A COMPARISON BETWEEN FENTANYL AND ESMOLOL IN PREVENTING INCREASE INTRACRANIAL PRESSURE DURING ENDOTRACHEAL SUCTION IN SEVERE HEAD INJURY PATIENT

BY
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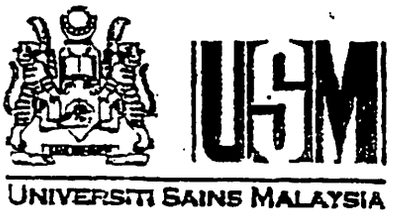

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ABBREVIATIONS

AARC	America Association of Respiratory Care
ABG	Arterial blood gases
ABP	Arterial blood pressures
BIS	Bispectral index
CBF	Cerebral blood flow
CMRO2	Cerebral metabolic rate of oxygen
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
ECG	Electrocardiogram
ETS	Endotracheal suction
GCS	Glasgow Coma Scale
HR	Heart rate
ICP	Intracranial pressure
ICU	Intensive care unit
IM	Intramuscular
IV	Intravenous
MAP	Mean arterial pressure
SaO2	Pulse oxymeter

ABSTRAK

Tajuk : Perbandingan diantara 'fentanyl' dan 'esmolol' dalam menghalang kenaikan tekanan intrakranial ketika penyedutan tiub trakea terhadap pesakit yang mengalami kecederaan kepala yang teruk.

Latarbelakang

Rawatan utama bagi pesakit yang mengalami kecederaan kepala yang teruk ialah menghalang kenaikan tekanan intrakranial di samping memastikan perfusi otak dalam keadaan yang baik. Proses perawatan boleh menyebabkan kenaikan tekanan intrakranial. Sebagai contohnya, penyedutan di dalam tiub trakea menyebabkan kenaikan tekanan intrakranial setiap kali penyedutan dijalankan. Fentany merupakan sejenis ubat untuk menahan sakit (opiod). Ia diberi kepada pesakit sebelum penyedutan dijalankan untuk menghalang kenaikan tekanan intrakranial dari rangsangan penyedutan itu. Esmolol merupakan sejenis ubat yang bertindak di reseptor beta1-adrenergik. Ia digunakan untuk menghalang tindakbalas kardiovascular ketika proses laryngoscopi dan juga digunakan sebagai pengawal tekanan dan peredaran darah.

Objektif

Matlamat kajian ini adalah untuk melihat keberkesanan fentanyl dan esmolol terhadap perubahan tekanan intrakranial, tekanan perfusi otak, tekanan darah dan denyutan jantung

ketika penyedutan dijalankan kepada pesakit yang mengalami kecederaan kepala yang teruk dan membandingkan kesan kawalan fentanyl dan esmolol terhadap tekanan intracranial ketika penyedutan itu dijalankan.

Tatacara

Seramai enam puluh dua orang pesakit yang dimasukkan ke unit rawatan rapi neuro dengan tahap Glasgow Coma Scale 8 dan kurang daripadanya, dipasang alat untuk mengukur tekanan intrakranial dan diberi bantuan pernafasan dengan mekanikal ventilator. Mereka secara rawak diberi samada fentanyl (1mcg/kg) atau esmolol (1mg/kg) sebelum penyedutan tiub trakea dijalankan. Tekanan darah arteri, purata tekanan darah arteri, denyutan jantung, tekanan intrakranial, tekanan perfusi otak, kandungan gas di dalam darah arteri dan indeks bispektral direkodkan sebelum penyedutan, selepas penyedutan, 5 minit, 10 minit dan 15 minit selepas penyedutan.

Keputusan

Fentanyl dan esmolol menunjukkan tiada perbezaan yang signifikan pada intracranial pressure dan bispectral index ketika penyedutan tiub trakea dijalankan. Perbezaan yang signifikan hanya didapati pada tekanan darah purata, tekanan perfusi otak dan denyutan jantung.

Kesimpulan

Kami merumuskan bahawa pesakit yang mengalami kecederaan kepala yang teruk, sekiranya mereka diberi ubat sedatif yang secukupnya dan mempunyai tekanan

intrakranial yang normal, penggunaan fentanyl atau esmolol dalam menghalang kenaikan tekanan intrakranial tidak menunjukan sebarang perbezaan. Walau bagaimana pun esmolol (1mg/kg) lebih baik berbanding fentanyl (1mcg/kg) dalam mengawal tekanan darah dan tekanan perfusi otak ketika proses itu.

ABSTRACT

TITLE: A Comparison Between Fentanyl And Esmolol In Preventing Increases In Intracranial Pressure During Endotracheal Suction In Severe Head Injury Patient.

Background

Preventing increases in intracranial pressure while maintaining adequate cerebral perfusion is a primary goal in the treatment of adults with a severe head injury. Routine nursing interventions can trigger reactive intracranial hypertension. For example, endotracheal suctioning causes a progressive increase in intracranial pressure with each insertion of the suctioning catheter. In current practice fentanyl, a rapid onset opiod was given before suctioning to blunt responses to noxious stimuli. Esmolol, a rapid- onset and short-acting selective beta1-adrenergic receptor antagonist is utilized to attenuate the cardiovascular response to laryngoscopy and as an adjunct to controlled circulatory techniques.

Objectives

The goals of this study are to observe the effect of fentanyl and esmolol on the changes in intracranial pressure, cerebral perfusion pressure, mean arterial pressure and heart rate responses during endotracheal suctioning in adults with severe head injuries and to compare the effect of fentanyl and esmolol in preventing increase in intracranial pressure during endotracheal suction.

Methods

Sixty two patients who are admitted to neurointensive care unit with Glasgow Coma Scale (GCS) of 8 and less, with intracranial pressure monitoring in place and mechanically ventilated. The patients were then randomly received either esmolol (1mg/kg) or fentanyl (1mcg/kg) before endotracheal suction. Arterial blood pressure (ABP), mean arterial pressure (MAP), heart rate (HR), intracranial pressure (ICP), cerebral perfusion pressure (CPP), arterial blood gases (ABG) and bispectral index (BIS) were recorded at baseline, immediately after and 5 minutes, 10 minutes and 15 minutes after endotracheal suctioning.

Results

There were no significant difference in ICP and BIS in patients who are given either fentanyl or esmolol in preventing a raise in intracranial pressure during endotracheal suctioning. A significant difference was seen in mean arterial pressure, cerebral perfusion pressure and heart rate.

Conclusion

We conclude that in patients with severe head injury who are well sedated and had a normal intracranial pressure, the used of fentanyl or esmolol in preventing a raise in intracranial pressure during endotracheal suction has no advantage. However, esmolol (1 mg/kg) is better than fentanyl (1mcg/kg) in control mean arterial pressure and cerebral perfusion pressure during endotracheal suctioning.

CHAPTER 1: INTRODUCTION

1.1 Introduction

Severe head injury is defined as head trauma or injury with Glasgow Coma Score (GCS) of 8 or less. Severe head injury is a significant cause of death and disability and associated with raised intracranial pressure (ICP) in 50–75% of patients. Raised ICP is defined as intracranial pressure greater than 20 mmHg. An ICP more than 20 mm Hg has been found to be a powerful predictor of poor neurological outcome in adults with severe head injury (Becker et al, 1977, Marshall et al, 1979). For that reason, intracranial pressure is the main parameter monitored in head-injured patients. It is a reflection of the relationship between alterations in craniospinal volume and the ability of the craniospinal axis to accommodate added volume. ICP normally increases with activities such as endotracheal or oral suctioning, coughing and painful stimuli, and does not warrant intervention unless it does not return to baseline within about 5 minutes.

Almost all severe head injury patients are mechanically ventilated. Routine nursing procedure such as endotracheal suction is frequently performed to remove pulmonary secretions and maintain an airway patency. This is a potentially dangerous procedure in patients with head injury because it can increase intracranial pressure. In most patients, elevations in intracranial pressure are transient and the pressure returns to the baseline level within minutes. In some patients, intracranial pressure may take more than 15 minutes to return to baseline. This need interventions such as drainage of cerebrospinal fluid and administration

of osmotic diuretics, sedatives or paralyzing agents to reduce the pressure to less than 20 mm Hg. Gemma et al, (2002) found that in well-sedated patients, endotracheal suctioning caused an increase in intracranial pressure, cerebral perfusion pressure (CPP) and jugular oxygen saturation (Sj02). Brucia et al, (1996) found that tracheal stimulation during suction catheter insertion initiates both cerebrovascular responses such as ICP and CPP and systemic vascular response such as mean arterial pressure (MAP). For such a reasons, several modalities have been advocated to reduce secondary brain damage such as use of sedation and muscle relaxant or lignocaine administration before endotracheal suction (Donegan et al, 1980).

Although opiates such as morphine sulfate and fentanyl citrate may prevent increases in intracranial pressure, reports of the efficacy of opiates in preventing increases in intracranial pressure in response to endoctracheal suctioning are inconsistent. As commonly practiced in this institution, intravenous (IV) fentanyl (0.5 - 1mcg/kg) was given before suctioning to blunt response to noxious stimuli. White et al, (1982) found that administration of fentanyl did not attenuate the increase in intracranial pressure that occurred with endotracheal suctioning in an animal model. Lauer et al, (1997) suggests that when opioids are titrated in head-injured patients, worsening intracranial pressure can be avoided. Schregel et al, (1994) concluded that opioids are often beneficial and not generally contraindicated for patients with cerebral diseases and compromised intracranial compliance.

Chung et al, (1992) found that the combination of a low dose of fentanyl and esmolol provides an alternative to a higher dose of fentanyl for blunting the haemodynamic responses to laryngoscopy and tracheal intubation during rapid-sequence induction in healthy patients. Intravenous esmolol (1.0 – 1.5 mg/kg) is utilized to attenuate the cardiovascular response to laryngoscopy, to treat supraventricular tachycardias and as an adjunct to controlled circulatory techniques. Subsequent experience with the drug has produced evidence for the efficacy of esmolol as anaesthetic adjunct. Menigaux et al, (2002) reported that esmolol not only attenuated haemodynamic and somatic responses to laryngoscopy and orotracheal intubation, but also prevented bispectral index (BIS) arousal reactions in patients anaesthetized with propofol. Bagshaw et al, (1995) reported that esmolol proved to be a satisfactory substitute for narcotics in a nitrous oxide/relaxant anaesthetic technique and was associated with shorter times to ambulation and discharge. Bensky et al, (2000) showed that small doses of esmolol (0.4mg/kg) may block the increases in heart rate and blood pressure resulting from laryngoscopy and intubation..

1.2 Objectives of the study

The goals of this study are to observe the effect of fentanyl and esmolol on the changes in intracranial pressure, cerebral perfusion pressure, mean arterial pressure, heart rate and bispectral index responses during endotracheal suctioning in adults with severe head injuries and to compare the effects of fentanyl and esmolol in preventing increase in intracranial pressure during endotracheal suctioning.

CHAPTER 2: LITERATURE REVIEW

2.1 Intracranial pressure

2.1.1 Physiology

Intracranial pressure is a term applied to the pressure inside the cranial vault relative to atmospheric pressure. Normal intracranial pressure in adults is between 5 mm Hg and 15 mm Hg. Intracranial pressure above 15 mm Hg is abnormal. Increased ICP has been defined as a pressure more than 20 mm Hg persisting for 5 min (Bullock et al, 2000). Lundberg (1960) suggested that mean levels above 20 mmHg are moderately elevated and sustained levels above 40 mmHg are severely increased. Miller et al, (1981) reported that the mortality rate increased from 18 to 92 % and that the frequency of good outcomes decreased from 74 to 3% when cases of normal ICP were compared with those of intracranial hypertension more than 20 mm Hg. ICP is not a static state, but is influenced by several factors. The recording of ICP shows 2 forms of pressure fluctuations. There is a rise with cardiac systole (due to distention of intracranial arteriolar tree) and a slower change in pressure with respiration, falling with each inspiration and rising with expiration. Straining and compression of neck veins can also cause a sudden, considerable rise in pressure.

The conception of the cranium acting as a near rigid container of incompressible substances in the form of brain, blood and cerebrospinal fluid (CSF) in known as the Monro Kellie doctrine. The composition of the intracranial contents and their volumes (%) are as follows:

Brain tissue/interstitial water	85%
Blood volume	10%
Cerebrospinal fluid (CSF)	5%

Intracranial pressure is determined by the interaction of the brain mass, cerebral blood volume and cerebrospinal fluid volume. As the Munro-Kellie doctrine dictates that a change in any one of these compartments must be counteracted by an opposite change in another compartment in order to maintain the same ICP. While volume of the brain (about 1400ml in an adult) being constant, intracranial pressure is a result of at least 2 factors:

a) CSF which is constantly secreted and after circulating absorbed at an equal rate. CSF circulation is slow (500 to 700 ml/day). At a given time the cranium contains 75 ml of CSF.

b) Intracranial circulation of blood which is about 1000 litres per day delivered at a pressure of 100 mmHg and at a given time, the cranium contains 75 ml of blood.

In the presence of haematoma or development of hydrocephalus the initial compensation is by displacement of blood and CSF from the vault, the brain volume remaining unchanged. However, once cerebral oedema develops, any further increase in the ICP results in the failure of the compensatory mechanisms with ensuing sharp rise in ICP. Once this state is reached, any minor increase in any one of the three compartments will lead to dramatic increase in ICP with a corresponding drop in the cerebral blood flow.

2.1.2 Control of intracranial pressure

a) Volume Buffering (Pressure – Volume Relationship)

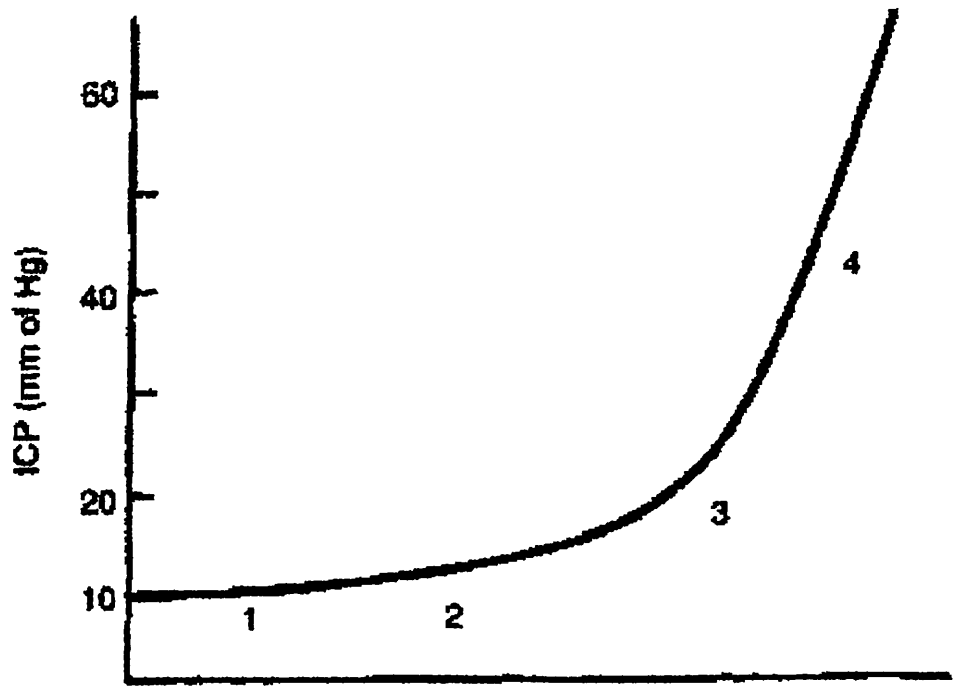

Figure 2.1 Intracranial Pressure – Volume Curve

(Gupta A.K and Summors A.C. 2001.Notes in Neuroanaesthesia and Critical Care. Greenwich Medical Media Limited.6,24)

During slow increase in volume in a continuous mode between points 1 and 2, the ICP raises to a plateau level at which the increase level of CSF absorption keeps pace with the increase in volume. At point 2, further increases in volume cause a slight rise in ICP.

Intermittent expansion causes only a transient rise in ICP at first. When sufficient CSF has been absorbed to accommodate the volume the ICP returns to normal. As volume increase, there is a steady decline in compliance which increase the ICP even more (point 3) until a small rise in volume is associated with a marked rise in ICP causing a fall in the perfusion pressure and ultimately cerebral ischaemia (between points 3 and 4). The ICP finally rises to the level of arterial pressure which itself begins to increase, accompanied by bradycardia or other disturbances of heart rhythm (Cushing response). This is accompanied by dilatation of small pial arteries and some slowing of venous flow which is followed by pulsatile venous flow. The rise in ICP to the level of systemic arterial pressure extinguishes cerebral circulation which will restart only if arterial pressure rises sufficiently beyond the ICP to restore CBF. If it fails, brain death occurs. In patients with parenchymal lesion (tumor, hematoma and contusion), because of the shift of brain and disturbed auto regulation, CBF may by compromised with relatively low levels of ICP.

The raise in ICP disturbs brain function by:

i. Reduction in CBF

ii. Transtentorial or foramen magnum herniation resulting in selective compression and ischaemia in the brain stem.

Transtentorial herniation with brainstem compression can lead to clinical deterioration even with adequate CBF. A temporal mass may cause uncal herniation without raised ICP. Similarly a frontal mass can cause axial distortion to impair brainstem perfusion.

b) Cerebrospinal Fluid

The reduction of the volume from one compartment as a result of an increase in another compartment is known as 'spatial compensation'. CSF plays the biggest role in spatial compensation. As a space occupying lesion expands, it will cause progressive reduction of the CSF space (reduced size of the ventricles/basal cistens). Rapidly growing masses (e.g. haematoma) exhaust spatial compensation quickly resulting in a rapid rise of ICP.

c) Cerebral Blood Volume (CBV)

Most of the intracranial blood volume is contained in the venous sinuses and pial veins. This acts as a buffer in the event of raised ICP. Factors affecting CBV include:

i. Venous distension – from jugular venous obstruction, increased intrathoracic pressure, raised central venous pressure, head down tilt and vasodilators.

ii. PaCO2 – Both cerebral blood flow (CBF) and CBV increase with raised PaCO2 (Figure 2.2), but the CBV response curve is flatter than the CBF curve. A reduction in PaCO2 from 40 mm Hg to 20 mm Hg results in a 65% reduction in CBF but only a 28% reduction in CBV (2.8 ml/100g). This small change in intracranial volume will have a significant reduction in ICP in the presence of intracranial hypertension because the system operates on the steep part of the pressure volume curve.

iii. PaO2 - Cerebral vasodilatation occurs with hypoxia resulting in a rise in CBV. There is evidence that hyperoxia causes vasoconstriction although there is no human evidence to suggest this is clinically significant.

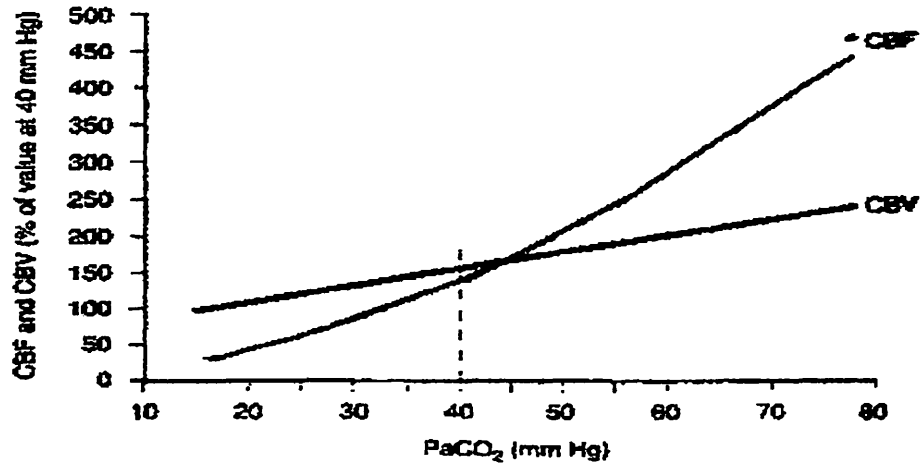

Figure 2.2 Relationship of Cerebral blood flow and cerebral blood volume with changes in arterial carbon dioxide.

(Gupta A.K and Summors A.C. 2001.Notes in Neuroanaesthesia and Critical Care. Greenwich Medical Media Limited. 6,24)

iv. Flow-metabolism coupling – Increased metabolic demand increases CBF, CBV and ICP.

v. Autoregulation – A fall in MAP can lead to a decrease in cerebrovascular tone causing cerebral vasodilatation and increase in CBV within limits.

2.1.3 Cerebral blood flow (CBF)

The brain accounts for only 2% of total body weight, yet its blood flow represents 15% of resting cardiac output and uses 20% total amount of oxygen consumed. Cerebral Blood Flow (CBF) in humans averages approximately 50 mL/100g of brain tissue per minute. Irreversible neuronal damage occurs if CBF drops to less than 18 mL/100 g of brain tissue per minute for a prolonged period of time, (Heiss et al, 1983). CBF is equal to the cerebral perfusion pressure (CPP), which is defined as the difference between the mean arterial blood pressure (MAP) and the ICP, divided by the cerebral vascular resistance. Because the CBF is difficult to measure clinically, the CPP is used as a guide to assessing the adequacy of cerebral perfusion.

$$CPP = MAP - (ICP + CVP)$$

where MAP = Mean Arterial Blood Pressure, CVP = Central Venous Pressure

Normal human values for CPP are between 70 mm Hg and 100 mm Hg. However as a result of autoregulation, CBF remains relatively constant when CPP is between 40 mm Hg and 140 mm Hg, (Kelly et al, 1993). Cerebrovascular autoregulatory mechanisms are disrupted following head trauma, with CBF dependent largely on the CPP. Any factor that decreases MAP or increases the ICP or jugular venous pressure decreases CPP and therefore CBF. Obrist et al, (1984) approximated that one half of patients with severe head injury had a variable degree of autoregulation impairment.

This auto regulation can divide into:

a. Myogenic regulation - suggests direct reaction of the cerebral arterial smooth muscles to the stretch.

b. The humoral regulation - involves regulations by the direct effect of by- products of metabolism.

c. Neurogenic regulation - autonomic nervous system mainly affects the large cerebral vessels. ß-1 adrenergic stimulation results in vasodilation whereas α-2 adrenergic stimulation causes vasoconstriction.

The ICP influences the CBF through the cerebral perfusion pressure (CPP) which is the difference between mean arterial pressure (MAP) and ICP. Raise in ICP would lead to a fall in CPP and every effort should be taken to maintain the CPP to 50 mm Hg or more during treatment of raised ICP.

2.1.4 Clinical features of raised ICP

Raised ICP causes arterial hypertension, bradycardia (Cushing's response) and respiratory changes. It is accepted that hypertension and bradycardia are due to ischaemia or pressure on the brainstem. There is also a suggestion that they could be due to removal of supratentorial inhibition of brainstem vasopressor centers due to cerebral ischaemia and that bradycardia is independent of the rise in blood pressure.

The respiratory changes depend on the level of brainstem involved. The midbrain involvement result in Chyne-Stokes respiration. When midbrain and pons are involved, there is sustained hyperventilation. There is rapid and shallow respiration when upper medulla involvement with ataxic breathing in the final stages.

Pulmonary edema seems to be due to increased sympathetic activity as a result of the effects of raised ICP on the hypothalamus, medulla or cervical spinal cord.

2.1.5 ICP monitoring

ICP monitoring is most often used in head trauma in the following situations:

a) GCS less than 8

b) Drowsy with CT findings (operative or non operative)

c) Post - operation hematoma evacuation

d) High risk patients :

   i. Above 40 yrs.

   ii. Low BP

   iii. Those who require ventilation.

Non invasive methods of ICP monitoring:

a) Clinical deterioration in neurological status is widely considered as sign of increased ICP. Bradycardia, increased pulse pressure, pupillary dilation are normally accepted as signs of increased ICP.

b) Transcranial doppler, tympanic membrane displacement, and ultrasound 'time of flight' techniques have been advocated. Several devices have been described for measuring ICP through open fontanelles. Ladd fiber optic system has been used extra cutaneously.

c) Manual feeling of the craniotomy flap or skull defect, if any, may give a clue to the ICP.

Invasive methods of ICP monitoring:

a) Intraventricular catheter is a 'Gold standard' of ICP measurement (The Brain Trauma Foundation, 2000). Advantage is the potential for draining CSF therapeutically. Disadvantages are include high bacterial colonisation rates (positive CSF or catheter tip culture, 1-5% after 3 days), difficult placement, injury to brain tissue and potential for leaks/blocks in the system. Guyot et al, (1998) found that ventriculostomy had more complications and infections than intraparenchymatous ICP devices (12.4% vs 1.2%) and if complications were present, the Glasgow Outcome Score was worse.

b) Other most commonly used devices are the hollow screw and bolt devices, and the sub dural catheter. Richmond screw and Becker bolt are used extradurally. A fluid filled catheter in the subdural space, connected to arterial pressure monitoring system is cost effective and serves the purpose adequately.

c) Ladd device is currently in wide use. It employs a fibre optic system to detect the distortion of a tiny mirror within with balloon system. It can be used in the subdural, extradural and even extra cutaneously.

d) A mechanically coupled surface monitoring device is the 'cardio search pneumatic sensor' used subdurally or extradurally. These systems are not widely used.

e) Electronic devices (Camino & Galtesh design) are getting popular. Intraparenchymal probes, the measured pressure may be compartmentalized and

not necessarily representative of real ICP. In addition to ICP monitoring, modern intraparenchymal sensors help study the chemical environment of the site of pathology.

f) Fully implantable devices are valuable in a small group who requires long term ICP monitoring for brain tumors, hydrocephalus or other chronic brain diseases. Cosmon intrcranial pressure telesensor can be implanted as a part of shunt system. Ommaya reservoir is an alternative which can be punctured & CSF pressure readings are obtained.

2.1.6 Benefits of ICP monitoring

Intracranial pressure measurement plays an important role in the management of patients with head injury and neurosurgical patients. Several studies have shown that under conditions of aggressive ICP management, the probability of a good outcome is inversely proportional to the maximum ICP and the percentage of the time spent at levels of more than 20 mm Hg. The association between the severity of intracranial hypertension and poor outcome after severe head injury is well recognized. Saul and Ducker, (1981) reported a 69% mortality rate in patients with an ICP greater than 25 mm Hg compared with that of 15% in those in whom the ICP remained less than 25 mm Hg. Monitoring is the only means by which therapy can be selectively employed and the effectiveness of therapy can be accurately studied.

2.1.7 Treatment of increased ICP

There is no doubt the best treatment for increased ICP is the removal of the causative lesion such as tumors, hydrocephalus, and hematomas. Treatment is aimed at preventing the secondary events. Current data suggest that an upper threshold of 20-25 mm Hg should be used to initiate intervention to reduce ICP. (The Brain Trauma Foundation, 2000).

The following therapeutic measures are available.

a) First line of management:

General measures of treatment essentially making the patient comfortable and ABC of trauma management are effectively instituted. Careful attention to nutrition and electrolytes, bladder and bowel functions and appropriate treatment of infections are instituted promptly. Adequate analgesia it is a must even in unconscious patients.

b) Second line of management

i. Induced cerebral vasoconstriction - Hyperventilation, hyper baric O2, hypothermia
ii. Osmotherapy - Mannitol, glycerol ,urea
iii. Anesthetic agents - Barbiturates, gamma hydroxybutyrate, Etomidate,
iv. Surgical decompression

Hyperventilation aims at keeping the pCO2 down to 30-25 mm Hg so that CBF falls and cerebral blood volume is reduced and thereby reducing the ICP. Prolonged hyperventilation should be avoided and becomes ineffective after about 24 hours. In

addition it causes hypotension due to decreased venous return. It is claimed a pCO2 under 20 mm Hg results in ischemia, although there is no experimental proof. The present trend is to maintain normal ventilation with pCO2 in the range of 30 - 35 mmHg. When there is clinical deterioration such as pupillary dilatation or widened pulse pressure, hyperventilation may be instituted until the ICP comes down.

Hyperbaric oxygen and hypothermia are still in the experimental stage. They basically induce cerebral vasoconstriction and reduce the cerebral blood volume and the ICP.

Osmotherapy is useful in the cytotoxic edema stage, when capillary permeability is intact, by increasing the serum osmolality. Mannitol is still the most common osmotic diuretic used to reduce to ICP. It may also act as a free radical scavenger. Glycerol and urea are hardly used these days. Several theories have been advanced concerning the mechanism by which mannitol reduces ICP.

a) It increases the erythrocyte flexibility, which decreases blood viscosity and causes a reflex vasoconstriction that reduces cerebral blood volume and decreases ICP and may reduce CSF production by the choroids plexus. In small doses it protects the brain from ischemic insults due to increased erythrocyte flexibility.

b) The diuretic effect is mainly around the lesion, where blood brain barrier integrity is impaired and there is no significant effect on normal brain. Intraaxial lesions respond better than extra axial lesions.

c) Another theory is mannitol withdraws water across the ependyma of the ventricles in a manner analogous to that produced by ventricular drainage.

Barbiturates can lower the ICP when other measures fail but have no prophylactic value. They inhibit free radical mediated lipid peroxidation and suppress cerebral metabolism; cerebral metabolic requirements and thereby cerebral blood volume are reduced resulting in the reduction of ICP.

Decompressive craniectomy such as sub temporal decompression are recommended only in highly selected patients. Herniation of brain through defect, cause further injury, further edema and further increased ICP. But in occasional cases, when every other measure has failed, such decompression craniectomy may be justified.

2.2 FENTANYL

2.2.1 Classification

Fentanyl citrate is chemically identified as N-(1-phenethyl-4-piperidyl) propionanilide citrate with a molecular weight of 528.60. The empirical formula is $C_{22}H_{28}N_2O \cdot C_6H_8O_7$.

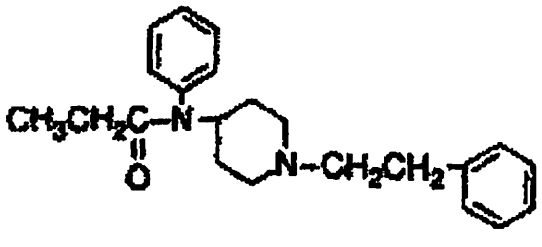

Figure 2.3 Chemical Structure of Fentanyl

2.2.2 Indications and usage

a) Analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period.

b) Use as a narcotic analgesic supplement in regional anesthesia.

c) Administration with a neuroleptic such as droperidol injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

d) Use as an anesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

2.2.3 Presentation

Each ml contains fentanyl citrate equivalent to 50 mcg of fentanyl base, adjusted to pH 4.0-7.5 with sodium hydroxide. It is clear, colourless, isotonic and preservative free solution.

2.2.4 Clinical pharmacology

Fentanyl citrate is a narcotic analgesic. A dose of 100 mcg is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of meperidine. The principal actions of therapeutic value are analgesia and sedation. It is highly selective mu agonist. Fentanyl had little hypnotic or sedative activity and miosis due to stimulation of Edinger-Westphal nucleus. Non-epileptic myoclonic movements with no epileptiform electroencaphalogram (EEG) patterns are seen in patient who are given fentanyl (Maninen et al, 1997). Opiods

are known to inhibit the release of different neurotransmitters in the central nervous system which may be expected to decrease cerebral metabolism (Snyder, 1978). Milde et al, (1989), studied in dogs the effect of fentanyl upon CBF and CMRO2 and found a small decrese in CMRO2 and a 14% increase in CBF. Alterations in respiratory rate, ventilatory response to hypoxia and hypercapnia. and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea and chest wall rigidity (wooden chest phenomenan). Fentanyl appears to have less emetic activity than either morphine or meperidine. Histamine assays and skin wheal testing in man, indicate that clinically significant histamine release rarely occurs with fentanyl. Fentanyl preserves cardiac stability and blunts stress-related hormonal changes at higher doses. Bradycardia of vagal origin is the most significant cardiovascular effect noted. High doses obtund metabolic stress response to surgery. Fentanyl decrease gastrointestinal motility and gastric secretions but it increase ureter, detrussor and vesicular sphincter tone.

The pharmacokinetics of fentanyl can be described as a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. The volume of distribution for fentanyl is 4 L/kg. Fentanyl has 81% - 94% protein binding in plasma. It more lipid soluble than morphine therefore crosses the blood brain barrier faster, resulting in a more rapid onset. It short duration of action is due to redistribution rather than metabolism. It accumulates in skeletal muscle and fat and is released slowly into the blood. The lungs also serve as a large, inactive storage site with an estimated 75% of the initial fentanyl dose undergoing first-pass pulmonary uptake (Roerig et al, 1987). Secondary peak of fentanyl is a result of washout

of opioid from the lungs as ventilation to perfusion relationships are reestablished in the postoperative period. This increases the plasma levels of opioid in the circulation and causes respiratory depression. As the duration of continuous infusion of fentanyl increases beyond 2 hours, the context-sensitive half-time become greater. This reflects saturation of inactive tissue sites with fentanyl during prolonged infusions and return from peripheral compartments to the plasma.

Fentanyl is metabolized rapidly in the liver by N-dealkylation to norfentanyl then hydroxylated to hydroxypropionyl derivatives. Approximately 75% of an intravenous dose is released in urine, mostly as metabolites with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites. The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30-60 minutes after a single IV dose of up to 100 mcg. Following intramuscular (IM) administration, the onset of action is from 7-8 minutes, and the duration of action is 1-2 hours.

2.2.5 Dosage and administration

Dosage should be individualized. Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used and the surgical procedure involved.

a) Premedication

A dose of 50-100 mcg may be administered intramuscularly 30-60 minutes prior to surgery.

b) Analgesic supplement to general anaesthesia

Dose ranges from 1- 50 mcg/kg. A dose of 1- 2 mcg/kg is usually useful in most cases. Dosages of higher ranges in particular 20 – 50 mcg/kg requires post operative ventilation and observation in view of the possibility of extended post operative respiratory depression.

c) Use as anaesthetic agent

Dose of 50 – 100 mcg/kg help attenuates surgical stress. It is used in cardiac surgery.

d) Adjunct to Regional Anesthesia

A dose of 50-100 mcg may be administered intramuscularly or slowly intravenously, over 1-2 minutes, when additional analgesia is required.

e) Postoperatively

A range of 50-100 mcg may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in 1-2 hours as needed.

2.2.6 Contraindications

Fentanyl citrate injection is contraindicated in patients with known intolerance to the drug or other opioid agonists and patient with monoamine oxidase (MAO) inhibitor as it may precipitate hypertensive crisis.

2.2.7 Precautions

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of fentanyl citrate combined with droperidol. This might be due to unexplained alterations in sympathetic activity following large doses however it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

Fentanyl may produce bradycardia, which may be treated with atropine. It needs to be used with caution in patients with cardiac bradycardias.

In severe head injury patients, who may be susceptible to respiratory depression, fentanyl should be used with caution. In addition, fentanyl may obscure the clinical course of patients with head injury.

2.2.8 Interactions

Other central nervous system depressant drugs (e.g. barbiturates, tranquilizers, narcotics and general anesthetics) will have additive or potentiating effects with fentanyl. The opioid – benzodiazepine combination displays marked synergism with respect to hypnosis and depression of ventilation (Vinik et al,1989). When patients have received such drugs, the dose of fentanyl required will be less than usual.

2.2.9 Adverse reactions

The most common serious adverse reactions reported to occur with fentanyl are respiratory depression, apnea, rigidity, and bradycardia. If these remain untreated respiratory arrest, circulatory depression or cardiac arrest will occur. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, diaphoresis, pruritus, urticaria, laryngospasm, anaphylaxis and secondary rebound respiratory depression.

2.3 ESMOLOL

2.3.1 Classification

The chemical name for esmolol hydrochloride is (±)-methyl p-[2-hydroxy-3-(isopropylamino)propoxy]hydrocinnamate hydrochloride. Esmolol hydrochloride has the empirical formula $C_{16}H_{26}NO_4Cl$ and a molecular weight of 331.8. It has one asymmetric center and exists as an enantiomeric pair. Esmolol hydrochloride injection is a clear, colourless to light yellow, sterile and nonpyrogenic solution.

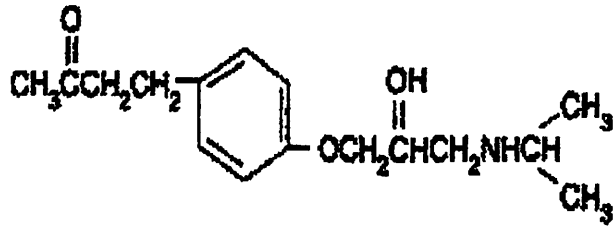

Figure 2.4 Chemical Structure of Esmolol

2.3.2 Indications and usage

a) treatment of supraventricular tachycardia

b) intraoperative and postoperative tachycardia and hypertension (at induction, tracheal intubation, during surgery or emergence from anaesthesia)

c) myocardial infarction

2.3.3 Clinical pharmacology

Esmolol is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action (Wiest 1995), and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Effects begin in 2 minutes and peak in 5 minutes, and the elimination half-life is 9 minutes. Esmolol inhibits the $beta_1$ receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit $beta_2$ receptors located chiefly in the bronchial and vascular musculature.

Esmolol is rapidly metabolized by hydrolysis of the ester linkage, chiefly by the esterases in the cytosol of red blood cells. Total body clearance in man was found to be about 20 L/kg/h, which is greater than cardiac output; thus the metabolism of esmolol is not limited by the rate of blood flow to metabolizing tissues such as the liver or affected by hepatic or renal blood flow. Esmolol has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes. Heart rate reduction begins more quickly than blood pressure reduction. (Ornstein et al, 1995).