Comparison of balanced anaesthesia with sevoflurane and remifentanil versus total intravenous anaesthesia with propofol and remifentanil for paediatric lower abdominal operation

Thesis

Submitted for the partial fulfillment of
MD Degree in Anaesthesiology

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AIN SHAMS UNIVERSITY
2009

INTRODUCTION

Fast emergency and short recovery with a low incidence of postoperative side effects are two important goals of anaesthesia for paediatric surgery. Both sevoflurane and propofol possess qualities that are desirable for infants and children who require ambulatory or inpatients surgery under general anaesthesia. Studies in children have confirmed the excellent induction characteristics, haemodynamic stability, rapid emergence and recovery qualities for both anaesthetics **(Schmidt et al., 2001).**

The esterase-metabolized opioid, remifentanil hydrochloride has pharmacokinetic properties that may translate into benefits for ambulatory anaesthesia and recovery. The pharmacokinetics of remifentanil allows easy titration, for changing intraoperative conditions and smooth emergence from anaesthesia and it may be a useful anaesthetic for paediatric inpatient and outpatient surgery **(Peacock and Philip, 1999).**

A total intravenous anaesthesia (TIVA) regimen with remifentanil and propofol is a useful anaesthetic technique and offer a several advantages, like controlling response to tracheal intubation and intense surgical stimulation and so commonly used in paediatric anaesthesia **(Torsten and Hans-Jochim, 2000).**

Even though published results of studies comparing TIVA with balanced anaesthesia in large population of children and infants under Bispectral index are still lacking **(Sven et al., 2003).**

AIM OF THE WORK

The aim of this study is to evaluate and compare the induction, maintenance, haemodynamic response, the recovery profile and cost-effectiveness of remifentanil-propofol combination (TIVA) versus balanced anaesthesia using sevoflurane and remifentanil under Bispectral index (BIS) for paediatric patients undergoing short lower abdominal procedures

Opioid Receptors

In 1973, three independent teams of investigators described the presence of an opioid receptor in nervous tisssues and hypothesized that endogenous substances probably stimulate this structure **(Pert and Snyder, 1973).**

The original classification of opioid receptors was based on response pattern to three different opioid compounds in the chronic spinal dog model and resulted in the description of three receptor types.

They were named after the drugs used in the studies mu (μ) (morphine), kappa (K) (ketocyclazocine) and sigma (σ) (SKF 10,047 or N-allylnormetazocine) **(Atcheson, 1994).** Sigma receptor is no longer considered an opioid receptor but rather has a high affinity binding site for phenycyclidine and related compounds **(Snyder and Pasternak, 2003).**

In 1977, Lord and colleagues described a binding site in the isolated mouse vas deferens with high affinity for enkephalins **(Rafael et al., 2001).**

The opioid receptor site named after vas deferens (delta δ receptor). Different characteristics of opioid receptors are compared in (table 1) .

The μ-opioid receptor manifests a high affinity for endogenous enkephalin **(Bailey et al., 2000).** μ-receptors are located in both the brain and the spinal cord with highest concentrations in the periaqueductal gray and substantia gelationosa respectively. μ receptors induced analgesia is dose dependant-no ceiling effect **(Hurley and Hammond, 2000).**

Pharmacological effect of μ receptor (μ) is mainly on analgesia, respiratory depression and euophoria is also suggested **(jack, 2000).** Investigations using opiate receptors knock out mice demonstrate that morphine induced analgesia is μ-receptor mediated **(Claire, 1998).**

A μ- receptor may be involved in immune processes because it has significant distribution in astrocytes, endothelial cells and macrophages. It is not clear whether or not these various receptor subtypes originate from separate genes or from post-translational modification **(Hatsukari et al., 2006)**.

The degree of analgesia produced by stimulation of δ-receptors appears to paly a role in producing mild to moderate analgesia at the spinal cord level for non-thermal stimuli **(Holdridge and Cahill, 2007)**

The Κ-receptor agonist, ethylketocyclazocine produces analgesia and sedation without causing much respiratory depression. At least three Κ-receptor subtypes have been isolated **(Liu-Chen, 2004).** Κ receptors are of particular interest

because of their high density within the brain and association with supraspinal analgesia, whereas other Ƙ-receptors are related to spinal analgesia **(Pick et al., 1992).**

Table (1): Characteristics of opioid receptors:

	Mu(μ)	**Delta(δ)**	**Kappa(Ƙ)**
Endogenous Ligand	Enkephalin B-Endorphin	Enkephalin	dynorphin
Exogenous Agonist ligand	Morphine phenylpiperidine	Deltrophin	Butorphanol Bremazocine
Antagonist	Naloxone Naltroxone	Naloxone Naltroxone	Naloxone
Subtypes	1,2,3	1,2,3	1,2,3
G-protein coupled	yes	yes	yes
Adenylate	Inhibits	inhibits	inhibits
Voltage-dependant Ca –channel	inactivates	inactivates	inactivates
k-channel conductance	increases	Increases	?
Actions	-Analgesia -Sedation -Respiratory depression -Misosis -Bradycardia -Nausea and vomiting -Decreased GIT mobility	-supraspinal analgesia -Respiratory depression	-Spinal analgesia -Diuresis -Dysphoria -Respiratory depression (weak)

(Bailey et al., 2000)

Table (2): Supraspinal and spinal sites and opioid receptor types mediating analgesia

Location	Receptor selectivity
Supraspinal:	
Periaqeductal grey area	μ ,K > δ
Raphe nuclei	
Caudal linear	K
Dorsal	K> μ
Median	μ> K
Magnus	μ> K
Pallidus	δ
Gigantocellular reticular	μ, K, δ
Spinal:	
Spinal cord	μ, δ, K
Dorsal root ganglia	μ, δ, K

(Bailey et al., 2000)

Cellular mechanisms:

Opioid receptors belong to the family of G-protien coupled receptors which possess seven membrane spanning regions **(Neves et al., 2002).** The amino acid sequences of the opioid receptors are approximately 60% identical to one another with greatest similarities existing in transmembrane and intracellular regions **(Law et al., 2000).**

Specific amino acid sequences of extracellular loops of opioid receptors are the key in determining ligand- specific actions. Phosphorylation and glycosylation sites are responsible for opioid-related effects **(Stefan et al., 2004**).

Studies indicate both presynaptic (indirect) and postsynaptic (direct) facilitatory and inhibitory actions of opioids on synaptic transmission in many regions of the nervous system **(Gjermund and Frode, 2008).** The opioid receptor-activated G-protein effectors systems can be divided into two categories: short term effectors (K and Ca channels) and long term effectors involving second messengers such as adenylate cyclase/cyclic adenosine monophosphate AMP) and phosphatidyl inositol **(Law et al., 2000).**

Both μ and δ receptors activate K channels and all opioid receptors can inhibit the opening of voltage-dependant Ca channels. μ–receptors antagonists can also directly increase Ca entry and intracellular Ca Concentrations **(Emma et al., 2006).**

Changes in cAMP may underlie opioid-induced modulation of the release of neurotransmitters such as substance P **(Bailey et al., 2000).**

K channels effects result in hyper polarization of neuronal membrane and decreased synaptic transmission. Decreased Ca influx can decrease neurotransmitter mobilization and release **(Stoelting, 1999).** Opioids also have excitatory actions, indirectly by interneuron disinhibition and directly by neuronal excitation via G proteins. This may explain some neuroexcitatory responses to opioids **(Rozan et al., 1998).**

REMIFENTANIL

Remifentanil is a synthetic opioid that was developed in the early 1990s. It is a methyl ester and is metabolized by nonspecific tissue and plasma esterases **(Egan, 1995)**.Remifentanil is a fentanyl derivative with an ester linkage. It is a hydrochloride salt of Propioinc acid (Figure1) **(Burkle et al., 1996)**.

Although chemically related to opioids such as fentanyl, alfentanil and sufentanil, remifentanil was synthesized by **Feldman and his colleagues in 1991** through specific analysis and modification of the basic anilidopiperidine structure. The introduction of a methyl ester group into the N-acetyl side chain of the piperidine ring conferred increased susceptibility to rapid elimination and had a reported terminal elimination half-life of between 10 and 35 minutes through hydrolytic metabolism by esterases and thereby rapid termination of effect. It was introduced into clinical use in United States and Europe in 1996 **(Wolfram and Sascha, 2008)**

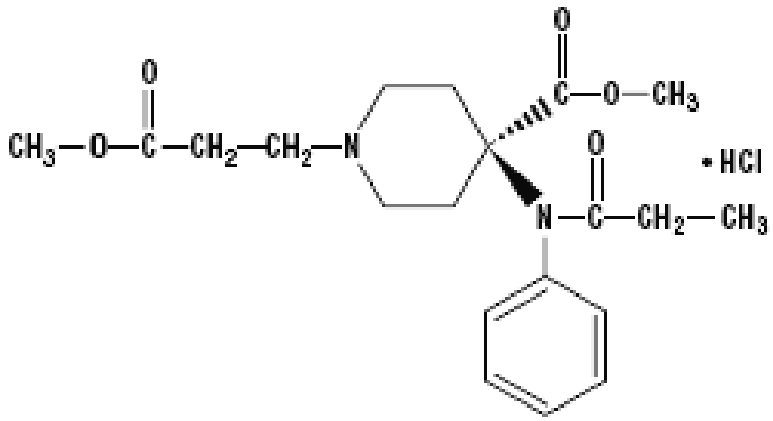

Figure (1): Chemical structure of remifentanil
Westmoreland et al., (1993)

Studying the structure activity of 4-anilidopiperidines as analgesic has led to development of several new synthetic opioids. All anilidopiperidines, including remifentanil, act on μ- receptor **(Makita and Ishikawa, 2006)**. This receptor type, first cloned in 1992, has seven transmembrane domains, intracellular and extracellular loops and several different glycosylation sites **(Uhl et al., 1994)**.

The analgesic effect is mediated through coupling to a guanine nucleotide binding protein (G-protein) which concomitantly results presynaptically in inhibition of excitatory neurotransmitter release and postsynaptically in inhibition of cAMP, suppression of voltage gated calcium channels and hyperpolarization of postsynaptic membrane through increased potassium conductance **(Zhao-Yang et al., 2008)**.

i. Physicochemical properties:

Remifentanil's physicochemical properties are characteristic of drugs in fentanyl family. Its molecular weight is *413 Dalton*. It is a weak base (pKa=7.07) and highly lipid soluble. Remifentanil is highly bound *(70%)* to plasma proteins **(Richard and Enrico, 2004)**.

It is commercially available as water soluble lyophilized powder containing the free base and glycine as a vehicle **(Talmage, 1998)**. Because remifentanil is unstable in solution for long period of time, the lyophilized powder must be reconstituted within *24hours* prior to use **(Patel and Spencer, 1996).**

Receptor binding studies have shown remifentanil's selectivity and affinity for **μ**-receptor which is greater than that for ***δ***-receptor or ***K***-receptor **(Servin and Billard, 2008).** Furthermore, it does not significantly bind to other non-opioid receptor groups. The specificity and affinity of remifentanil at μ-receptor is also demonstrated by competitive antagonism with naloxone **(Amin et al., 1995).**

Remifentanil and propofol can be mixed in polypropylene syringes and used for up to 36 hours, provided that the remifentanil concentration is 15μg/mL, and propofol concentration 10mg/ml, given 0.1 ml/kg **(James et al., 2000).**

ii. Pharmacokinetics:

The pharmacokinetics of remifentanil are characterized by small volume of distribution *(V_d=30 liters)*, and rapid clearance *(4000ml/minute)* compared to other IV anaesthetic drug **(Stoelting, 1999)**. The rapid metabolism of remifentanil and its small volume of distribution mean that the remifentanil will accumulate less than other opioids. Because of its rapid systemic clearance, remifentanil provides pharmacokinetic advantages in clinical situations requiring predictable termination of drug effect **(Bailey et al., 2000).**

Its clearance is several times greater than normal hepatic blood flow, consistent with widespread extrahepatic metabolism **(Egan, 1995)**. The combination of rapid clearance and small volume of distribution produces a drug with uniquely evanescent effect. In fact, the rate of decline *(context-sensitive half-time)* of remifentanil plasma concentration will be nearly independent of infusion duration (Figure 3) **(Talmage, 1998).**

It is estimated that remifentanil plasma concentration will reach a steady state within 10 minutes of beginning an infusion at rate (0.5µg/kg/min) . The relationship between infusion rate and opioid concentration will be less variable for remifentanil than for other opioids **(Wolfram and Sascha, 2008).**

After a rapid IV injection, the peak effect of remifentanil will be present within 1.1 minute **(Egan et al., 2004)**.Remifentanil's pharmacokinetics is best described by multi-compartmental model **(Hughes et al., 1992).**

a) Metabolism:

Remifenitanil is unique among the opioids in undergoing metabolism by non-specific plasma and tissue esterases to inactive metabolites **(Martens et al., 2003).**

Remifentanil undergoes hydrolysis by non specific plasma and tissue esterase's (major pathway) to a carboxylic acid metabolite *(GI 90291)* that has no clinically significant agonist activity at opioid receptors. N-dealkylation of remifentanil to (GI 94219) is a minor pathway metabolism **(Egan, 1995)** (figure 2). GI 90291 is dependent on renal clearance mechanism **(Martens et al., 2003)**. Almost 90% of the drug is recovered in the urine in form of acid metabolite **(Glass et al., 1993).** A unique feature of remifentanil metabolism is that its pharmacokinetics are not appreciably influenced by renal or hepatic failure **(Hoke et al., 1997).**

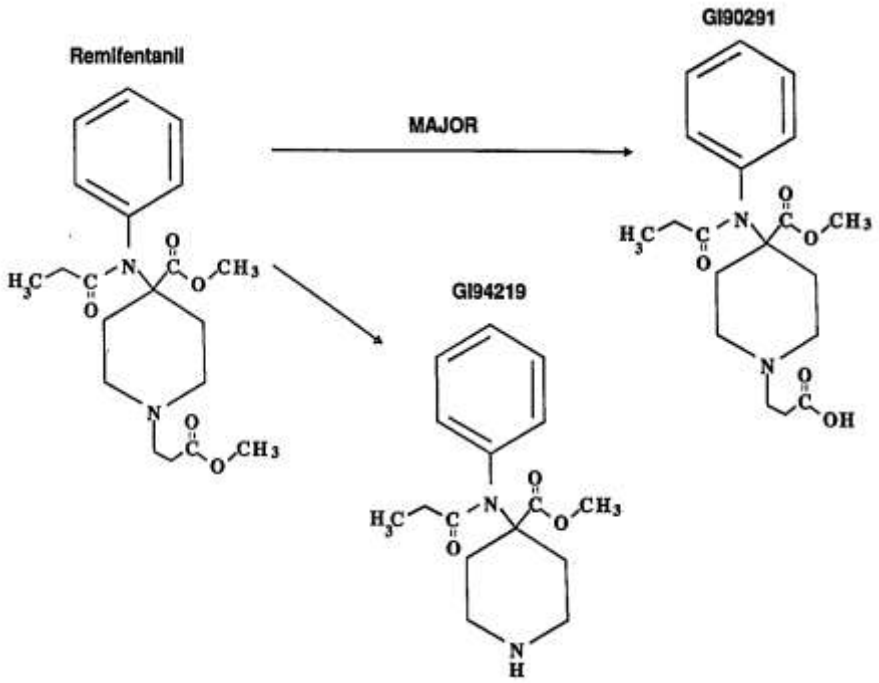

Figure (2): Chemical structure and proposed metabolic pathway of remifentanil
(Westmoreland et al., 1993)

In blood, remifentanil is metabolized primarily by an enzyme within the red cells **(Johnson et al., 2001).** Remifentanil is not a good substrate for pseudocholinestrase and therefore is not influenced by pseudocholinesterase deficiency **(stiller et al., 1995).** The clearance of remifentanil is not altered during the anhepatic phase of liver transplantation **(stoelting, 1999).** Hypothermic cardiopulmonary bypass decreases clearance of remifentanil by an average of 20% presumably reflecting the effect of hypothermia on blood and tissue esterase activity **(Russell et al., 1997).**

b) Elimination half –life:

Elimination half-life is defined as, the time it takes for the body to eliminate or breakdown half of a dose of a pharmacologic agent. An estimated 99.8% of remifentanil is eliminated during the distribution *(0.9 minute)* and elimination *(6.3 minutes)* half-time. Clinically, remifentanil behaves like a drug with an elimination half time of 6 minutes or less **(Stoelting, 1999).**

Remifentanil was found to have age-related changes in clearance and volume of distribution. Elder population have a small volume of distribution (V_d) which is decreased by 20% in old age, clearance by tissue esterases is decreased by 30% in old age, also there is 50% reduction in effective concentration 50 (EC 50) in the elderly. This is consistent with halving the dose in elder people **(Minto et al., 1997).**

c) Context-sensitive half-time:

Context-sensitive half-time; is the time to a 50% decrease of an effective site concentration after infusion is stopped; for remifentanil is independent of the duration of infusion and is estimated to be about 3 minutes **(Egan, 1997).**

In contrast alfentanil, sufentanil and fentanyl, (figure 3), their context sensitive half time is much longer and dependent on the infusion duration **(Theodore HS, 2000).** A similar result was reported in a volunteer study by **Kapilo and**