A Comparative Study Of The Efficacy And Requirement Of Remifentanil Infusion Alone Versus Remifentanil Infusion + Midazolam For End Stage Renal Failure (ESRF) Patient During Tenckhoff Insertion In Monitored Anaesthesia Care (MAC) : A Randomized Controlled Double Blinded Trial

BY

DR. YAP KIM LIP

Dissertation Submitted in Partial Fulfillment of the Requirement for

The Degree of Master of Medicine

(ANAESTHESIOLOGY)

UNIVERSITI SAINS MALAYSIA

2015

ACKNOWLEDGEMENT

I would like to take the opportunity to extend my utmost appreciation and gratitude to those who have helped me right from the beginning till the completion of my dissertation.

- My dissertation supervisor, A.P Dr Shamsul Kamalrujan , Head Of Department , Anaesthesiology and Intensive Care Unit, School of Medical Science, University Sains Malaysia for his untiring, timely, guidance supervision for my research.
- My co-supervisor, Dr Rhendra Hardy Mohamed Zaini, Consultant Anaesthesiology in the Department of Anaesthesiology and Intensive Care Unit, School of Medical Science, University Sains Malaysia , for his suggestion and advice on this research.
- My co-supervisor, Dr Ng Kim Swan ,Consultant Anaesthesiology in the Department of Anaesthesiology and Intensive Care Unit, Hospital Selayang , for her suggestion of this topic and her guidance for my research
- All others lecturers in Department of Anaesthesiology and Intensive Care Unit, School of Medical Science, University Sains Malaysia , for their suggestion towards the successful of my study
- To supporting staff from Operation theater , for their help throughout the study
- To my parents Mr. Yap Voon Yan and Mrs. Lee Yoon Chin for their prayers for me. Last but not least my dearest wife Lou Khee Fang who have inspired me with her endless support, love and most important her patience in ensuring the completion of this study.

TABLE OF CONTENT

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ASA	America Society Of Anesthesiology Classification
ESRF	End Stage Renal Failure
LA	Local Anesthetics
MAC	Monitored Anesthesia Care
OASS	Observer Assessment Of Alertless And Sedation Score
TCI	Target Controlled Infusion
VAS	Visual Analogue Score

ABSTRAK

TAJUK: PERBANDINGAN KEBERKESANAN BAGI INFUSI “REMIFENTANIL” SAHAJA DENGAN INFUSI “REMIFENTANIL” DITAMBAH “MIDAZOLAM” SEMASA PEMBEDAHAN “ TENKCHOFF” DALAM RAWATAN PENGAWASAN ANESTHESIA BAGI PESAKIT KEGAGALAN BUAH PINGGANG

Pengenalan:

Ubat “Remifentanil” ialah sejenis ubat tahan sakit, digunakan untuk tujuan meningkatkan keberkesanan pembiusan setempat bagi mengurangkan ketidakselesaan dan kesakitan pesakit semasa rawatan pengawasan anesthesia. Tetapi, dos remifentanil yang diperlukan, interaksi dengan ubat penenang seperti “midazolam”, dan profil keselamatan terutamanya dalam pesakit kegagalan buah pinggang yang menjalani pembedahan ‘tenckhoff ’ belum dikenal pasti lagi. Oleh itu, kajian ini telah dijalankan untuk menentukan dos infusi yang sesuai untuk ‘remifentanil’ sahaja atau apabila ditambah dengan ‘midazolam’, dan dalam masa yang sama untuk menilai keselamatan dan keberkesanan ‘remifentanil’ dalam pembedahan tenckhoff.

Kaedah:

58 pesakit yang dijadualkan untuk operasi ‘tenckhoff’ semasa rawatan pengawasan anesthesia telah mengambil bahagian dalam kajian ini setelah kajian ini mendapat kelulusan oleh Jawatankuasa Penyelidikan dan Etika, Pusat Pengajian Sains Perubatan, Universiti Sains Malaysia, Kampus Kesihatan Kelantan. Walau bagaimanapun, 3 pesakit terpaksa dikeluarkan dari kajian ini kerana bertukar kepada pembiusam am penuh. Pesakit- pesakit dibahagikan secara rawak kepada dua Kumpulan: (1) ‘remifentanil’

bermula pada dos 0.5ng /ml , dan plasebo ditambahkan, (2) ‘remifentanil’ bermula pada 0.5ng /ml dan ‘midazolam’ 0.02 mg/kg ditambahkan . Ubat bius setempat ‘levobupivacaine’ dengan dos maksimal dos 2 mg /kg kemudian dibenarkan untuk disuntik. Penilaian lisan tahap kesakitan, ketidakselesaan dan ketenangan dijalankan. Tahap kesakitan, ketidakselesaan dan ketenangan seterusnya dinilai setiap 5 minit. Saturasi oksigen pesakit, kadar pernafasan dan dengutan jantung akan diawasi pada setiap 5 minit. Dos ‘ Remifentanil’ ditmabah secara berperingkat 0.1ng / ml daripada kadar permulaan untuk mengawal ketidakselesaan atau kesakitan pesakit. Selepas operasi , pesakit akan dinilai kesan sampingan ubat tahan sakit seperti loya, muntah dan gatal

Keputusan:

Pada masa suntikan bius setempat, lebih banyak pesakit dalam kumpulan ‘remifentanil + plasebo’ mengalami sakit yang paling teruk (78.6%) dan ketidakselesaan yang paling teruk (46.4%) apabila dibandingkan dengan Kumpulan ‘midazolam + remifetanil’ (29.6% dan 11.1%, masing-masing). Dos ‘Remifentanil’ ‘mean ±SD’ bagi operasi ini ialah 1.57 ± 0.11 ng/ml (kumpulan remifentanil + plasebo) bagi dan 0.92 ± 0.11 ng/ml (kumpulan remifentanil + midazolam). Kumpulan ‘midazolam + remifentanil’ mencapai skor kesakitan < 4 dalam masa (minit) lebih cepat berbanding kumpulan plasebo (9.78 dan 22.36 minit masing masing ; $p < 0.05$) Secara amnya, kumpulan pesakit-pesakit ‘ Midazolam + remifentanil’ mempunyai lebih banyak komplikasi semasa operasi . 7 pesakit (25.9%) dalam Kumpulan ‘remifentanil + midazolam’ dan 2 pesakit (7.1%) dalam Kumpulan ‘remifentanil

sahaja' mengalami kekurangan kadar penafasan dalam tempoh yang singkat (< 8 nafas/min). Di sisi lain, Kumpulan pesakit- pesakit 'Remifetanil plasebo' mempunyai kejadian kesan sampingan ubat tahan sakit yang lebih tinggi . *7 pesakit (*25%) dalam Kumpulan 'remifentanil plasebo' dan 1 pesakit (3.7%) dalam Kumpulan 'remifentanil + midazolam' muntah selepas operasi

Kesimpulan :

Ubat 'remifentanil' adalah berkesan dan dapat memberikan keselesaan sepanjang operasi dijalankan dalam rawatan pengawasan anesthesia pada dos 1.57ng / ml apabila digunakan persendirian sahaja, atau pada dos 0.92ng/ml apabila bercampur dengan ubat 'midazolam'. Oleh itu, menambahkan 'midazolam' dengan 'remifentanil' boleh mengurangkan dos 'remifentanil' yang digunakan, dan mnencapai masa yang lebih singkat untuk mendapatkan skor kurang sakit yang dihendaki semasa pembedahan. Walau bagaimanapun, terdapat peningkatan kejadian komplikasi (penurunan nadi pernafasan , penurunan nadi jantung dan penurunan tekanan darah) dalam Kumpulan 'midazolam + remifentanil' dan pada aspek yang lain, terdapat peningkatan kejadian kesan sampingan ubat tahan sakit (loya, muntah dan gatal) dalam kumplan 'remifetanil placebo' sahaja

Kata kunci: rawatan pengawasan anesthesia, kegagalan buah pinggang peringkat akhir , pembedahan' tenkchoff', ubat 'midazolam', ubat 'remifentanil' , infusi sasaran dikawal (TCI)

ABSTRACT

TITLE: COMPARING THE EFFICACY AND REQUIREMENT OF REMIFENTANIL INFUSION ALONE VERSUS REMIFENTANIL INFUSION + MIDAZOLAM FOR END STAGE RENAL FAILURE (ESRF) PATIENT DURING TENCKHOFF INSERTION IN MONITORED ANAESTHESIA CARE (MAC)

Introduction:

Remifentanil ,an ultra-short acting opioid analgesic, may be useful as an intravenous adjuvant to local anaesthetic for treating patient discomfort and pain during monitored anesthesia care (MAC). However , the remifentanil dose requirement , interaction with other commonly used sedative drug (such as midazolam), and the safety profile especially in ESRF patient for tenckhoff surgery have not been determined . Therefore , this study was designed to define the appropriate dose of remifentanil hydrochloride alone or combined with midazolam , and at the same time to evaluate the safety and efficacy of remifentanil during tenckhoff surgery MAC setting .

Methods:

58 patients scheduled for tenckhoff catheter insertion under MAC setting were recruited in this double-blind study after approved by Research and Ethics Committee, school of Medical Sciences, University Sains Malaysia, Kelantan Health Campus. However, 3 patients had drop off due to convert general anaesthesia. Patients were randomly assigned

to one of two groups: (1) remifentanil TCI starting at 0.5ng/ml plasma concentration + placebo normal saline , (2) remifentanil TCI starting at 0.5ng/ml plasma concentration + midazolam 0.02mg/kg . Standard local anesthetic (LA) (max dose of 2 mg /kg levobupivacaine) was allowed to be injected after that. Verbal assessments of pain, discomfort and sedation according to modified OAA/S score were assessed with 1st LA injection. The level of pain , discomfort and sedation were subsequently assessed every 5 minutes. Patient oxygen saturation, respiratory rate and heart rate were monitored at 5 minutes interval. Remifentanil was titrated (in increments of 0.1ng/ml from the initial rate) to limit patient discomfort or pain intraoperatively and the infusion was terminated at the completion of skin closure. Post operatively, patient were assessed for incidence of opioid's side effect such as nausea , vomiting and pruritus

Results:

At the time of the local anaesthetic, more patients in the remifentanil + placebo group experienced severe pain (78.6%) and severe discomfort (46.4%) as compared with midazolam + remifetanil group (29.6% and 11.1%, respectively). The final mean $\pm$SD remifentanil TCI were 1.57 $\pm$ 0.11 ng/ml (remifentanil + placebo) and 0.92 $\pm$ 0.11 ng/ml (remifentanil + midazolam). Midazolam + remifentanil group achieved pain score <4 in the faster time (minutes) compared with placebo group (9.78 vs 22.36 minutes ; $p < 0.05$)

Generally, Midazolam + remifentanil group patients had higher incidences of all adverse evenst intraoperatively. 7 patients (25.9%) in the remifentanil + midazolam group and 2 patients (7.1%) in the remifentanil alone group experienced brief periods hypoventilation (< 8 breaths/min). On the other hand, Remifetanil placebo group patient had higher incidence of post operative opioid side effects . 7 patients (25%) in the remifentanil

placebo group and 1 patients (3.7%) in the remifentanil + midazolam group experienced vomiting .

Conclusions

TCI remifentanil provided effective analgesia and comfort during MAC at a mean plasma concentration 1.57ng/ml when administered alone, or at a mean plasma concentration of 0.92ng/ml in combination with midazolam. Thus , the adding of midazolam in combination with TCI remifentanil could reducing the dose of TCI remifentanil used , and faster time to achieve satisfactory pain score during surgery.

However, there were increased incidences of intraoperative adverse even (hypotension , bradycardia and respiratory depression) with midazolam + remifentanil group and on the other hand, increase incidences of opiods side effecst (nausea , vomiting , prutitus) with remifentanil alone .

Keyword: Monitored Anesthesia Care , End Stage Renal Failure , Tenkchoff Surgery , Midazolam Remifentanil , Target Controlled Infusion

Chapter 1 INTRODUCTION

ESRF patient often possess high anesthesia risk even come for minor surgery due to their underlying co–morbidity such as hypertension , ischemic heart disease , diabetes mellitus and congestive heart failure with poor functional status, electrolyte imbalance and impair kidney function. This cause them have a higher risk of intraoperative cardiac event.

In addition, because of the alter drug metabolism due to impair renal function, most of the anesthetists are having difficulty in finding a balance between adequate dose of iv induction agent and systemic opioids to provide a good anesthesia and analgesic and at the same time avoiding the exaggerating of drug's side effect which is common in this group of patient. Vigilance are utmost important when provide general anesthesia for this group of patient, yet this group of patient often presented unexpected general anesthesia complication that putting the anesthetist in the difficult situation.

On the other hand, the most common operation done on ESRF patient are fistula creation , tenckhoff catheter insertion for the purpose of dialysis, and operation related to complication of underlying co-morbid illness. These operation usually done under local anesthetics and sedation giving by surgeon, but are often result in inadequate pain and anxiety controlled which induce physiological stress and dissatisfaction among ESRF patient .

Thus, monitored anesthesia care (MAC) is a good choice that suited all the parties , it can offer a safe anesthesia to this group of patient without the risk of general anesthesia , can improve patient satisfaction and provide a clam and pain free surgical field for the surgeon .

However, the type and dose of sedation and analgesic used especially in ESRF patient is a continuously topic of research as it is determined by age, cardiac function , underlying co-morbidity and renal function. Thus, the challenge remained in avoiding the complication of sedative and analgesic agent but at the same time providing a conscious sedation with the aim of

1. Good pain control obtain by local anaesthetics and analgesic drugs
2. Safe sedation with correct monitoring
3. Anxiety control and reduction of external stress during the operation

Midazolam is a short-acting benzodiazepine that possesses anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant, and sedative properties. Midazolam has a fast recovery time and is the most commonly used benzodiazepine as a premedication for sedation, less commonly it is used for induction and maintenance of anesthesia. Sedation in adult is achieved within 3 to 5 minutes after intravenous (IV) injection. Titration to effect with multiple small doses is essential for safe administration.

Although midazolam and fentanyl are widely used during MAC, their potent synergistic interaction can result in significant respiratory depression (Bailey *et al* 1990) especially in renal impairment patient . Even though this synergistic effect is well known for midazolam and fentanyl, but there is not much data regarding interaction between midazolam and remifentanil, in view of the unique pharmacokinetic of remifentanil, which is much different from fentanyl.

The usage of remifentanil in the new era of anesthesia care is growing rapidly due to its unique features. Remifentanil is a potent ultra-short-acting synthetic opioid analgesic drug. It is given to patients during surgery to relieve pain and as an adjunct to an anaesthetic. It has a rapid blood-brain equilibration half-time and a rapid onset of action. The pharmacodynamics effects of remifentanil closely follow the measured blood concentrations, allowing direct correlation between dose, blood levels, and response.

Since the post-operative opioid analgesic effect may not be essential for procedure under MAC because of residual LA effect , a rapid and ultra – short acting opioids analgesic such as remifentanil could prove to be a valuable supplement to LA in the intra operative management of patient pain during MAC (Rosow 1993) , which make it a good choice in ESRF patient . However, the side effect of opioids remain a concern and so far there are minimal data regarding the requirement and efficacy of remifentanil in ESRF patient undergoing MAC surgery.

Chapter 2: OBJECTIVE AND HYPOTHESIS

General Objective

To compare the efficacy and requirement of remifentanil TCI alone versus remifentanil TCI + midazolam for ESRF patient dztedfgnuring tenckhoff surgery in MAC setting

Specific Objective

A) Primary Outcome

1. To compare the effectiveness of remifentanil alone in terms of time (minutes) to achieve adequate analgesic during tenckhoff surgery MAC setting versus combination with midazolam

2. To determine the target plasma concentration (ng/ml) of remifentanil alone and when combined with midazolam to achieve adequate analgesic during tenckhoff surgery MAC setting.

B) Secondary Outcomes

1. To evaluate the occurrence of opioids side effects (nausea, pruritus, vomiting) with remifentanil TCI with or without midazolam

2. To correlate the occurrence of adverse events in term of hypotension , respiratory depression and bradycardia with remifentanil TCI with or without midazolam

Research Hypothesis

The combination of midazolam with TCI remifentanil can reduce the mean plasma concentration (ng/ml) of remifentanil requirement during tenkhoff surgery in ESRF patient in MAC setting

Null Hypothesis

There is no different in mean plasma concentration (ng/ml) between remifentanil TCI alone or remifentanil TCI combined with midazolam during tenckhoff surgery in ESRF patient in MAC setting

Chapter 3 LITERATURE REVIEW

3.1 Midazolam

3.1.1 Overview

Midazolam is a short-acting benzodiazepine that possess anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant, and sedative properties. (Mandrioli *et al* 2008).

Midazolam has a fast recovery time and is the most commonly used benzodiazepine as a premedication for sedation, less commonly it is used for induction and maintenance of anaesthesia (Stoelting 2006).

Midazolam, like many other benzodiazepines, has a rapid onset of action, high effectiveness and low toxicity level. Drawbacks of midazolam include drug interactions, tolerance, and withdrawal syndrome, as well as adverse events including cognitive impairment and sedation. (Riss 2008). Paradoxical effects occasionally can occur, including restless and delirium, most commonly in children and the elderly (Riss 2008) , particularly after intravenous administration.

Midazolam is characterized by a pH-dependent ring opening phenomenon in which the ring remains open at pH values of <4, thus maintaining the water solubility of the drug (Fig. 3.1). The ring closes at pH values of >4, as when the drug is exposed to physiologic pH, thus converting midazolam to a highly lipid-soluble drug (stoelting 2006), and this characteristic is responsible for the fast onset of action of midazolam as compare with others benzodiazepines.

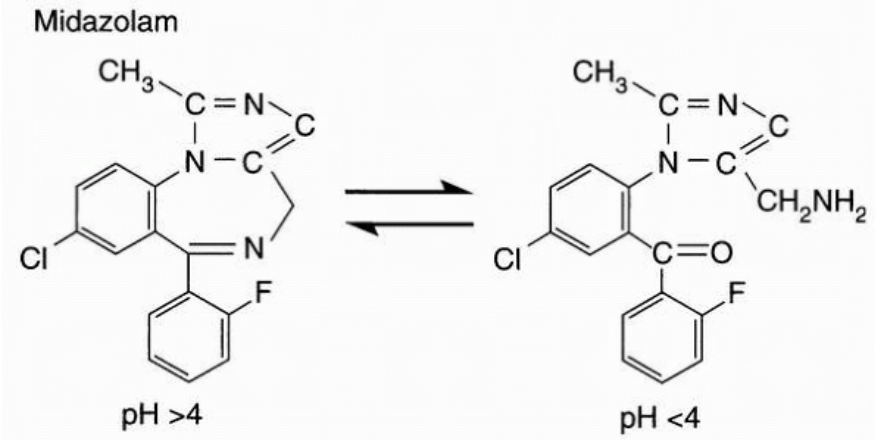

Figure 3.1 Reversible ring opening of midazolam above and below at pH of 4

(Mohler H, Richards JG. The benzodiazepine receptor: a pharmacologic control element of brain function. Eur J Anesthesiol Suppl 1988;2:15-24)

3.1.2 Mechanism Of Action

Midazolam produce all the pharmacologic effects by facilitating the actions of γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the CNS (figure 3.2) . Benzodiazepines do not activate GABA receptors but rather enhance the affinity of the receptors for GABA (Mohler H, Richards JG 1988).

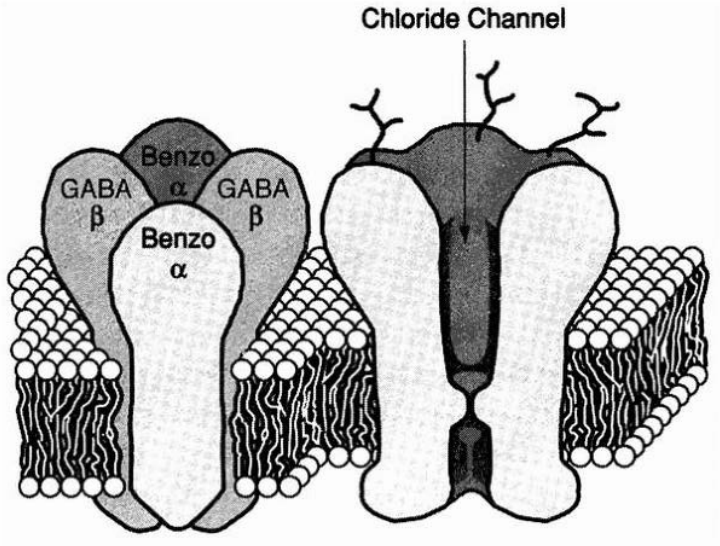

Figure 3.2. Model of the γ-aminobutyric acid (GABA) receptor

(Mohler H, Richards JG. The benzodiazepine receptor: a pharmacologic control element of brain function. Eur J Anesthesiol Suppl 1988;2:15-24)

As a result of this drug-induced increased affinity of GABA receptors for the inhibitory neurotransmitter, an enhance opening of chloride gating channels results in increased chloride conductance, thus producing hyperpolarization of the postsynaptic cell membrane and rendering postsynaptic neurons more resistant to excitation (stoelting 2006).

The GABA receptor is a large macromolecule that contains physically separate binding sites (principally α, β, and γ subunits) not only for GABA and the benzodiazepines but also for barbiturates, etomidate, propofol, neurosteroids, and alcohol (stoelting 2006).

3.1.3 Pharmacokinetic Of Midazolam

Midazolam undergoes rapid absorption from the gastrointestinal tract and achieves prompt passage across the blood-brain barrier. Despite this prompt passage into the brain, midazolam is considered to have a slow effect-site equilibration time (0.9 to 5.6 minutes) compared with other drugs such as propofol and thiopental. In this regard, intravenous doses of midazolam should be sufficiently spaced to permit the peak clinical effect to be appreciated before a repeat dose is considered (stoelting 2006).

Table 3.1 : Comparative Pharmacology Of Benzodiazepines

	Equivalent Dose (mg)	Volume of Distribution (liter /kg)	Protein binding (%)	Clearance (mg/kg/min)	Elimination Half- time (hrs)
Midazolam	0.15-0.3	1.0-1.5	96-98	6-8	1-4
Diazepam	0.3-0.5	1.0-1.5	96-98	0.2-0.5	21-37
Lorazepam	0.05	0.8-1.3	96-98	0.7-1.0	10-20

(Stoelting, Robert K.; Hillier, Simon C.Pharmacology and Physiology in Anesthetic Practice, 2nd Edition 2006 Lippincott Williams & Wilkin)

Metabolism

Midazolam is rapidly metabolized by hepatic and small intestine cytochrome P-450 (CYP3A4) enzymes to active 1-hydroxymidazolam that may accumulate in critically ill patients and inactive metabolites. The metabolism of midazolam is slowed in the presence of drugs that inhibit cytochrome P-450 enzymes (cimetidine, erythromycin, calcium channel blockers, and antifungal drugs) and may result in unexpected CNS depression. Age related deficits, renal and liver status affect the pharmacokinetic factors of midazolam as well as its active metabolite (Spina *et al* 2007). Thus, dose reduction should be consider when administrated midazolam to these group of patient. However, the active metabolite of midazolam is minor and contributes to only 10 percent of biological activity of midazolam.

Renal Clearance

The elimination half-time, volume of distribution (Vd), and clearance of midazolam are not altered by renal failure. Midazolam had an elimination half-life of one to four hours. However, in the elderly, as well as young children and adolescents, the elimination half-life is longer (Rosenbaum et *al* 2009)

3.1.4 Pharmacodynamic Of Midazolam

A .Central Nervous System

Midazolam, like other benzodiazepines, produces decreases in cerebral metabolic oxygen requirements ($CMRO_2$) and cerebral blood flow analogous to barbiturates and propofol. In contrast to these drugs, midazolam is unable to produce an isoelectric EEG, emphasizing that a ceiling effect exists with respect to the decrease in $CMRO_2$ produced by increasing doses of midazolam

Similar to thiopental, induction of anaesthesia with midazolam does not prevent increases in ICP associated with direct laryngoscopy for tracheal intubation (stoelting 2006). Midazolam is also a potent anticonvulsant effective in the treatment of status epilepticus

B. Respiratory system

Patients with chronic obstructive pulmonary disease experience a greater midazolam-induced depression of ventilation. Transient apnoea may occur after the rapid injection of large doses of midazolam, especially in the presence of preoperative medication that includes an opioid. Benzodiazepines also depress the swallowing reflex and decrease upper airway activity (stoelting 2006). 0.15 mg/kg of midazolam may cause respiratory depression, which is postulated to be a central nervous system (CNS) effect (Reves 1985). When midazolam is administered in combination with fentanyl, the incidence of hypoxemia or apnea becomes more likely (Bailey *et al* 1990)

C. Cardiovascular System

In the presence of hypovolemia, the administration of midazolam results in enhanced blood pressure-lowering effects similar to those produced by other intravenous induction drugs. Midazolam does not prevent the blood pressure and heart rate responses evoked by intubation of the trachea. (stoelting 2006)

D. Antagonist

Flumazenil, a benzodiazepine antagonist drug, can be used to treat an overdose of midazolam, as well as to reverse sedation (Olkkola 2008). However, flumazenil can trigger seizures in mixed overdoses and in benzodiazepine-dependent individuals, so is not used in most cases.

3.1.5 General Usage Of Midazolam

A. Preoperative Medication

Midazolam is the most commonly used oral preoperative medication. Oral midazolam at a dose of 0.25 mg/kg is effective for producing sedation and anxiolysis with minimal effects on ventilation and oxygen saturation. The anterograde amnesia property of midazolam is useful for premedication before surgery to inhibit unpleasant memories (Riss 2008)

B. Intravenous Sedation

Midazolam in doses of 1.0 to 2.5 mg IV is effective for sedation during regional anaesthesia, as well as for brief therapeutic procedures. Midazolam-induced depression of ventilation is exaggerated (synergistic effects) in the presence of opioids and other CNS depressant drugs (stoelting 2006). It is important to appreciate that increasing age greatly increases the pharmacodynamics sensitivity to the hypnotic effects of midazolam. Midazolam is also used for endoscopy procedural sedation (McQuaid *et al* 2008) and sedation in intensive care (Brown *et al* 2005)

C. Induction of Anaesthesia

Anaesthesia can be induced by administration of midazolam, 0.1 to 0.2 mg/kg IV, over 30 to 60 seconds. Onset of unconsciousness (synergistic interaction) is facilitated when a small dose of opioid (fentanyl, 50 to 100 µg IV or its equivalent) precedes the injection of midazolam by 1 to 3 minutes.

D. Maintenance of Anaesthesia

Midazolam may be administered to supplement opioids, propofol, and/or inhaled anaesthetics during maintenance of anaesthesia. Anaesthetic requirements for volatile anaesthetics are decreased in a dose-dependent manner by midazolam (stoelting 2006).

E. Postoperative Sedation

The long-term intravenous administration of midazolam (loading dose 0.5 to 4 mg and maintenance dose 1 to 7 mg/hr) to produce sedation in intubated patients results in the relative saturation of peripheral tissues with midazolam, and clearance from the systemic circulation becomes less dependent on redistribution into peripheral tissues and more dependent on hepatic metabolism. Emergence time from midazolam is increased in elderly patients, obese patients, and in the presence of severe liver disease.

F. Seizure

Administration of midazolam by the intranasal or the buccal route (absorption via the gums and cheek) as an alternative to rectally administered diazepam is becoming increasingly popular for the emergency treatment of seizures in children (Appleton *et al* 2008).

However long-term use for the management of epilepsy is not recommended, due to the significant risk of tolerance (which renders midazolam and other benzodiazepines ineffective) and the significant side effect of sedation (Isojärvi 1998)

3.1.6 Usage of Midazolam in ESRF patient

Caution is required in the renal impairment patient, as they are more sensitive to the pharmacological effects of benzodiazepines, metabolize them more slowly, and are more prone to adverse effects, including drowsiness, amnesia (especially anterograde amnesia), ataxia, and hangover effects (Verbeeck 2008)

3.2 Remifentanil

3.2.1 Overview Of Opioids

An opioid is any psychoactive chemical that resembles morphine or other opiates in its pharmacological effects. Opioids work by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the gastrointestinal tract. The receptors in these organ systems mediate both the beneficial effects and the side effects of opioids.

Opiods can be classify as

- Natural opiates: primarily morphine, codeine, and thebaine,
- Semi-synthetic opioids: created from either the natural opiates or morphine esters, such as hydromorphone, hydrocodone, oxymorphone and buprenorphine
- Fully synthetic opioids: such as fentanyl, pethidine , methadone , tramadol and remifentanil

There are also endogenous opioids that are produced in the body include:

- Endorphins
- Enkephalins
- Dynorphins
- Endomorphins

β-endorphin is expressed in Pro-opiomelanocortin (POMC) cells in the arcuate nucleus, in the brainstem and in immune cells, and acts through μ-opioid receptors. β-endorphin has many effects, including on sexual behavior and appetite. β-endorphin is also secreted into the circulation from pituitary corticotropes and melanotropes. α-neo-endorphin is also expressed in POMC cells in the arcuate nucleus. (stoelting 2006)

met-enkephalin is widely distributed in the CNS and in immune cells; [met]-enkephalin is a product of the proenkephalingene, and acts through μ and δ-opioid receptors.

leu-enkephalin also a product of the proenkephalin gene, acts through δ-opioid receptors.

Dynorphin acts through κ-opioid receptors, and is widely distributed in the CNS, including in the spinal cord andhypothalamus, including in particular the arcuate nucleus and in both oxytocin and vasopressin neurons in the supraoptic nucleus.

Endomorphin acts through μ-opioid receptors, and is more potent than other endogenous opioids at these receptors

Opioid Receptors

Opioid receptors are classified as μ, δ, and κ receptors. These opioid receptors belong to a superfamily of guanine (G) protein-coupled receptors. μ or morphine-preferring receptors are principally responsible for supraspinal and spinal analgesia. Naloxone is a specific μ receptor antagonist, attaching to but not activating the receptor.

Usage of Opioids

Opioids have long been used to treat acute pain , such as post-operative pain (Alexander *et al* 2012). They have also been found to be invaluable in palliative care to alleviate the severe, chronic, disabling pain of terminal conditions such as cancer, and degenerative conditions such as rheumatoid arthritis. However, opioids should be used cautiously in chronic non-cancer pain (Okie 2010). High doses are not necessarily required to control the pain of advanced or end-stage disease.

Tolerance (in which the body becomes less responsive to the same dosage of the drug) may occur. In spite of tolerance, the dose required to achieve analgesia can level off for many months at a time depending on severity of pain, which varies. Thus in many cases opioids are a successful long-term care strategy for those in chronic cancer pain.

3.2.2 Overview Of Remifentanil

Remifentanil is a congener of the fentanyl family of opioids that is approved for use as a supplement to general anaesthesia (and monitored anaesthesia care/acute pain management) by the United States Food and Drug Administration in 1996 (Egan TD 1996) . Remifentanil is structurally unique (Fig. 3.3) because of its ester linkage, which renders it susceptible to hydrolysis to inactive metabolites by nonspecific plasma and tissue esterases.

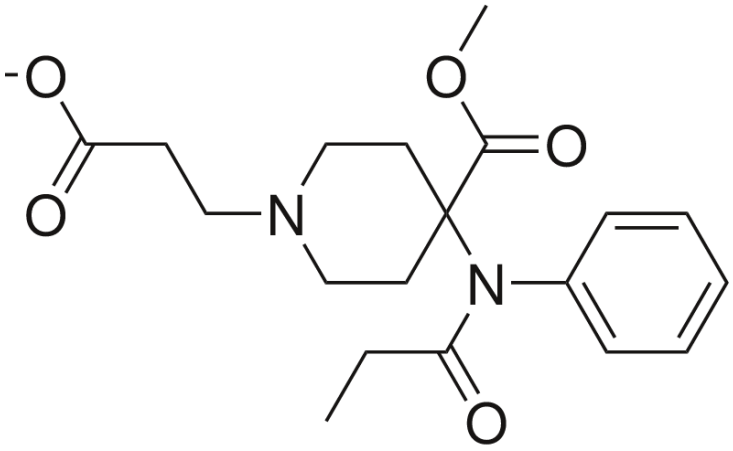

Figure 3.3 structural of Remifentanil

(Stoelting, Robert K.; Hillier, Simon C. Pharmacology and Physiology in Anaesthetics Practice, 2nd Edition 2006 Lippincott Williams & Wilkin)

This unique pathway of metabolism imparts to remifentanil

(a) Brevity of action,

(b) Precise and rapidly titratable effect due to its rapid onset (similar to that of alfentanil) and offset,

(c) Noncumulative effects, and

(d) Rapid recovery after discontinuation of its administration (stoelting 2006)

3.2.3 Pharmacokinetic Of Remifentanil

The rapid metabolism of remifentanil and its small Volume of distribution mean that remifentanil will accumulate less than other opioids (predictable termination of drug effect). The combination of rapid clearance and small Volume of distribution produces a drug with a uniquely evanescent effect. The peak effect-site concentration of remifentanil will be present within 1.1 minutes, compared with 1.4 minutes for alfentanil. (Ultiva 1998)

A. Metabolism

Remifentanil is unique among the opioids in undergoing metabolism to inactive metabolites by nonspecific plasma and tissue esterases. Remifentanil is metabolized to a compound (remifentanil acid) which has 1/4600 the potency of the parent compound (Hoke *et al* 1997 , Egan TD 1996). Remifentanil does not appear to be a substrate for butyrylcholinesterases (pseudocholinesterase), and thus its clearance should not be affected by cholinesterase deficiency or anticholinergics.

B. Elimination Half-Time

Unlike other opioids, remifentanil has a short elimination half-life of 3–10 min, (Glass *et al* 1993) and the duration of action does not increase with increasing duration of administration because of rapid clearance and lack of drug accumulation

C. Context-Sensitive Half-Time

The context-sensitive half-time for remifentanil is independent of the duration of infusion and is estimated to be about 4 minutes (Edan *et al* 1993) (figure 3.4) .

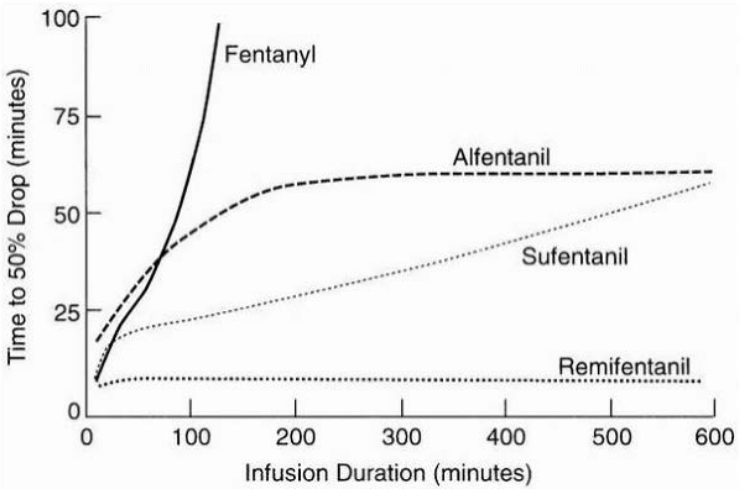

Figure 3-4. Computer simulation-derived context-sensitive half-times (time necessary for the plasma concentration to decrease 50% after discontinuation of the infusion) as a function of the duration of the intravenous infusion.

(From Egan TD, Lemmens HJM, Fiset P, et al. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anaesthesiology 1993;79:881-892;)

3.2.4 Pharmadynamic Of Remifentanil

As a pure mu-agonist, remifentanil produces all the opioid effects characteristic of the fentanyl family of opioids (Egan TD 1996). Its therapeutic effects therefore include dose-related analgesia and sedation. In terms of potency, remifentanil is substantially more potent than alfentanil and slightly less potent than fentanyl (Edan *et al* 1996 ,Glass *et al* 1999)

A. Cardiovascular Effects

As with morphine and fentanyl, remifentanil can result in hypotension due to histamine release (Sebel *et al* 1995).Bradycardia can also occur and may lead to occasional decreases in blood pressure and cardiac output (Dershwitz *et al*1995)

B. Respiratory effect

Remifentanil produce a dose-dependent and gender-specific depression of ventilation, primarily through an agonist effect at μ_2 receptors, which leads to a direct depressant effect on brainstem ventilation centers. (Bowdle et *al* 1996)

Its depression of ventilation is characterized by decreased responsiveness of these ventilation centres to carbon dioxide, as reflected by an increase in the resting $PaCo_2$ and displacement of the carbon dioxide response curve to the right.

Advanced age and the occurrence of natural sleep increases the ventilatory depressant effects of opioids, whereas pain from surgical stimulation counteracts the ventilation depression produced.

C. Nervous System

In the absence of hypoventilation, opioids decrease cerebral blood flow and possibly intracranial pressure (ICP).

However, These drugs must be used with caution in patients with head injury because of their

(a) Associated effects on wakefulness,

(b) Production of miosis , and

(c) Depression of ventilation with associated increases in ICP if the $PaCo_2$ becomes increased.

Skeletal muscle rigidity, especially of the thoracic and abdominal muscles, is common when large doses of remifentanil are administered rapidly intravenously.

D. Nausea and Vomiting

Nausea and vomiting induced by opioids reflects their direct stimulation of the chemoreceptor trigger zone in the floor of the fourth ventricle. (patel *et al* 1996 edan *et al* 1993)

In a study by Gold *et al* (1997) , almost half of the patient develop side effect of opioids including nausea , vomiting , headache and pruritus when giving remifentanil infusion during conscious sedation , where else another study showed there were 16% of patient in remifentanil alone group develop respiratory depression with respiratory rate < 8 breath per min (Avramov *et al* 1996)