COMPARISON OF THE EFFECTS OF PROPOFOL-KETAMINE (KETOFOL) MIXTURE IN COMBINATION OF IV FENTANYL PRETREATMENT DURING INDUCTION AND PROSEAL LARYNGEAL MASK AIRWAY (LMA) INSERTION

Dr Nor Fahmi bin Ahmad Bahuri

PUM 00126/12

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TABLE OF CONTENTS

ACKNOWLEDGEMENTS ..... **ii**

TABLE OF CONTENTS ..... **iii**

LIST OF FIGURES ..... **v**

LIST OF TABLES ..... **vi**

LIST OF ABBREVIATIONS ..... **vii**

ABSTRAK ..... **viii**

ABSTRACT ..... **xi**

CHAPTER 1 INTRODUCTION **1**

CHAPTER 2 LITERATURE REVIEW **3**

2.1 PROPOFOL **3**

2.2 KETAMINE **12**

2.3 FENTANYL **22**

2.4 SUPRAGLOTTIC AIRWAY DEVICES **24**

2.6 RATIONALE FENTANYL-'KETOFOL': DIFFERENT MIXTURE **29**

CHAPTER 3 OBJECTIVES **30**

3.1 GENERAL OBJECTIVES **30**

3.3 NULL HYPOTHESES **30**

3.4 JUSTIFICATION OF THE STUDY **31**

CHAPTER 4 METHODOLOGY **32**

4.1 RESEARCH DESIGN **32**

4.4 SAMPLE SIZE DETERMINATION **32**

4.4 METHODS **34**

4.8 STATISTICAL ANALYSIS **38**

CHAPTER 5 RESULTS **47**

5.1 DESCRIPTIVE ANALYSIS 47

5.2 COMPARISON OF HAEMODYNAMIC PROFILES BETWEEN INTERVENTION GROUPS 51

5.3 PROSEAL LARYNGEAL MASK AIRWAYS (PROSEAL-LMA) SCORES AND INTERVENTION GROUPS 71

5.4 FACTORS ASSOCIATED WITH APNOEA AND PROLONGED APNOEA BETWEEN INTERVENTION GROUPS 74

CHAPTER 6 DISCUSSION 80

6.1 SYSTOLIC BLOOD PRESSURE 82

6.2 DIASTOLIC BLOOD PRESSURE 84

6.3 MEAN ARTERIAL PRESSURE 85

6.4 HEART RATE 86

6.5 PROSEAL LMA SCORE 87

6.6 OCCURRENCE OF APNOEA 93

CHAPTER 7 LIMITATION OF STUDY 95

CHAPTER 8 CONCLUSION 96

CHAPTER 9 REFERENCES 97

CHAPTER 10 APPENDICES 110

A: INFORMATION SHEET 110

B : CONSENT FORM 114

DATA COLLECTION SHEET 122

LIST OF FIGURES

Figure 2-1 Pharmacokinetic variables for commonly used intravenous anaesthetics..4

Figure 2-2 Apparent volume of distribution at steady state.....5

Figure 2-3 Stereoisomers of ketamine as it is formulated.....12

Figure 2-4 Simulated time course of plasma levels of ketamine 14

Figure 2-5 Techniques of inserting LMA 26

Figure 5-1 Profile plots showing the trend of systolic blood pressure (SBP) for each propofol / ketamine groups. 55

Figure 5-2 Profile plots showing the trend of diastolic blood pressure (DBP) for each propofol / ketamine groups 60

Figure 5-3 Profile plots showing the trend of Mean Arterial Pressure (MAP) for each propofol / ketamine ratio groups.....65

Figure 5-4 Profile plots showing the trend of heart rate (HR) for each propofol / ketamine ratio groups.....70

LIST OF TABLES

Table 4-1 LMA scoring system 35
Table 5-1 Clinical and demographic profiles of study participants classified by intervention groups.....48
Table 5-2 Haemodynamic profiles of study participants classified by intervention groups 50
Table 5-3 Comparison of sbp across measurement time points.....53
Table 5-4 Comparisons of sbp between different propofol/ketamine ratio groups ..54
Table 5-5 Comparisons of dbp across measurement time points.....58
Table 5-6 Comparisons of dbp between different propofol/ketamine ratio groups ..59
Table 5-7 Comparisons of map across measurement time points.....63
Table 5-8 Comparisons of map between different propofol/ketamine ratio groups .64
Table 5-9 Comparisons of hr across measurement time points 68
Table 5-10 Comparisons of hr between different propofol/ketamine ratio groups ...69
Table 5-11 Comparison of mean proseal lma score between the two groups.....71
Table 5-12 Simple linear regression analyses of possible predictors for proseal lma score 72
Table 5-13 Association of apnoea score to intervention group.....74
Table 5-14 Simple ordinal logistic regression analyses of possible predictors for apnoea status score 76
Table 5-15 Multiple ordinal logistic regression analyses of possible predictors for apnoea status score 78

LIST OF ABBREVIATIONS

LMA	LARYNGEAL MASK AIRWAY
IV	INTRAVENOUS
BMI	BODY MASS INDEX
MAP	MEAN ARTERIAL PRESSURE
NIBP	NON-INVASIVE BLOOD PRESSURE
HR	HEART RATE
SPO2	PERIPHERAL OXYGEN SATURATION
SBP	SYSTOLIC BLOOD PRESSURE
DBP	DIASTOLIC BLOOD PRESSURE
ANCOVA	ANALYSIS OF COVARIANCE

ABSTRAK

Latar belakang dan Tujuan:

Peningkatan minat dalam penggabungan propofol-ketamine sebagai campuran untuk sedasi dan pembiusan telah membawa kepada kajian untuk mendapatkan campuran yang sesuai. Kajian ini dilakukan untuk membandingkan kesan dari dua campuran propofol-ketamine yang berbeza dari sudut kestabilan hemodinamik, keadaan yang sesuai untuk kemasukan Proseal LMA dan kadar apnoea selepas induksi.

Bentuk kajian:

Kajian random di satu pusat, melibatkan dua kumpulan dilakukan di Hospital Universiti Sains Malaysia di antara June 2014 dan October 2014.

Pesakit dan kaedah:

Seramai 88 orang peserta telah direkrut dan dibahagikan secara rawak kepada dua kumpulan menggunakan ‘blok’ rawak. Satu kumpulan pesakit diberikan propofol ketamine dengan nisbah 1:1, manakala satu lagi kumpulan menggunakan propofol-ketamine nisbah 1:0.5. Rekod hemodinamik dilakukan pada waktu permulaan, 1 minit, 5 minit and 10 minit selepas induksi.

Proseal dimasukkan untuk setiap pesakit selepas induksi. Markah skor LMA dan skor ‘apnoea’ direkodkan.

Keputusan

Berdasarkan perbandingan dalam kumpulan, kedua-dua kumpulan propofol-ketamine menunjukkan perubahan yang signifikan dari aspek statistic dalam SBP, DBP, MAP dan HR hampir pada setiap masa yang direkodkan. Walaubagaimanapun, perbandingan di antara kedua-dua kumpulan tidak menunjukkan perubahan yang signifikan dari aspek statistik

Peratusan median untuk saturasi oksigen dan markah kemasukan Proseal LMA adalah hampir sama bagi kedua-dua kumpulan. Tidak ada perbezaan yang signifikan antara kedua-dua kumpulan dalam min Proseal LMA skor. Begitu juga dalam faktor yang berkaitan dengan markah proseal LMA, tidak ada perbezaan yang signifikan.

Kumpulan propofol / Ketamine nisbah 1:1 mempunyai peratusan ‘prolonged apnoea’ yang lebih tinggi dari kumpulan propofol/ketamine 1:0.5 (90.9% vs 13.6%; $p<0.001$). terdapat dua faktor berkaitan dengan skor ‘apnoea’ yang signifikan iaitu BMI (OR disesuaikan 1.148, 95% CI 0.964, 1.583) dan kumpulan intervensi (OR disesuaikan 49.765, 95% CI 12.789, 193.649).

Kesimpulan:

Campuran propofol/ketamine nisbah 1:0.5 adalah lebih baik dari propofol/ketamine nisbah 1:1 kerana ia kurang assosiasi dengan kadar ‘apnoea’. Walaubagaimanapun, kesan hemodinamik adalah stabil dan agak sama dalam kedua-dua kumpulan.

Keywords: *Propofol-ketamine, fentanyl, Proseal*

ABSTRACT

Background and Aims:

The renewed interest in combination of propofol-ketamine as a mixture for sedation and anaesthesia had leaded us to search for a suitable mixture to be used for induction of anaesthesia. This study was conducted to compare the effects of two different mixture of propofol–ketamine on haemodynamic stability, adequate condition for Proseal LMA insertion and occurrence of apnoea after induction.

Settings and Design:

A randomized double-blinded, controlled trial was conducted in Hospital Universiti Sains Malaysia between June 2014 and October 2014.

Patients and Methods:

A total of 88 patients were recruited and randomized into two groups using block randomization. One group of patients was given propofol-ketamine with 1:1 ratio; whereas another group was given propofol-ketamine 1:0.5 ratio. Haemodynamic monitoring was measured at baseline, 1 minute, 5 minute and 10 minutes after induction. Proseal was inserted in each patient after successful induction. LMA scoring and apnoea scoring were recorded.

Results:

In regard to within-intervention-group-effect comparisons, both 1:0.5 and 1:1 propofol / ketamine ratio groups showed statistically significant changes in SBP, DBP, MAP and HR nearly across all time points. However, regarding between-and-within-intervention-group comparisons (i.e. comparison of SBP, DBP, MAP and HR between intervention groups across time points), there were no significant marginal mean differences noted between both propofol / ketamine ratio groups across time. The medians percentage of oxygen saturation was exactly the same for both groups of intervention. There was no significant difference in mean Proseal LMA score between the two groups. There were also no significant predictors between associated with Proseal LMA score. The 1:1 propofol / ketamine ratio group has higher percentage of prolonged apnoea than 1:0.5 propofol/ketamine group (90.9% vs 13.6; $p < 0.001$). There were two significant predictors for apnoea score which were BMI (adjusted OR 1.148, 95% CI 0.964, 1.583) and intervention group (adjusted OR 49.765, 95% CI 12.789, 193.649)

Conclusions:

Propofol/ketamine mixture with 1:0.5 ratio was better than propofol/ketamine 1:1 because it caused lesser association to apnoea occurrence. However the haemodynamic response were stable and comparable in both groups.

Keywords: *Propofol-ketamine, fentanyl, Proseal*

CHAPTER 1 INTRODUCTION

Propofol as an induction agent produces loss of consciousness by facilitation of inhibitory neurotransmission mediated by GABA. Its main strong points are its quick induction and recovery, with antiemetic effects, an anticonvulsant effects and an amnestic agent (Short and Aun, 1991). Although propofol is exceptionally effective and potent, its use is limited by high incidence of hypotension and respiratory depression (Hug *et al.*, 1993).

Ketamine is an anaesthetic agent that acts by stimulating the sympathetic nervous system and increasing blood pressure along with increasing the heart rate. Ketamine as anaesthetic agent provides powerful amnesia and analgesia, and it able to maintain airway reflexes and spontaneous respiration (Warncke *et al.*, 1997).

Improved haemodynamic stability after induction has been shown with the usage of propofol-ketamine, commonly referred to as 'ketofol' (Ghatak *et al.*, 2012). The anaesthetic agent ketamine stimulates the sympathetic nervous system and increases blood pressure along with increasing the heart rate. It was observed that addition of ketamine reduced consumption of propofol and opioids and ensured better respiratory stability in patients.

There are numerous ways been done to combine propofol and ketamine. Many studies compared different concentration of propofol-ketamine. Badrinath *et al.* (2000) reported that ratio of 1:5 ketofol with local anaesthesia provides good analgesia and sedation for breast biopsy procedure. They reported that combination of propofol and ketamine (5:1) provides effective sedation/analgesia during monitored anaesthesia care. A study was performed using a mixture of the 1:1 compared with 1:2 ketamine-propofol. Nausea, hallucination and recovery time were observed more in 1:1 ratio solution. Andolfatto and Willman (2010) reported 1:1 ratio of ketofol is highly effective in paediatric emergency procedures.

The role of fentanyl in improving PLMA insertion prior to propofol has been studied. It enhances the insertion conditions with success rate up to 85-95% (Cheam and Chui, 2000). The ProSeal Laryngeal Mask Airway (PLMA) has significant advantage over Classic LMA in that it protects the lungs from aspiration and the stomach from gastric insufflations by facilitating passage of a gastric tube and monitoring devices into the ooesophagus. Its insertion technique is the same as the Classic or Intubating LMA (Brimacombe and Keller, 2000). Insertion of the PLMA after induction of anaesthesia requires adequate depth of anaesthesia for suppression of airway reflexes.

The primary goal of this study is to determine a better mixture of ketofol for general anaesthesia induction for Proseal LMA insertion in terms of haemodynamic stability, easiness of insertion and percentage of occurence of apnoea. No study has been done to compare the different concentration of ketamine-propofol (ketofol) on LMA Proseal insertion with the effect of fentanyl pretreatment in both group.

CHAPTER 2 LITERATURE REVIEW

2.1 PROPOFOL

2.11 CHEMISTRY AND FORMULATIONS

Propofol was introduced in 1970s as 2,6-diisopropofol. At first, it was prepared with Cremophor EL because of its insolubility. However, reports of anaphylcatoid reactions emerged resulting in production of propofol in emulsion. Currently, propofol is used for induction and maintenance of anaesthesia and for sedation. Now, propofol is the most popular IV anaesthetic used by clinicians.

Propofol is classified as alkylphenols, which is oil at room. Propofol is produced for IV administration as a 1% (10 mg/mL) emulsion in 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide. This formulation is slightly viscous, with milky white substance and has a pH of 7. It is insoluble in aqueous solutions. In some countries, a formulation in which the emulsion contains a mixture of medium-chain and long-chain triglycerides has been used. A 2% formulation has also been developed. Propofol is stable at room temperature and are not light sensitive.

2.12 PHARMACOKINETICS

Propofol is a lipophilic weak acid. Two-compartment and three-compartment models have been used to described the pharmacokinetics of propofol. Blood propofol levels will decrease rapidly after a single bolus injection, due to redistribution and elimination. The initial distribution half-life of propofol is 2 to 8 minutes and slow distribution half-lives is 30 to 70 minutes and an elimination half-life of 4 to 23.5 hours. The long elimination half-life

points toward a deep compartment with limited perfusion, which cause a slow return of propofol back to the central compartment.

Elimination	Elimination Half-Life (hr)	Clearance (mL/kg/min)	Vd_{SS} (L/kg)
Dexmedetomidine	2-3	10-30	2-3
Diazepam	20-50	0.2-0.5	0.7-1.7
Droperidol	1.7-2.2	14	2
Etomidate	2.9-5.3	18-25	2.5-4.5
Flumazenil	0.7-1.3	5-20	0.6-1.6
Ketamine	2.5-2.8	12-17	3.1
Lorazepam	11-22	0.8-1.8	0.8-1.3
Methohexital	2-6	10-15	1.5-3

FIGURE 2-1 PHARMACOKINETIC VARIABLES FOR COMMONLY USED INTRAVENOUS ANAESTHETICS

The context-sensitive half-time for infusion of propofol up to 8 hours is less than 40 minutes (Hughes *et al.*, 1992). The recovery from propofol remains rapid even after prolonged infusions because propofol concentration usually just need to be less than 50% for awakening after anaesthesia or sedation. The volume of distribution of the central compartment is from 20 to 40 L, and the volume of distribution at steady state has been calculated as 150 to 700 L. The clearance of propofol is greater than hepatic blood flow, which is at 1.5 to 2.2 L/min. This suggests that extrahepatic metabolism has played a role in propofol clearance.

Propofol is able to decrease hepatic blood flow and reduce its own clearance. Changes in cardiac output may influence propofol concentrations as shown after a bolus dose and during constant infusion. Propofol concentrations in plasma decrease by increasing cardiac output, and increases when cardiac output decreases.

In general children have about 50 percent larger central compartment volume than adult patient with a more rapid clearance. Children are usually divided between those older

than 3 years, and younger than 3 years old. In the latter group, they have larger central compartment and systemic clearance values than in adults or older children (Kataria *et al.*, 1994).

2.13 METABOLISM

Propofol metabolism via conjugation results in production of glucuronide and sulfates and will be excreted by the kidneys. Most of the propofol will be metabolized, with 2% is excreted in faeces and less than 1% is excreted in urine. As mentioned above, it has been suggested that propofol clearance exceeds hepatic blood flow and extrahepatic metabolism has been recommended. These extrahepatic metabolism include renal and lung system.

Elimination	Elimination Half-Life (hr)	Clearance (mL/kg/min)	Vd_{SS} (L/kg)
Midazolam	1.7-2.6	6.4-11	1.1-1.7
Propofol	4-7	20-30	2-10
Thiopental	7-17	3-4	1.5-3

FIGURE 2-2 APPARENT VOLUME OF DISTRIBUTION AT STEADY STATE

2.14 PHARMACODYNAMICS

2.141 CENTRAL NERVOUS SYSTEM

Propofol exerts its effect in CNS by binding to the ß-subunit of $GABA_A$ receptor hence increasing aminobutyric acid (GABA)–induced chloride current through it. Propofol will modulate $GABA_A$ receptors in the hippocampus to stop acetylcholine release in the hippocampus and prefrontal cortex (Kushikata *et al.*, 2002).

Another mechanism by which propofol may contribute to the drug's hypnotic effects

is by inhibition of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor. This will occur through its effect on sodium channel gating. In spinal cord propofol cause a direct depressant effect on its neurons. Two notable side effects of propofol are its antiemetic effect and a sense in patients.

Induction dose is influenced by patient's age with the largest at ages younger than 2 years old. After 2 years old, induction dose decreasing with increasing age (Aun *et al.*, 1992). At lower doses, sedation and amnesia may be provided by propofol. A peak effect of 90 to 100 seconds has been shown for the onset of hypnosis after a dose of 2.5 mg/kg. For loss of consciousness, the median effective dose (ED_{50}) of propofol is 1 to 1.5 mg/kg after a bolus. Five to 10 minutes of hypnosis has been witnessed after 2 to 2.5 mg/kg of propofol, and this duration of hypnosis is dose-dependent.

High infusion rates of propofol could produce burst suppression in EEG (Reddy *et al.*, 1992). After 2.5 mg/kg of propofol followed by an infusion EEG shows an initial increase in alpha rhythm followed by a change to gamma and theta frequency. In BIS, propofol shows a concentration-dependent decrease in its level. 50% and 95% of patients unable to respond to a verbal command at BIS of 63 and 51. At a BIS value of 77, 95% of patients shows lack of recall (Glass *et al.*, 1997).

Seizures have been reported after propofol administration, as the effect of propofol on EEG activity is controversial. The seizure occurs usually on induction or recovery from anaesthesia and occasionally in the postoperative period. Propofol produces a direct anticonvulsant effect and it is dose-dependent.

2.142 CARDIOVASCULAR

Propofol reduces systemic vascular resistance, cardiac contractility, and preload. Patients with impaired ventricular function poorly tolerate significant reductions in cardiac output as a result of decreases in ventricular filling pressures and contractility. Heart rate

increases secondary to activation of baroreceptor-mediated compensatory mechanisms in response to the reduction in cardiac output and systemic vascular resistance

Propofol produces a dose-dependent decrease in blood pressure that is significantly greater than that produced by thiopental; the effect is explained by vasodilation and mild depression of myocardial contractility. Propofol appears to blunt the baroreceptor reflex or is directly vagotonic. As with thiopental, propofol should be used with caution in patients at risk for or intolerant of decreases in blood pressure. Propofol result in decrease in arterial blood pressure during induction of anaesthesia. Systolic blood pressure and diastolic blood pressure reduces from 25% to 40% and lead to a reduction of cardiac output, cardiac index and stroke volume index and left ventricular stroke work.

Systemic blood pressure decrease after administration of propofol due to vasodilation and direct myocardial depressant effects of propofol. At concentrations more than 10 μg/mL the inotropic effect is abolished, and the lusitropic (relaxation) effect of ß stimulation is increased. The vasodilatory effect of propofol is dose-dependent and contributed by direct effect on intracellular smooth muscle calcium mobilization, reduction in sympathetic activity, reduction in angiotensin II–elicited calcium entry and inhibition of prostacyclin synthesis in endothelial cells.

Propofol may reduce the tachycardic response to hypotension by inhibiting the baroreflex, and result in insignificant change of heart rate. It also has minimal effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction. The heart rate response to atropine is also reduced by propofol. This is shown in a study where propofol infusion with concentration of 10 mg/kg/hr which result in cumulative dose of atropine of 30 μg/kg increased heart rate greater than 20 beats/min in only 20% of subjects compared with 100% in the absence of propofol. Mixture of propofol and 0.5mg/kg of ketamine could prevent decreases in haemodynamics after induction of anaesthesia with propofol.

Arterial systolic blood pressure also is decreased to 30% less than baseline level prior to induction during maintenance. After a bolus dose of propofol, peak plasma concentrations

are considerably higher than the concentrations seen with a continuous infusion.

2.143 RESPIRATORY SYSTEM

An induction dose of propofol results in 30% incidence of apnoea. The incidence and duration of apnoea depend on dose, premedication and speed of injection of propofol. The apnoea may occur more than 30 seconds and may increase by contribution of premedication or opiate. The apnoea usually preceded by significant decrease of tidal volume and tachypnoea. Decrease in tidal volume up to 40%, with an increase in respiratory frequency up to 20% may occur during maintenance of propofol infusion. The response to carbon dioxide also is affected during propofol infusion. A 58% decrease in the slope of the carbon dioxide–response curve may occur at 100 μg/kg/min infusion. By increasing the infusion rate to twice its level leads to minimal decrease in carbon dioxide responsiveness.

Propofol influence carotid body chemoreceptors to reduce the ventilatory response to hypoxia in the range of 50 to 120 μg/kg/min. In patients with chronic obstructive pulmonary disease, propofol may cause bronchodilation. It reduces vagal and methacholine- induced bronchoconstriction and may also modulates muscarinic receptors. Propofol also may improve patients lung pathology as shown in animal model where propofol with concentration of 10 mg/kg/hr significantly reduced free radical mediated and cyclooxygenase catalyzed lipid peroxidation. This may help patients with adult respiratory distress syndrome. However these benefits are yet to confirmed in humans.

2.144 OTHER EFFECTS

Reports of anaphylactoid reactions to the propofol have emerged. A large number of these cases had a previous history of allergic responses. Therefore propofol should be used carefully in patients with known drug allergies.

Its antiemetic activity is effective at low doses as shown in study where a bolus dose of 10 mg has been used to treat postoperative nausea. A propofol infusion of 10 to 20 mg loading dose followed by 10 μg/kg/min can achieve median concentration of 343 ng/mL that is linked to its antiemetic effect.

Propofol also been shown to be effective to treat cholestatic pruritus and may be as good as naloxone in treating pruritus induced by spinal opiates. However, this result has not been confirmed in other studies.

Measures such as aseptic technique must still be adhered during propofol infusion. The intralipid that acts as the solvent for propofol may act as an excellent culture medium. To prevent the bacterial growth, propofol has been added with preservative Disodium edetate or metabisulfite.

Pancreatitis has been associated with the administration of propofol which may be associated with hypertriglyceridaemia. Induction of anaesthesia with propofol is associated with several side effects, including pain on injection, myoclonus, apnoea, hypotension, and, rarely, thrombophlebitis of the vein into which propofol is injected.

Higher incidence of prolonged apnoea has been observed with propofol than other anaesthetic agent such as thiopental. Combination with opiate may increase the apnoea duration. Hypotension is usually observed during anaesthetic induction, and this could be worsened by addition of opioids. Haemodynamic changes such as MAP, heart rate, and systemic vascular resistance are less affected by laryngoscopy and endotracheal intubation when propofol is used, compared to thiopental.

2.15 USES

2.151 INDUCTION AND MAINTENANCE OF ANAESTHESIA

The main indication for Propofol is for the induction and maintenance of anaesthesia at dose of 1 to 2.5 mg/kg. The induction dose can be markedly reduced by addition of opiate or a benzodiazepine as a premedication. Older and sicker patients may need lower dose of induction because the hypotension effect is more significant. These patients may need cautious loading with fluid prior to induction to reduce the severity of hypotension.

Propofol result in faster recovery and an earlier return of psychomotor function when used for short procedure compared to other anaesthetic agent. Desflurane produce recovery slightly faster than propofol. In a procedure, propofol maintenance can be given via propofol infusion or intermittent boluses of 10 to 40 mg is needed every few minutes.

There are a few ways to use propofol as an infusion. Combination of propofol with other drugs such as of opiates, midazolam, clonidine, or ketamine may reduce its required dose. Opioids will reduce the opioid also affects the time from termination of drug to awakening and recovery.

After a satisfactory induction dose, a bolus of 10 to 40 mg is needed every few minutes to maintain anaesthesia. Because these doses need to be given frequently, it is more suitable to administer propofol as a continuous infusion. The usual dosage for propofol for induction of general anaesthesia is 1-2.5 mg/kg IV. For maintenance of anaesthesia 50-150 μg/kg/min IV combined with an opiate and the range of blood concentration of propofol for maintenance of anaesthesia are 2.5 to 4.5 μg/mL. Propofol pharmacokinetics has allowed us to use propofol as a continuous infusion for the maintenance of anaesthesia.

2.152 SEDATION

Propofol has been used for sedation in ICU because it can be easily titrated to a desired level of sedation and provide a fast recovery after infusion is completed. One study showed patients regain consciousness within 10 minutes after being sedated in the ICU for 4 days with propofol. The rate of recovery and the decrease in plasma concentration were similar at 24 hours and at 96 hours, when the infusion was discontinued.

2.2 KETAMINE

2.21 CHEMISTRYAND FORMULATIONS

Ketamine is a type of phencyclidine, water soluble but is 5 to 10 times more lipophilic than thiopental. It was first introduced into clinical anaesthesia in 1966. Compared to other anaesthetic drugs it has a significant analgesic effect. Ketamine also does not cause impair cardiovascular and respiratory systems. There are of two stereoisomers, S(+) and R(-) of ketamine. The S(+) is more powerful compared to R (-) counterpart. Ketamine is also used in chronic pain states, potential neuroprotective effects, total IV anaesthesia and its effects on hyperalgesia and opiate tolerance.

Ketamine is partially water soluble with molecular weight of 238 kD. It is in a white crystalline salt form with a pK_a of 7.5.

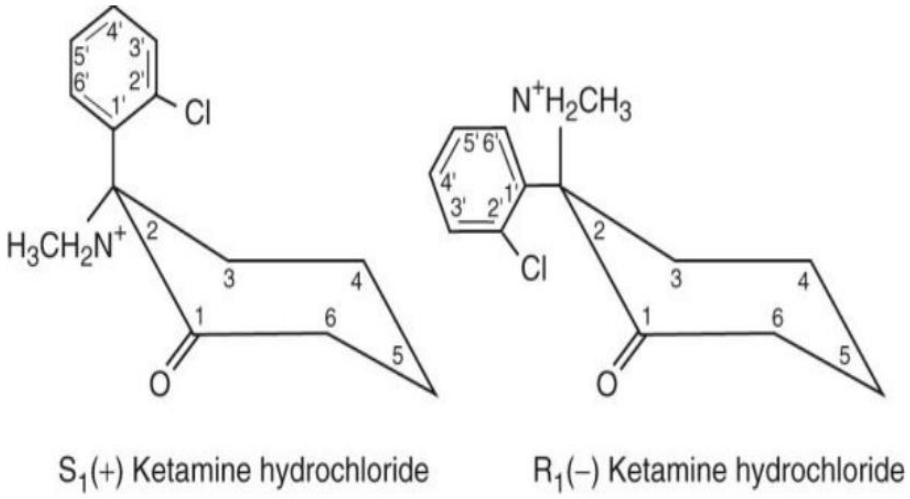

FIGURE 2-3 STEREOISOMERS OF KETAMINE AS IT IS FORMULATED

2.22 PHARMACOKINETICS AND METABOLISM

The onset and duration of an induction dose of ketamine are determined by the same distribution/redistribution mechanism for all the other parenteral anaesthetics. Ketamine is hepatically metabolized to norketamine, which has reduced CNS activity; norketamine is further metabolized and excreted in urine and bile. Ketamine has a large volume of distribution and rapid clearance that make it suitable for continuous infusion without the drastic lengthening in duration of action seen with thiopental (Table 13–2 and Figure 13–2).

Ketamine has large volume of distribution of 3 L/kg which is reflected by its high lipid solubility. Ketamine clearance is high at 890 to 1227 mL/min, which result in short elimination half-life of 2 to 3 hours. Any changes in liver blood flow affect ketamine clearance because its mean total body clearance at 1.4 L/min is about equal to liver blood flow.

However there are differences in the pharmacokinetics of the two isomers. S(+) ketamine has a larger elimination clearance and larger volume of distribution than R (-) ketamine.. The S(+) enantiomer also seems to be more potent in suppressing the EEG than either R(-) or the racemic mixture.

Ketamine can be given via an intranasal spray or by oral routes, but they are subject to significant first-pass metabolism. The bioavailability via oral administration is 20% to 30%, and via the intranasal route is approximately 40% to 50%.

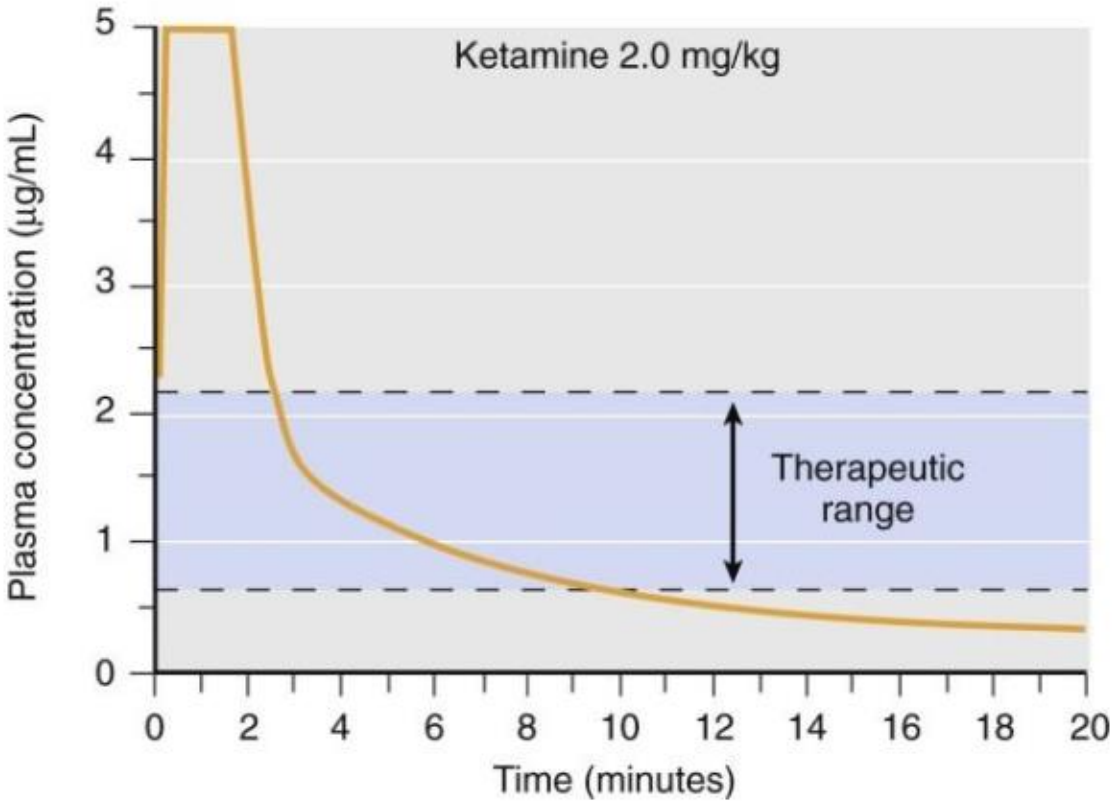

FIGURE 2-4 SIMULATED TIME COURSE OF PLASMA LEVELS OF KETAMINE

After an induction dose of 2mg/kg, plasma levels required for hypnosis and amnesia during surgery are 0.7 to 2.2mcg/ml, with awakening usually occurring at levels less than 0.5mcg/ml. Ketamine is metabolized by *n*-demethylation to form norketamine by hepatic microsomal enzymes. Norketamine is then hydroxylated to hydroxynorketamine and both metabolites will be conjugated to water-soluble glucuronide derivatives. These products will be excreted in urine. Norketamine may prolong the analgesic effect of the parent drug although some study showed it has less activity than ketamine.

2.23 PHARMACODYNAMICS

2.231 NERVOUS SYSTEM

Ketamine produces *dissociative anaesthesia where* patients appear to be in a cataleptic state. This has been described as profound analgesia, where patients keep their eyes open and maintain many reflexes. Patients could not recall surgery but amnesia effect will be better with benzodiazepines. The unconsciousness and analgesic effect is dose-dependent.

With a pK_a of 7.5, and high lipid solubility, the onset of action starts within 30 to 60 seconds of administration as it can cross the blood-brain barrier fast. The peak effect occurs in about 1 minute. Minimum concentrations for general anaesthesia are 0.6 to 2 μg/mL plasma concentration with interindividual variability. Typically, a general anaesthetic dose (2 mg/kg) will last for 10 to 15 minutes, and patients will regain full orientation within 15 to 30 minutes.

After bolus of ketamine, lacrimation and salivation will occur, pupils will dilate, and nystagmus may be observed. Purposeless movements of the legs, arms and trunk may be noted as well. Larger doses will result in longer anaesthesia and combination with other anaesthetics may prolong the time of emergence. Short duration of ketamine is due to its redistribution from the brain and blood to the other tissues in the body. The effect will last until drug redistributes from the well-perfused to the less well-perfused tissues.

The S(+) enantiomer result in more rapid recovery than the racemic mixture due (Kharasch and Labroo, 1992) to the 10% faster hepatic biotransformation. If the S(+) enantiomer is combined with a benzodiazepine result showed no different in terms of awareness at 30 minutes, but it was considerably better at 120 minutes than the racemic mixture.

Ketamine provides effective postoperative analgesia at significantly lower blood

levels than anaesthetic doses. Pain thresholds are elevated at plasma ketamine concentration more than 0.1 μg/mL. The analgesic effect can occur subanaesthetic doses. Ketamine acts to inhibit nociceptive central hypersensitization and it is able to reduce acute tolerance after opiate administration

Ketamine act primarily at the thalamoneocortical projection system. The drug will depresses neuronal function in parts of the cortex and thalamus while at the same time it will stimulate parts of the limbic system. This process creates what is termed a *functional disorganization* of nonspecific pathways in midbrain and thalamic areas

Ketamine may also occupies opiate receptors in the brain and spinal cord and give its analgesic property, especially S(+) enantiomer which has been shown to have some opioid μ-receptor. Ketamine also interact with NMDA which contribute to its anaesthetic and analgesic effect.

Ketamine results in CNS excitations, increases cerebral metabolism, CBF, and ICP. The CNS effect is reflected in generalized EEG development of theta wave activity and by petit mal seizure–like activity in the hippocampus. Overall, the ICP will increase secondary to increase in CBF and the generalized increase in sympathetic nervous system response. Ketamine preserves cerebrovascular responsiveness to carbon dioxide. Animal models showed ketamine reduces necrosis and improves neurologic outcome. It is suggested that ketamine mediate the reduction of necrotic cell death and involved in antiapoptotic mechanisms.

However in study with younger animals, ketamine accentuate apoptosis in the newborn brain of animals, similar with other anaesthetics either at high relative doses or with prolonged exposure and this create controversy over the use of ketamine in neonates. The spinal cord analgesic effect of ketamine is postulated to be due to inhibition of dorsal horn wide dynamic range neuronal activity. Although some drugs have been used to antagonize ketamine, no specific receptor antagonist is yet known that reverses all the CNS effects of ketamine.

Ketamine produces emergence reactions, which are described as vivid dreaming,

sense of floating out of body, and illusions which vary in severity. Excitement, confusion, euphoria, and fear are associated with dreaming and illusion. The incidence ranges from 3% (White *et al.*, 1982) to 100% and about 10% to 30% of adult patients. These emergence reactions may be due to ketamine-induced depression of auditory and visual relay nuclei, leading to misperception or misinterpretation of auditory and visual stimuli. Typically it occurs in the first hour of emergence and usually abate within 1 to several hours.

The incidence of emergence reactions is low in paediatric patients. Certain personality types such as individuals who commonly dream at home or patients who score high in psychotism on the Eysenck Personality Inventory are more likely to develop emergence reactions. In general the emergence reactions are influenced by age, dose, gender, psychological susceptibility, and concurrent drugs. The most effective drug to suppress these reactions is the benzodiazepines.

2.232 CARDIOVASCULAR SYSTEM

Ketamine stimulates the cardiovascular system by increasing in blood pressure, heart rate, and cardiac output. This is in contrast with other anaesthetic induction drugs which either cause no change in haemodynamic variables or produce vasodilation with cardiac depression. As a result of these stimulations, there is an increased work and myocardial oxygen consumption of the heart. However the haemodynamic changes are not dose dependent. Some author stated that there is no haemodynamic difference between IV administration of 0.5 mg/kg and 1.5 mg/kg. The haemodynamic change after ketamine induction is similar between healthy patients and in patients with heart diseases. Patients with elevated pulmonary artery pressure may have more significant increase in pulmonary than systemic vascular resistance. However, no considerable changes were noted in shunt directions or fraction or systemic oxygenation in patients with congenital heart disease.

Ketamine may reduce baroreceptor function via an effect on NMDA receptors in the

nucleus tractus solitaries. Ketamine also causes the sympathoneuronal release of noradrenaline, which can be detected in venous blood

In vitro, ketamine reduce inotropic effects as shown in chronically instrumented dogs which shows myocardial depression. However this is in contrast with another study involving isolated guinea pig hearts where ketamine was the least depressant of all the major induction drugs. This direct depressant effects of ketamine may be override by ketamine centrally mediated sympathetic responses. Stimulation of the cardiovascular system is not always advantageous to the patients, and some drugs have been used such adrenergic antagonists (a and ß), various vasodilators and clonidine to suppress these effects.

The most common method is administration of benzodiazepines prior to ketamine induction. Propofol and inhalation anaesthetics may also blunt the haemodynamic effect of ketamine.

2.233 RESPIRATORY

Ketamine may cause transient decrease in minute ventilation after the bolus administration of an induction dose of ketamine (2 mg/kg intravenously). Overall effect on the central respiratory drive is minimal, as shown by an unaltered response to carbon dioxide. Arterial blood gases generally are preserved when ketamine is used alone for anaesthesia or analgesia. Apnoea may occur, but its incidence is rare if ketamine is used alone. However large doses of ketamine, or administration of adjuvant sedatives or anaesthetic drugs may result in respiratory depression.

Ketamine could improve pulmonary compliance and has a role as a bronchial smooth muscle relaxant. Ketamine has been used to treat asthmatic patient unresponsive to conventional therapy and sometimes given to patients with reactive airway disease and bronchospasm to improve compliance.

In children, ketamine may increases salivation that lead to upper airway obstruction,

and laryngospasm. Ketamine also may affect ventilatory control in children and should be considered a possible respiratory depressant when the drug is given to them in bolus doses.

2.234 OTHER SIDE-EFFECTS

Ketamine is generally contraindicated for patients with increased ICP and with intracranial mass lesions because it can increase ICP and has been reported to cause apnoea. Ketamine also may be contraindicated in patients with an open eye injury or other ophthalmologic disorder, in which a ketamine-induced increase in intraocular pressure would be harmful.

Ketamine also not suitable to used as the sole anaesthetic in patients with ischaemic heart disease due to its susceptibility to cause hypertension and tachycardia and increase in myocardial oxygen consumption. Similarly patients with vascular aneurysms are contra indicated due to the potential sudden change in arterial pressure.

2.24 USES

2.241 INDUCTION AND MAINTENANCE OF ANAESTHESIA

Ketamine is an excellent choice for induction in patients with reactive airway disease due to its bronchodilation and analgesic action. Patients with haemodynamic compromise based on either hypovolaemia or cardiomyopathy, or trauma patient with large blood loss are candidates for rapid- sequence anaesthesia induction with ketamine. However intrinsic myocardial depressant effect of ketamine may manifest if trauma or sepsis has caused depletion of catecholamine stores before the patient's arrival in the operating room.

Ketamine properties that preserves heart rate and right atrial pressure through its

sympathetic stimulation also makes it a good choice for patients with other cardiac diseases such as cardiac tamponade and restrictive pericarditis.

Patients with valvular and ischaemic heart disease may be given satisfactory cardiac anaesthesia by ketamine combined with propofol or midazolam infusion. Propofol with combination of low-dose ketamine has become more popular as a total IV anaesthesia technique for patients undergoing noncardiac surgery. The haemodynamic changes are minimal and slight ventilatory depression is noted when spontaneous ventilation is used.

2.242 SEDATION

Ketamine has been used for sedation for many paediatric procedures such as cardiac catheterization, radiation therapy, radiologic studies, dressing changes and dental work. Usually it is combined with premedication of a barbiturate or benzodiazepine and an antisialagogue such as glycopyrrolate to facilitate procedures. Paediatric patients have fewer adverse emergence reactions compared to adult, and this put ketamine superior to other sedative agent.

Ketamine has also been used as an adjunct to regional anaesthesia. Procedures such as application of painful blocks or during long or uncomfortable procedures, IV ketamine (0.5 mg/kg) can be given. Its combined sedative and analgesic properties and favourable effects on haemodynamics make ketamine a good choice as a sedation for patients in a critical care unit.

2.243 PAIN MANAGEMENT

A few meta-analyses have showed an overall reduction in opiate use or improved analgesia and a decrease in opiate-induced side effects, especially incidence of post op nausea vomiting when ketamine given perioperatively. Ketamine combination with

morphine using an 8-minute lockout interval provided optimal postoperative analgesia in a mixture of 1:1 ratio. Another study involving total knee arthroplasty showed successful analgesia with an initial bolus of 0.5 mg/kg of ketamine followed by a continuous infusion of 3 μg/kg/min during surgery and 1.5 μg/kg/min for 48 hours after surgery.

Ketamine direct analgesic activity and its action on opiate tolerance and hyperalgesia have made ketamine becoming more popular in chronic pain states. Few trials have shown ketamine effectiveness in the treatment of cancer pain, chronic peripheral and central neuropathic pain, phantom and ischaemic limb pain, fibromyalgia, complex regional pain syndrome, visceral pain, and migraine.

2.3 FENTANYL

2.31 CHEMISTRYAND FORMULATIONS

Fentanyl is a synthetic opioid related to the phenylpiperidines. Due to its short time to peak analgesic effect, rapid offset of effect after small bolus doses, and favourable cardiovascular profile, fentanyl has become a popular anaesthetic agent. Dose of fentanyl depends on factors such as age, body weight, physical status, underlying pathological condition, use of other medicines, type of anaesthesia to be used, and the surgical procedure involved. In general dosage should be individualized. Elderly and sick patients usually need lower initial dose. Fentanyl can be given as a slow intravenous infusion or by patient-controlled infusion device. An infusion may be started during surgery as an adjunct to general anaesthesia with a dose of 100 µg, increased as required until the desired effect is achieved. Epidural and intrathecal infusions, with or without local anaesthetic, are used in the management of chronic malignant pain and selected cases of nonmalignant pain.
Sustained release of fentanyl for 48 hours or more are available as transdermal patches.

2.33 PHARMACOKINETICS AND METABOLISM

Fentanyl is most commonly administered intravenously, and it is 100 times more potent than morphine. Fentanyl is more lipid soluble than morphine, result in less risk of delayed respiratory depression from rostral spread of opioid given intrathecally. Fentanyl reach peak effect after 5 minutes compared to morphine which reach peak effect after 15 minutes with faster recovery, as well. Prolonged infusion will prolong the drug effect with similar duration with other longer-acting opioids.

Fentanyl decreases the heart rate and blood pressure mildly, and in general provides cardiovascular stability. Fentanyl is usually used for cardiovascular surgery or for patients

with poor cardiac function due to this property. Since fentanyl undergo hepatic metabolism and renal excretion, prolonged infusions result in longer duration of action.

With a single I.V. dose of fentanyl 100 micrograms, the usual duration of action of analgesic effect is 30 to 60 minutes. The duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect. Following administration of fentanyl, reduced sensitivity to CO2 stimulation may persist longer than depression of respiratory rate. Altered sensitivity to CO2 stimulation has been showed for up to four hours after a single IV dose of 600 micrograms fentanyl to healthy volunteers. In general the length of time and degree of respiratory depression is dose-dependent. Diaphragm rigidity can be solved by neuromuscular blocking agent. Fentanyl is metabolized in the liver, by cytochrome P450 3A4 (CYP 3A4) to norfentanyl via oxidative N-dealkylation.

2.34 SIDE EFFECTS

Fentanyl may result in bradycardia and asystole if fentanyl is combined with non-vagolytic muscle relaxants. Bradycardia may be reversed with atropine. Suitable measures to keep a stable blood pressure should be taken because fentanyl may induce hypotension, especially in hypovolaemic patients.

The other actions of fentanyl such as euphoria, miosis, analgesia, bradycardia, bronchoconstriction, muscle rigidity and suppression of cough reflexes can be treated by specific antagonists, i.e. naloxone.

Changes in respiratory system which includes respiratory rate, alveolar ventilation are usually longer than the analgesic effect. The reduction in pulmonary exchange becomes greater with higher narcotic dose and may lead to apnoea in higher dose.

Histamine release rarely occurs with fentanyl, as shown in studies involving histamine assays and skin wheal testing in man. Higher doses of fentanyl, between 100-400 micrograms/kg, cause a rapid reduction in blood pressure, which may last up to 30 minutes.

Like morphine, fentanyl has the potential to be abused due to its drug dependence. Chronic pain patients may require higher doses of opioid. Muscle rigidity caused by fentanyl is related to the speed of injection. It can be avoided by slow intravenous injection, muscle relaxants or premedication with benzodiazapines.

2.4 SUPRAGLOTTIC AIRWAY DEVICES

Supraglottic Airway Devices are designed to form a seal in the pharynx between the respiratory and digestive tracts to protect the airway and facilitate gas exchange. They are inserted blindly and the proximal tube will be connected to an anaesthesia circuit or other device. A better seal can be achieved with larger LMA, but this may increase the risk of sorethroat. There are several insertion techniques with gentleness is very important aspect of it. The "sniff" position is recommended for insertion of an LMA. Techniques developed over many years by Archie Brain may not be succesful in all patients and different techniques are sometimes needed to insert it.

Many drugs have been tested for LMA insertion with propofol or sevoflurane is considered the most favourable agent used. Opioids such as fentanyl, alfentanil may suppresses swallowing, coughing, gagging, and improve the ease of insertion and airway patency.

A sufficient depth of anaesthesia must be achieved before LMA insertion. LMA will be pushed along the palate and then the posterior pharyngeal wall until resistance increases which may indicates the tip lie within the upper oesophageal sphincter. Jaw thrust or direct laryngoscopy may be used to aid placing. Air is inflated into the cuff with cuff pressure not higher than 60 cm H_2O. Too high pressure may reduce its effectiveness. After connected to the anaesthesia circuit, gentle manual ventilation will be carried out. Lung expansion is observed. Features of airway obstruction such as slow refill of the reservoir bag or detect sounds of respiratory obstruction from auscultation must be checked before proceed with