastolic blood pressure [mean (s.d.): 59 ± 8mmHg vs 66 ± 13 mmHg (p=0.000)], mean arterial pressure [mean (s.d.): 76 ± 9 mmHg vs 86 ± 15 mmHg (p=0.000)] and mean heart rate [mean (s.d.): 88 ± 13 beats per minute vs 102 ± 24 beats per minute (p=0.000)] were significantly lower in dexmedetomidine group than those in midazolam and morphine mixture. There was significant difference of mean Ramsay sedation score between dexmedetomidine and midazolam morphine mixture (p=0.000). However, there was no significant difference of mean dose of morphine per hour between dexmedetomidine groups and midazolam morphine mixture [(mean (s.d.); 1.4 ± 0.7 mg/hour) versus mean (s.d.); 1.1 ± 0.8 mg/hour), p= 0.157].

Conclusion: Dexmedetomidine provides safe, effective sedation and analgesia for postoperative long surgical patient in intensive care unit. Haemodynamic variables of dexmedetomidine group was more stable than midazolam and morphine mixtures group. Thus dexmedetomidine provides better perioperative

haemodynamic control for a long surgery. The use of dexmedetomidine also allowed for more rapid tracheal extubation.

ABSTRAK

Pengenalan: α_2 agonist dexmedetomidine ialah agen sedatif dan analgesik baru yang telah dilesenkan di Amerika untuk sedatif rawatan rapi bagi pesakit selepas pembedahan. Kami membandingkan dexmedetomidine dengan campuran midazolam dan morfin untuk pesakit selepas pembedahan yang memerlukan ventilasi mekanikal di unit rawatan rapi (ICU).

Objektif: Untuk membandingkan di antara dexmedetomidine dan campuran midazolam dan morfin di kalangan pesakit selepas pembedahan di Unit Rawatan Rapi (ICU); dalam segi jumlah keperluan analgesia (PCA morphine), skor sedatif, profil hemodinamik dan masa ekstubasi.

Methodologi: Kajian prospektif secara 'double-blinded randomized controlled trial' melibatkan pesakit selepas pembedahan yang dimasukkan ke Unit Rawatan Rapi (ICU), Hospital Universiti Sains Malaysia (HUSM) di antara Jun 2003 hingga Jun 2004. 34 pesakit selepas pembedahan dengan ventilasi mekanikal telah diagihkan secara rawak untuk menerima sedatif jangka pendek iaitu samada infusi intravena berterusan dexmedetomidine (kumpulan Dex, n = 17) atau campuran midazolam morphine (kumpulan MM, n = 17). Kedua-dua kumpulan menerima regim anesthetic intra-operatif yang sama. PCA Morphine telah diberikan kepada pesakit sebagai analgesik tambahan, jika diperlukan. Penggunaan analgesik (PCA morphine) (mg/hour), pemarkahan sedatif Ramsay, masa ekstubasi (minit), tekanan darah sistolik, tekanan darah diastolik, purata

tekanan arteri dan kadar jantung telah diukur. Jawatankuasa Penyelidikan dan Etika, Pusat Pengajian Sains Perubatan, Kampus Kesihatan, Universiti Sains Malaysia telah meluluskan kajian ini pada 9 April 2003.

Keputusan: Purata masa ekstubasi pesakit dexmedetomidine didapati lebih rendah secara signifikan berbanding campuran midazolam morphine [purata (s.d.): 40.3 ± 16.5 minit berbanding 57.9 ± 17.7 minit, nilai p kurang 0.05]. Dalam masa 4 jam pertama infusi ubat, purata tekanan darah sistolik [purata (s.d.): 105 ± 14 mmHg vs 127 ± 24 mmHg (nilai p kurang 0.000)], purata tekanan darah diastolik [purata (s.d.): 59 ± 8 mmHg vs 66 ± 13 mmHg (nilai p kurang 0.000), purata tekanan arteri [purata (s.d.): 76 ± 9 mmHg vs 86 ± 15 mmHg (p = 0.000)] (nilai p kurang 0.000) dan purata kadar jantung [purata (s.d.): 88 ± 13 denyutan seminit vs 102 ± 24 denyutan seminit (nilai p kurang 0.000) didapati lebih rendah secara signifikan berbanding campuran midazolam morphine. Terdapat perbezaan signifikan peratusan skor sedatif Ramsay di antara dexmedetomidine dan midazolam morphine mixture (p = 0.000). Tetapi, didapati tiada perbezaan signifikan purata dos morphine per jam di antara kumpulan dexmedetomidine dengan campuran midazolam morphine [(purata (s.d.); 1.4 ± 0.7 mg/jam) berbanding purata (s.d.); 1.1 ± 0.8 mg/jam), nilai p = 0.157].

Kesimpulan: Dexmedetomidine adalah sedatif yang selamat, efektif dan analgesik untuk pesakit pembedahan lama di Unit Rawatan Rapi. Variabel

hemodinamik bagi kumpulan dexmedetomidine didapati lebih stabil daripada kumpulan campuran midazolam morphine. Oleh itu, dexmedetomidine memberikan kawalan hemodinamik peri-operatif lebih baik untuk pembedahan yang makan masa lama. Penggunaan dexmedetomidine juga memudahkan ekstubasi trakea lebih cepat dilakukan.

CHAPTER 1: INTRODUCTION

The postsurgical mechanically ventilated patients (e.g. as illustrated in Fig. 1) in the intensive care unit (ICU) often experience anxiety, pain and sleep deprivation due to the stressful nature of ICU environment (Wheeler, 1993). So, the important goals in the treatment of ICU patients are to achieve sedation (while maintaining rousability and cooperation), analgesia and anxiolysis with minimal haemodynamic and respiratory effects (Bhana, 2000).

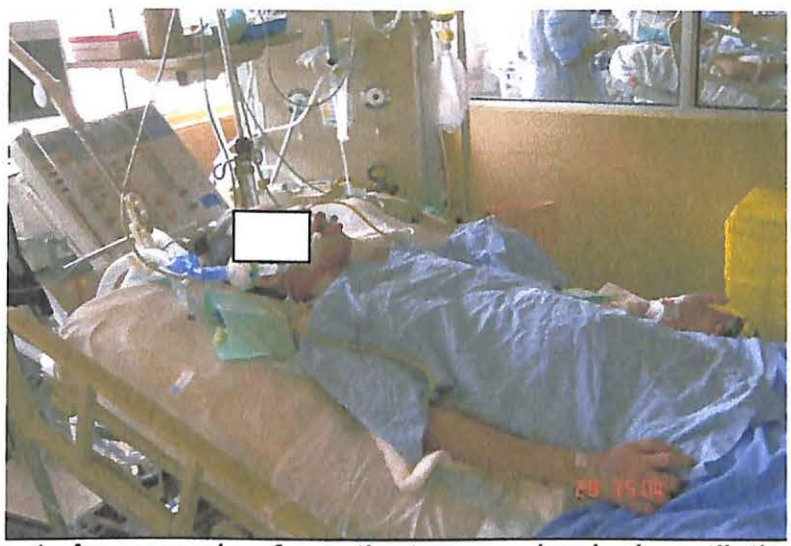

Fig. 1: An example of a patient on mechanical ventilation

The commonly used agents in the ICU include sedatives (e.g. midazolam, lorazepam, diazepam, propofol) and analgesics (e.g. opiates like morphine). However, these drugs are associated with complications such as respiratory depression, lack of orientation, severe hypotension and gastrointestinal hypomotility (Cohen, 2002). The choice of appropriate sedative agents is often difficult and must be individualized for each patient. Among characteristics of an ideal sedative include easily titratable level of adequate sedation, rapid onset of

action, short acting, no adverse effects, no interactions with common ICU drugs, ease of administration, lack of accumulation with prolonged administration, easily prepared with long shelf-life and cost effective (Cohen, 2002). However, the introduction of emerging sedative agents such as dexmedetomidine which produce sedative, analgesic and anxiolytic effects with haemodynamic stability can broaden clinician options in managing ICU patients (Lawrence, 1996). Since 2000, dexmedetomidine has been approved in the United States for use as sedative for patient in the ICU. It has shown clinical efficacy in providing sedation and analgesia in postsurgical ventilated patients (Bhana, 2000). It was also approved by the FDA as a short-term sedative (less than 24 hours) and analgesic in the critical care setting especially during the early postoperative period (Shapiro, 1995).

Dexmedetomidine is a lipophilic imidazole derivative and active dextroisomer of medetomidine, a widely used veterinary anaesthetic (Savola and Virtanen, 1991). It is a highly selective α- adrenoreceptor agonist with 8 times greater affinity for the $\alpha 2$ adrenoreceptor than clonidine (Coughlan et al., 1992). It is also shorter acting than clonidine. It stimulates $\alpha 2$ adrenergic receptors in the locus ceruleus to provide sedation by reducing sympathetic activity and the level of arousal (Lawrence, 1996). In the spinal cord, it enhances analgesia. It also causes sympatholysis via central and peripheral mechanisms. The advantages of dexmedetomidine as sedative in the ICU include: (i) patient can be extubated without prior discontinuation because it does not cause respiratory depression

(ii) as dexmedetomidine infusion can be continued during the postextubation period, the drug allows easier weaning process (iii) easy arousability of treated patients i.e. they can be calmly and easily awakened (Shapiro, 1995). Other advantages of dexmedetomidine include reduction in the need for supplemental propofol and midazolam of sevenfold and fourfold respectively and 50% reduction for morphine requirements. Meanwhile, some adverse effects of dexmedetomidine are hypotension, hypertension (with loading dose) and bradycardia (Bhana, 2000).

Midazolam is short acting, water-soluble benzodiazepine acting on the GABA system which provide anxiolysis and amnesia without analgesic properties. It is transformed to a lipophilic compound in the blood. It rapidly penetrates the central nervous system to produce short onset of sedation of 2-5 minutes. Midazolam exhibits dose-related respiratory depression, hypotension, vasodilatation (large dose), withdrawal syndrome, tolerance, dependence and even addiction (Cohen, 2002). Meanwhile, the opioids (e.g. morphine, fentanyl citrate, hydromorphine) are lipid soluble stereospecific agonists at endorphin receptor sites in the central nervous system and other tissues (Mirski, 1995). At low dose, morphine provides analgesia but not anxiolysis. At high doses, they act like sedative. Opioids is associated with side effects such as respiratory depression, difficult extubation, hypotension, slowing of gastrointestinal motility and withdrawal symptoms (Cohen, 2002).

CHAPTER 2: LITERATURE REVIEW

This study compared postoperative monitoring profiles between dexmedetomidine and the mixture of midazolam and morphine, in term of haemodynamics, sedation score, analgesic requirements and extubation time for long operation which required ICU admission.

2.1 Overview Of Haemodynamic Profiles, Sedation Score, Difference In Analgesic's Dosage Requirements And Time Of Extubation Of Post-Operative Patients In ICU Between Dexmedetomidine And Mixtures Of Midazolam Morphine Groups.

Bloor reported that when dexmedetomidine 1μg/kg administered as a 2-minute infusion to six healthy male volunteers caused significant maximum reductions in heart rate and blood pressure (17 and 23%, respectively, $p<0.005$ vs baseline) (Bloor et al., 1992). In another two phase III trials, patients receiving dexmedetomidine 0.2 to 0.7 μg/kg/h consistently had larger mean decreases in blood pressure and heart rate during the infusion than placebo recipients (Grounds M, 1999).

In a randomized controlled trial involving 20 adults whom undergone 8 hours artificial ventilation, Venn and Grounds had randomized the subjects to receive either dexmedetomidine or propofol. If required, an additional analgesia was provided by an alfentanil infusion. They found that the patients receiving dexmedetomidine significantly lower heart rate, mean (SD) was 72 (10) beats per

minute compared to propofol [90 (18)] ($p < 0.001$) but no differences were found in arterial pressures between the groups. The median (interquartile range) Random Sedation Score (RSS) was 5 (4-6) for the dexmedetomidine subjects and 5 (4-5) for the propofol group ($p = 0.68$). Then, the percentage of time spent at the ideal depth of sedation (i.e. RSS 2-4) was 46.3% (33.1) for the dexmedetomidine subjects and 49.1% (43.7) for the propofol subjects. The propofol group received three times more alfentanil compared with patients sedated with dexmedetimidine (2.5 (2.2 – 2.9) mg per hour versus 0.8 (0.65 – 1.2) mg per hour ($P = 0.004$). Mean (range) extubation time in dexmedetomidine (Dex) group of subjects was 29 (15-50) minutes which almost similar to propofol group i.e. 28 (20-50) minute (Venn and Ground, 2001).

In the European multicentre trial, about 119 post-operative cardiac and general surgical patients who required ventilation and sedation in ICU were enrolled in 4 centres in the United Kingdom. Later, the subjects were randomized to receive dexmedetomidine and placebo with rescue sedation and analgesia provided by midazolam and morphine respectively. Compared with the control group, intubated patient receiving dexmedetomidine required 80% less midazolam (mean 4.9 (5.8) mcg/kg/hour versus 23.7 (27.5) mcg/kg/hour, $p<0.0001$), and 50% less morphine (11.2 (13.4) mcg/kg/hour versus 21.5 (19.4) mcg/kg/hour, $p=0.0006$) (Venn, 1999).

From the Department of Anaestesiology, Medical College of Wisconsin and VA Medical Centre, 34 patients scheduled for elective inpatient surgery were randomized equally to receive either dexmedetomidine (initial loading dose of 1mcg/kg over 10 min followed by 0.4mcg/kg/hour for 4 hours) or morphine sulfate (0.08mg/kg) 30 minutes before the end of surgery. Dexmedetomidine- treated patient had slower heart rate in the Post Anaesthetic Care Unit (PACU) (by an average of 16 bpm), whereas MAP, RR and level of sedation were similar between groups. Average visual analogue score (VAS) sedation scores for the dexmedetomidine and morphine groups were 46 ± 14 and 49 ± 20 respectively. During phase 1 recovery, dexmedetomidine treated patients required significantly less morphine to achieve equivalent analgesia (PACU dexmedetomidine group, 4.5 ± 6.8 mg; morphine group, 9.2 ± 5.2 mg). Sixty minutes into recovery only 6 of 17 dexmedetomidine patients required morphine in contrast to 15 of 17 in the morphine group (Shahbaz, 2004).

A prospective, randomized trial in a paediatric intensive care unit in a tertiary center sought to compare the efficacy of midazolam versus dexmedetomidine for sedation during mechanical ventilation in infants and children. Continuous infusion of either midazolam (starting dose of 0.1 mg/kg/hour) or dexmedetomidine (starting dose of either 0.25 or 0.5 mcg/kg/hour) with intermittent morphine, as needed was given. There were 10 patients in each group. Sedation was equivalent in the 3 groups. There were 36 morphine

boluses administered to the midazolam group versus 29 and 20 morphine boluses administered respectively to the 0.25 and 0.5 mcg/kg/hour dexmedetomidine groups (p= 0.02 for midazolam versus 0.5 mcg/kg/hour dexmedetomidine). Total morphine use (mg/kg/24 hour) was 0.74 ± 0.5, 0.55 ± 0.38, and 0.28 ± 0.12 in the midazolam and the two dexmedetomidine groups respectively (p-value=not significant for midazolam versus 0.25 dexmedetomidine, p-value=0.01 for midazolam versus 0.5 dexmedetomidine (Tobias and Berkenbosch, 2001).

Washington Hospital Centre compared dexmedetomidine-based to propofol-based sedation after coronary artery bypass graft (CABG) surgery in the ICU involved 25 centers in the United States and Canada. They found that there were no significant differences in mean Ramsay sedation scores between groups during assisted ventilation (4.5, dexmedetomidine versus 4.7, propofol; p=0.259). Mean times to weaning and extubation were similar. Median (25^{th}, 75^{th} percentiles) times to the start of weaning were 295 minutes (215, 410) for dexmedetomidine and 300 minutes (210, 482) for propofol. Median times to extubation were 410 minutes for dexmedetomidine and 462 minutes for propofol. Morphine use was significantly reduced in the dexmedetomidine group. Only 28% of the dexmedetomidine patients required morphine for pain relief while ventilated versus 69% of propofol-based patient ($p < 0.001$). Mean blood pressure increased initially in both groups (between 30 minutes and 2 hours after sternal closure), then decreased to 3 mmHg below baseline after 30 minutes in

dexmedetomidine patients; whereas mean arterial pressure remained at 9 mmHg above baseline in propofol patients. Mean heart rates were similar between groups throughout the study period (Daniel, 2003).

2.2 Overview of Sedative Drugs

2.2.1 Midazolam Hydrochloride (Dormicum)

Dormicum is a water-soluble imidazobenzodiazepine. It is presented as clear, colourless solution containing 5mg/ml midazolam hydrochloride, oral tablets 7.5mg or 15mg tablets.

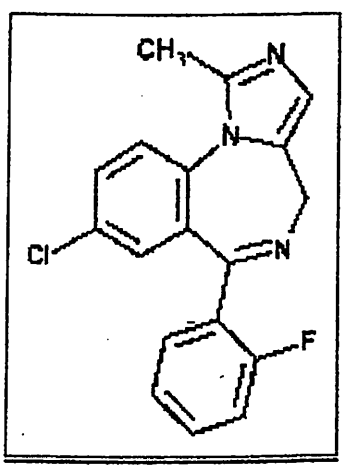

Figure 2.2.1A Chemical structure of midazolam

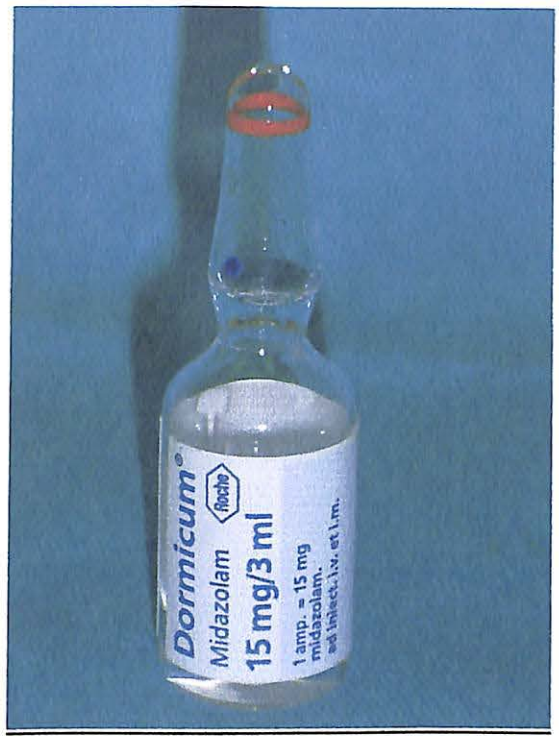

Figure 2.2.1B Midazolam

i. Uses of Midazolam:

Midazolam is used as short acting parenteral benzodiazepine, premedication, induction during general anaesthesia, sedation during short diagnostic and endoscopic procedures as well as during intensive care, hypnotic supplement to balanced anaesthesia for short procedures (anterograde amnesia).

ii. Pharmacodynamic of Midazolam:

a. Central Nervous System:

Sedative, hypnotic, anxiolytic, muscle relaxant, anterograde amnesic and anti-convulsant effects. Intensifies activity of GABA (gamma-aminobenzoic acid), a major inhibitory neurotransmitter of the brain. Dose dependant reduction in

cerebral oxygen consumption and cerebral blood flow. Midazolam causes dose-related changes in regional cerebral blood flow in brain regions associated with the normal functioning of arousal, attention and memory (Veselis et al., 1997).

b. Alimentary System

Lower incidence of postoperative vomiting with midazolam-fentanyl induction sequence versus thiopentone-fentanyl.

c. Cardiovascular System

Clinically, midazolam has minimal cardiovascular effects but will cause variable respiratory depression.

d. Respiratory System and Metabolic

Midazolam impairs ventilatory response to hypercapnia, reduces tidal volume but offset by increase in respiratory rate. Apnoea especially when used as an induction agent. Midazolam decreases adrenergic but not cortisol or renin response to stress for metabolic response.

iii. Pharmacokinetics of Midazolam

The onset of midazolam's absorption is 1 to 5 minutes intravenously. It's bioavailability via oral route is 44%. Midazolam has 96% protein binding with volume of distribution of 0.8-1.5 litre/kg. Midazolam is completely metabolized in

the liver via conjugation. Midazolam is excreted in the urine. The elimination half-life of midazolam is 1.5 to 3.5 hours. Its clearance is 5.8 to 9ml/min/kg.

iv. Route and Dosage of Midazolam

Sedation in ICU loading dose IV is 0.03- 0.3 mg/kg then maintenance at 0.03 to 0.2 mg/kg/hr. When combined with other CNS depressants, reduce dosage by about 30%.

v. Contraindications/ Precautions of Midazolam

Contraindicated in acute narrow angle glaucoma, acute alcohol intoxication, shock. Cautious use in elderly, chronic obstructive airway disease, congestive heart failure and chronic renal failure patients.

vi. Adverse (side effects)

The adverse effects of midazolam include euphoria, confusion, emergence delirium, muscle tremor, ataxia, dysphoria, dysphonia, slurred speech, hypotension, nodal rhythm, respiratory arrest, bronchospasm, nausea, vomiting (low incidence) and pain or induration at site of injection.

Remarks:

Short duration of action is due to its high lipid lipophilicity, high metabolic clearance and rapid rate of elimination. However, may not be true in prolonged

use example infusion in ICU. Clinical effects can be reversed by flumazenil, physostigmine and glycopyrronium.

2.2.2 Morphine Sulphate

Morphine is a phenanthrine derivative. It is the prototype opioid agonist to which all other opioids are compared. Morphine is used for premedication, as an analgesic in the management of moderate to severe pain, for cancer pain and in the treatment of left ventricular failure. Morphine presents as 10/ 30/ 60/ 100 mg tablets, a syrup containing 2/ 10/ 20 mg/ml, as 15/ 30 mg suppositories and as a clear, colourless solution for injection containing 10/ 15/ 30 mg/ml of morphine sulphate.

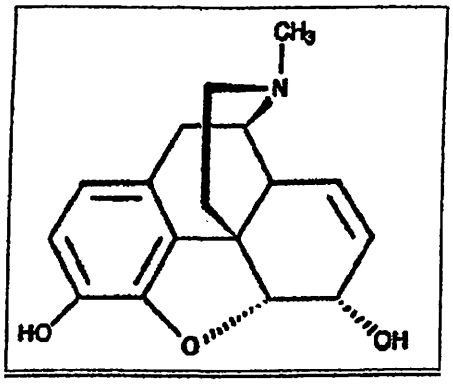

Fig. 2.2.2A Chemical structure of morphine

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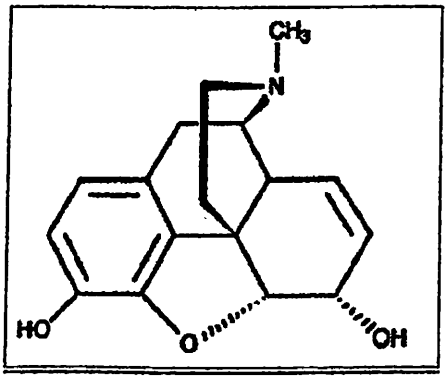

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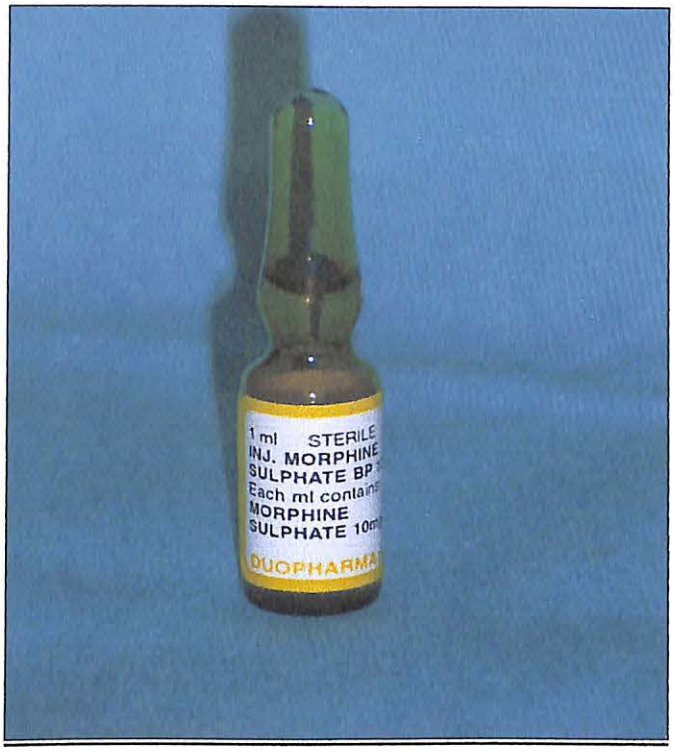

Fig. 2.2.2B Morphine

i. Pharmacodynamic of Morphine

a. Central Nervous System

A potent analgesic agent. Mu and kappa opioid receptor agonist. In humans, morphine produces analgesia, euphoria, sedation and a diminished ability to concentrate. The cause of pain persists, but even low doses of morphine increases the threshold to pain and modify the perception of noxious stimulation such that it is no longer experienced as pain. Continuous, dull pain is relieved by morphine more effectively than is sharp, intermittent pain. In contrast to monopioid analgesics, morphine is effective against pain arising from the viscera as well as from skeletal muscles, joints and integumental structures. Analgesia is

benzodiazepine, whereas these effects do not accompany the administration of either drug alone (Tomicheck et al., 1983).

c. Respiratory system

Morphine has potent anti-tussive action. It also depresses respiration, initially respiratory rate is affected than tidal volume, but as the dose of morphine increased, periodic breathing and apnoea occur.

d. Genitourinary system

Ureteric tone and contractions are increased. Vesicular sphincter tone increased. Morphine also has an anti-diuretic effect.

e. Metabolic

Diaphoresis and pruritus from histamine release. Increase anti-diuretic hormone. Secretion and causes transient decrease in adrenal steroid secretion.

ii. Pharmacokinetics of Morphine

The bioavailability of morphine via oral route is 30% due to first pass metabolism. The protein binding of morphine is about 35% and it's volume of distribution is 3.2 litres/kg. The major pathway for the metabolism of morphine is conjugation which produces morphine 3 glucuronide and morphine 6 glucuronide. It also undergoes demethylation to normophine. Less than 10% is excreted unchanged in the urine. The conjugates of morphine are mainly excreted in the urine and

partially in the bile. The clearance of morphine is 15 ml/kg/min and its elimination half-life is 3 hours. Cummulation of morphine 6 glucuronide occurs in renal failure. The dosage of morphine for intramuscular and subcutaneous is 0.1-0.2mg/kg and for intravenous is 0.05-0.2 mg/kg 3-4 hourly. The peak analgesic effect of morphine is 20 min after IV. Its infusion rate is 0.5- 10mg/hour. Morphine is contraindicated for known allergy. Caution is needed for liver and renal impairment patients, head injury patients and hypovolaemic patients (Stoelting, 1999).

iii. Adverse / Side-effects of Morphine

a. Central Nervous System

The adverse effects of morphine include drowsiness, euphoria, miosis, seizure and muscular rigidity (use of high doses of morphine), dependence, pruritus, hypotension, bradycardia, respiratory depression, bronchoconstriction (use of high doses of morphine), urinary retention, nausea, vomiting, ileus, spasm of spincter of Oddi and constipation.

2.2.3 Dexmedetomidine (Dex)

i. Classification

Dexmedetomidine is a selective alpha 2 adrenoreceptor agonist.

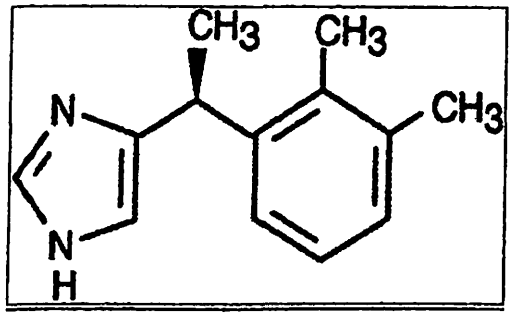

Figure 2.2.3A Chemical structure of dexmedetomidine

ii. Uses

The uses of dexmedetomidine include sedation in initially intubated and mechanically ventilated adult patients during treatment in a intensive care setting for up to 24 hours only, reduces postoperative concurrent analgesic and sedative requirements and being readily arousable and interactive when stimulated without respiratory depression. Most clinical experiences with dexmedetomidine are in postoperative patients.

iii. Presentation

Dexmedetomidine is supplied in the form of 2 ml clear glass ampoule/ vial, 100 mcg/ml as the base. Dexmedetomidine must be diluted in 0.9% sodium chloride to achieve the required concentration prior to administration.

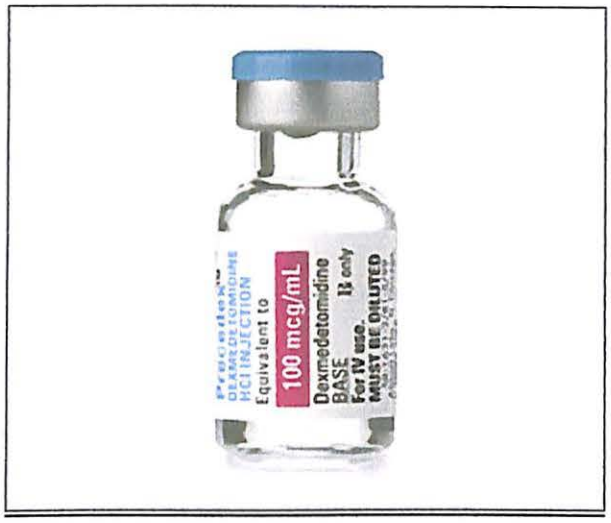

Figure 2.2.3B Dexmedetomidine

iv. Pharmacodynamic/ Action of Dexmedetomidine

a. Mechanism of action:

Alpha 2 receptor are found in the peripheral and central nervous systems, platelets and many other organs, including the liver, pancreas, kidney and eye. Stimulation of the receptors in the brain and spinal cord inhibits neuronal firing causing hypotension, bradycardia, sedation and analgesia. The responses from other organs include decreased salivation, decreased secretion, decreased bowel motility, inhibition of renin release, increased glomerular filtration, increased secretion of sodium and water in the kidney, decreased intraocular pressure and decreased insulin release from the pancreas. The mechanism of action of dexmedetomidine differs from clonidine as it posses selective alpha 2-adrenoreceptor agonism especially for the 2A subtype of this receptor, which causes it to be a much more effective sedative and analgesic agent than clonidine (Bhatia, 2002).

b. Central nervous system

The majority of patients receiving dexmedetomidine were effectively sedated yet were easily arousable, a unique feature not observed with other sedatives (Venn RM et. al, 1999). Additional sympatholytic properties include less anxiety. The sedative actions of dexmedetomidine are believed to be mediated primarily by post-synaptic alpha 2 adrenoreceptors, which in turn act on inhibitory pertussis-toxin-sensitive G protein, thereby increasing conductance through potassium channels. The site of the sedative effects of dexmedetomidine has been attributed to the locus ceruleus. The analgesic actions are believed to be mediated by a similar mechanism of action at the brain and spinal cord level.

c. Cardiovascular system

Dexmedetomidine does not appear to have any direct effects on the heart (Housmans PR., 1990). A biphasic cardiovascular response has been described after the administration of dexmedetomidine (Ralph Gertler et al., 2001; Dyck JB et al., 1993; Bloor BC et al., 1992; Hall JE et al., 2000). The bolus of 1 mcg/ kg dexmedetomidine initially results in a transient increase of the blood pressure and a reflex fall in heart, especially in younger, healthy patients (Blow BC et al., 1992). Stimulation of alpha B2 adrenoreceptor in vascular smooth muscle seems to be responsible for the initial rise in the blood pressure, which can be attenuated by a slow infusion. However, even at slower infusion rates, the increase in mean arterial pressure over the first 10 minutes was shown to be in

the range of 7%, with a decrease in heart rate between 16% and 18% (Hall JE et al., 2000). The initial response lasts for 5 to 10 minutes and is followed by a slight decrease in blood pressure due to the inhibition of the central sympathetic outflow.

The presynaptic alpha 2 adrenoreceptors are also stimulated decreasing the norepinephrine release resulting in fall blood pressure and heart rate (Aantaa R et al., 1990). These effects may also be observed in the postoperative period, and can be easily managed with atropine, ephedrine and volume infusion (Jalonen J et al., 1997). However, these effects may be deleterious in hypovolaemic patients or patients with fixed stroke volume.

d. Respiratory system

The respiratory depression caused by dexmedetomidine has been reported to be much less than with other sedatives.

v. Pharmacokinetics of Dexmedetomidine

Dexmedetomidine exhibits linear kinetics in a dosage range of 0.2 to 0.7 mcg/kg/hr when administered by IV infusion for up to 24 hours. Following infusion, dexmedetomidine exhibits a rapid distribution phase with a half-life (t ½) of about 6 minutes. Steady-state volume of distribution (Vss) of dexmedetomidine is approximately 118L. The average protein binding of dexmedetomidine is a 93.7%. Gender and renal impairment have no effect on

protein binding, however, patients with hepatic impairment may experience changes in protein binding resulting in lower clearance values. There is negligible change in the plasma protein binding of dexmedetomidine in the presence of several drugs administered typically in an intensive care unit setting e.g. fentanyl, ketorolac, theophylline, digoxin and lidocaine. In addition, there is no significant plasma protein binding displacement of other drugs that can be co-administered with dexmedetomidine (e.g. phenytoin, ibuprofen, propranolol, theophylline and digoxin).

Dexmedetomidine undergoes almost complete hydroxylation through direct glucuronidation and cytochrome P450 metabolism in liver. Metabolites are excreted in the urine (about 95%) and in the feces (4%). It is unknown whether they posses intrinsic activity. The elimination half-life is approximately 2 hours. It may be necessary to decrease the dose in patients with hepatic failure, since they will have lower rates of metabolism of the active drug. In cases of renal failure, the metabolites may accumulate, the effects of which have not been studied.

vi. Dosage and clinical duration

Dosing for ICU sedation: initial loading infusion of 1 mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2-0.7 mcg/kg/hour (individualized and titrated to clinical effect).

vii. Contraindication/ Precautions

Dexmedetomidine hydrochloride is contraindicated in patients with a known hypersensitivity to dexmedetomidine. Reports of bradycardia and hypotension have been associated with dexmedetomidine. If medical intervention is required, treatment may include increasing the rate of fluid administration, elevation of lower extremities or use of vasopressor agents. The intravenous administration of anticholinergics (e.g. atropine) should be considered to modify vagal tone. Caution should be exercised when administering dexmedetomidine to patients with advanced heart block. In addition, transient hypertension has been observed primarily during the loading dose, associated with initial peripheral vasoconstrictive effects of dexmedetomidine. If intervention is necessary, reduction of loading infusion rate may be desirable. Dexmedetomidine should not be co-administered through the same intravenous catheter with blood or plasma because physical compatibility has not been established. Dexmedetomidine is primarily metabolized in the liver. Dose reduction should be considered in patients with hepatic impairment.

viii. Adverse/ side-effects of Dexmedetomidine

Bolus dosing of dexmedetomidine is to be avoided as it may be associated with transient hypertension, bradycardia, and sinus arrest in presence of hypovolaemia or high sympathetic tone. Patient may also experience nausea, vomiting, pain, fever and oliguria. Apart from that, patient may develop haematologic manisfestations such as anaemia and leukocytosis.

ix. Drug interactions of Dexmedetomidine

a. General

In vitro studies indicate that clinically relevant cytochrome P450 mediated drug interaction are unlikely.

b. Anaesthetics/ sedatives/ hypnotics/ opioids

Co-administration of dexmedetomidine is likely to lead to an enhancement of effects with anaesthetics, sedative, hypnotics and opioids. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil and midazolam. No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam were demonstrated. However, due to pharmacodynamics effects, when co-administered with dexmedetomidine, a reduction in dosage with these agents may be required.

c. Neuromuscular blockers

No clinically meaningful increases in the magnitude of neuromuscular blockade and no pharmacokinetic interactions were observed with dexmedetomidine and rocuronium administration.

d. Carcinogenesis, mutagenesis, impairment of fertility

Animal carcinogenicity studies have not been performed with dexmedetomidine. Dexmedetomidine was not mutagenic in vitro. Dexmedetomidine did not affect