PROPOFOL - ANAESTHESIA

A LITERATURE REVIEW AND CLINICAL EXPERIENCE AT MUHIMBILI MEDICAL CENTRE)

BY

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I HAVE READ THE DISSERTATION AND APPROVE IT FOR THE EXAMINATION

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ABSTRACT

Propofol (Diprivan), a new intravenous induction agent, was studied in one hundred and sixty healthy unpremedicated patients undergoing short surgical procedure (<60 minutes). Mean duration of anaesthesia in this series was 30± 12 minutes. Propofol at the induction dose of 2.5mg/Kg was found to produce rapid and smooth onset of anaesthesia. Characteristics of concern at induction was pain on injection in 34.4%, of patients, transient apnea of 42.8%, and a significant fall in both systolic and diastolic blood pressure at two minutes after induction ($P<0.001$) which was tolerable in the American Society of Anaesthesiologist class I and II patients included in this study. Immediate changes in pulse rate was insignificant ($P > 0.1$).

Though patients in this series had supplemental Halothane apart from nitrous oxide and oxygen, early recovery phase as assessed by awakening and orientation times were rapid, but was affected by the duration of anaesthesia, age of the patient and use of opiods. Immediate post operative sequelae was minimal.

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DECLARATION

I declare that this dissertation is my own original work and it has not been submitted for a similar degree in any other University.

Date: 29/10/96

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INTRODUCTION

Anaesthesia like any other clinical specialty is dynamic. Over the years anaesthetists have witnessed many changes in anaesthetic practice because they have been looking for ideal anaesthetic agent to use either singly or in a suitable balanced technique, all aiming at improving safety by minimizing anaesthetic complication and improve quality of anaesthesia.

An ideal agent of interest to the anaesthetist should produce rapid and smooth onset of action, intraoperative amnesia and analgesia, good surgical condition, and short recovery period with minimal side effects.

Together with the changing of anaesthetic technique surgical procedures have been increasing together with the cost involved thus increasing the anaesthetic load implying anaesthesia need to be better planned than ever with a technique which is cost effective and allow increase in patient turn over.

The increasing cost of hospitalization is out of proportion with the economic capability of most patients and facilities in most hospitals are limited compared to patients load. In the past patients preferred hospitalization as long as the cost involved was covered by the government. But with the changing concept of cost sharing programme which is currently being introduced in

the country the cost of hospital service may have direct impact on the care of patients themselves in near future.

Anaesthetic agents sometimes contribute to prolong hospital stay thus increasing the cost and limit maximal utilization of hospital services. This is because of perioperative complications of induction agents namely prolonged emergence, dizziness, headaches and nausea & vomiting which delay discharge (B, Kay, 1991). Delayed discharge may predispose patient especially children, the elderly and the immunocompromized to nosocomial infections which are costly to treat (Nimmo and Smith 1989).

Hospital costs are decreased by 40 - 80% for most operation performed on out patient basis (Kitz et al 1987).

In planning for day case surgery which is the surgery of today (Tom.W. Ogg 1980) there is need to have an induction agent which produces a smooth and rapid onset of anaesthesia. This must be coupled with optimal surgical condition, short recovery time and minimal complication and sequelae. (Nimmo & Smith 1989, Hitchcock 1993, B Kay 1991).

Propofol, a new intravenous induction agent seems to possess the above qualities of an ideal intravenous induction agent, thus a need to be studied in our patients to evaluate its anaesthetic properties and find its role in our day to day practice so that we can advise in a better way towards day case surgeries.

In the department, Propofol is not used routinely. It was first introduced in the department in November 1994, but the drug has not yet been on the list of regular supplies to the department.

LITERATURE REVIEW:

HISTORY:

The concept of intravenous anaesthesia was known to Sir Christopher Wren since 1665, but intravenous anaesthesia first became established in the 1920's with use of the intravenous alcohol tribromoethanol and the barbiturates pernoston. The latter was popularized by a German obstetrician Bum, the name pernoston being adopted in 1935 for the 10% aqueous solution of this barbiturates. (R.S. Atkinson et al 1987, Nimmo & Smith 1989.

The next major advance was the preparation of a more rapidly acting hexobarbitone in the laboratories of Helmit Weese in 1932, hexobarbitone became the first drug capable of producing loss of consciousness in one arm-brain circulation time. During the 1930's and 1940's hexobarbitone was very popular despite causing muscle movements, and it has been estimated that it was used in 10 million patients in the first ten years after its introduction (Nimmo & Smith 1989).

Since then there has been continued research in the field of intravenous agents leading to the introduction of

a variety of agents trying to find a drug with properties which approach those of the "ideal" intravenous agent.

In 1930's it became increasingly appreciated that thio-(sulphur) derivatives of barbiturates were valuable hypnotics and had advantages for use as intravenous anaesthetic. Clinical trials on thiopental sodium were started in 1934 by Lundy and his co-workers at the Mayo clinic in Minnesota. (R.S. Atkinson et al 1987, Nimmo & Smith 1989) Thiopental sodium gradually displaced hexobarbitone because it provided smoother induction of anaesthesia and was shorter acting. Since then thiopental has remained the most popular intravenous anaesthetic agent.

Other barbiturates were also in clinical use. Thiamylal (Surital)^{R} a sulphurated barbiturate, and methohexitone an oxybabiturate had many similarities with thiopental.

Non barbiturates intravenous anaesthetics were also investigated in search of an ideal agent, that ranges from γ aminobutyric acid which was introduced in anaesthesia in 1960, its onset of action is slow and often associated with extrapyramidal motor activity.

Ketamine is unique among intravenous anaesthetics because it has amnesic and analgesic properties in addition to a hypnotic effect entered clinical use in 1971 and became a popular drug for high risk patients.

Etomidate a carboxylated imidazole derivative underwent initial animal studies in Belgium in 1971. This drug was more potent than thiopental and methohexatone, unfortunately the propylene glycol vehicle causes pain on induction and had increased incidence of tremor, hypertonias, muscle movements and hiccup and its use is associated more commonly with nausea and vomiting than barbiturates, these side effects have limited its usefulness. (Churchill, HC, 1984) Smith & Nimmo 1989, RS Atkinson et al 1987).

Another drug is propanidid. This is an eugenol derivative which was formulated in Cremophor EL, adverse anaphylactic reaction were known to be so common to warrant discontinuation of its use in Clinical Practise. The same applies to Althesin, a drug which was a mixture of two water insoluble steroids Alphadolone and Alphaxalone which were solubilized in cremophor EL. This agent has also been withdrawn, it was very useful agent particularly in Neurosurgery, it did not sensitize the respiratory tract to stimuli as does thiopentone, it caused a degree of muscular relaxation allowing early introduction of airway. An agent with overall qualities of althesin but with lower incidence of allergic reaction would be welcomed (Nimmo & Smith 1989).

A recent advance in this field was in 1977 when a phenolic compound propofol was introduced in anaesthesia.

Originally it was formulated in cremophor EL but with concern expressed on allergic reaction to this vehicle it was reformulated in fat emulsion in 1983. The emulsion form is the one in current practice, it offers a great challenge to thiopental with regards to rapid and smooth induction of anaesthesia, non cumulative effects and rapid and clear headed recovery.

Propofol does not mark the end of pursuits for newer intravenous anaesthetic agent. Search for more ideal agents will continue.

1.2 PHARMACOLOGY OF PROPOFOL.

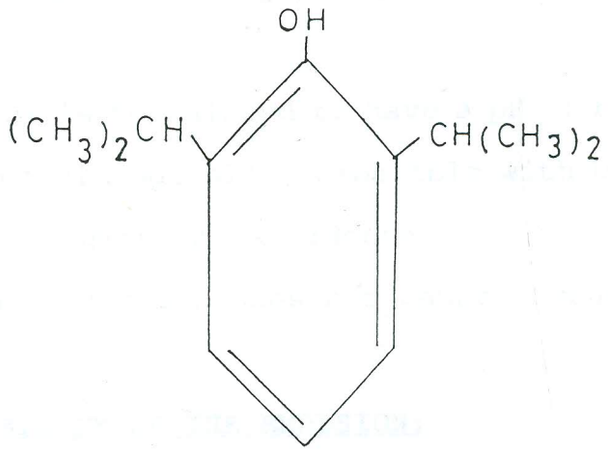
1.2.1. CHEMICAL STRUCTURE OF PROPOFOL.

Propofol is a new intravenous anaesthetic agent with a unique spectrum of physical - chemical properties and clinical effects.

Chemically it is unrelated to barbiturates, steroids, imidazole, eugenol agents or benzodiazepines.

It is one of a series of alkylphenols found to have anaesthetic properties in animals (B.V. Wetchler 1991).

During investigation trials it was referred to as Diprofolane and disopropofol, but these names have been abandoned in favour of its current generic name
Propofol it is also known as Diprivan (Trade Name), its chemical name is 2,6 DIISOPROPYLPHENOL.



Chemical structure of Propofol 2,6 diisopropyl phenol.

1.2.2. **PHYSICAL & CHEMICAL PROPERTIES**

Propofol is a white, sterile oily liquid, that is virtually insoluble in water. For this reason it was originally formulated in an aqueous solution in the solubilizing agent cremophor EL (Polyoxyethylated Castor oil). However owing to high incidence of pain on injection and to the association between cremophor EL and Anaphylactoid reaction (Clarke RSJ et al 1975, Dye D, Watkins J. 1980) propofol was reformulated in an oil in water emulsion containing:

Soya Bean oil 10%

Glycerol 2.25%

Purified egg phosphatide (1.2%)

Although Propofol contain purified egg york constituents it is devoid of protein from egg albumin and should not cause allergic reaction in egg sensitive individuals.

Propofol is formulated to have a pH of between 7.0 and 8.5 and is physiologically compatible with blood. Because of its physiological pH accidental perivascular injection does not cause tissue necrosis.

1.2.3: **STABILITY OF THE EMULSION:**

The emulsion vehicle of Propofol 1% is sensitive to adverse storage condition, at higher temperatures 30 - 40'C will significantly reduce its shelf life. Following higher temperature storage the free fatty acid content increases and pH decreases. (Diprivan Hospital formulary Tanzania 1993). The physical quality and appearance of Propofol can be affected by severe and rapid temperature changes such condition lead to emulsion breakdown.

Propofol should be stored between (2° - 8°C) but under no circumstances should propofol be frozen (0°C or below) this will disrupt emulsion.

In tropical climates (ambient temperature >25°C) the shelf life of Propofol is 2 years (Diprivan Hospital formulary Tanzania 1993).

1.2.4 MECHANISM OF ACTION

Like all general anaesthetics, the mechanism by which Propofol exerts its action is poorly understood, but may involve a non specific effect on lipid membranes. For example Propofol was shown to affect sodium ion channels function in an in vitro lipid bilayer preparation of human Central nervous system sodium channels (Freakel & Urban 1991). In other in Vitro test system propofol has also been shown to potentiate GABA - mediated synaptic inhibition in rat olfactory cortex slices (Diprivan Hospital formulary Tanzania 1993).

1.2.5 PHARMACOKINETICS AND PHARMACODYNAMICS:

A multicentre study determined that the dose of propofol required to induce anaesthesia measured by loss of eyelash reflex in 95% of healthy unpremedicated patients was 2.5mg/kg (Peter S Sebel and J.D Lowdon 1989).

Several authors have conducted pharmacokinetics analysis using the emulsion formulation following single bolus injection of propofol in volunteers, normal patients, and those with liver and kidney impairments.

The decline in blood propofol concentration following a bolus dose is best described by a three compartment open model representing.

1. Distribution of Propofol from blood into tissues (half-life 2 - 4 minutes).
2. Metabolic clearance of Propofol from blood (half life 30 - 60 minutes).
3. A terminal phase in which metabolic clearance is constrained by a slow return of propofol into blood from a poorly perfused deep compartment most probably comprising fat (Cockshot - 1985).

Blood concentration of propofol fall rapidly after a single bolus injection owing to its extensive distribution and rapid elimination.

The total - body clearance rate of propofol has been reported to exceed hepatic blood flow suggesting extrahepatic sites of drug elimination (eg kidneys lungs). (Bernard Wetchlar, 1991, P.S. Sebel and JD Lowdon 1989).

When a subanesthetic dose of 14c-labelled propofol (0.5mg/kg) was administered to male volunteers, blood accounted for 94% of the radioactive Propofol two minutes after dozing (Simon et al 1988). This Proportion fell rapidly to 39% by ten minutes, to 14% by one hour and to 5% by eight hours.

88% of radioactivity was excreted in the urine while the faeces contained less than 2% (PS Sebel and JD Lowdon 1989). Less than 0.3% was excreted unchanged in urine; the remainder consisting of the principle inactive metabolites

1 and 4 glucororide and 4 sulphate conjugates and a corresponding quinol.

In patient with renal failure (Morcos WT, Payne JP 1985) or hepatic (cirrhotic) disease (Servin et al 1986) no statistically significant alteration in pharmacokinetics parameters were found, suggesting Propofol can be used in both group of patients.

In the elderly patients, (Kirk Patrick et al 1988) the clearance of propofol was significantly lower than in the younger patients. The volume of the central compartment in the elderly patients was also significantly smaller than in the younger patients.

There was no difference in the volume of distribution at a steady state or in the half lives of distribution and elimination, these pharmacokinetic differences can be explained by decreases in cardiac output and hepatic blood flow in the elderly (Dundee JW et al 1986) These findings would suggest that propofol be used in reduced doses in the elderly and this is borne out by clinical experience. Lower induction doses of propofol (1.25 - 2.25mg/kg compared to 1.5 - 3.0mg/kg) are required in the elderly.

1.2.6 **TOXICITY:**

With regards to toxic plasma level, animal toxicology studies have shown that the LD50 in the Rat was 42mg/kg (i/v Route) and 600mg/kg (orally) in Mice it was 53mg/kg

(i/v Route) and 1230mg/kg (oral).

Doses of 15mg/kg (i/v Route) in Rabbits were associated with no histopathological changes attributed to administration of Propofol.

1.2.7 **CARDIOVASCULAR EFFECTS:**

Cardiovascular effects of propofol were earlier investigated in four different studies of premedicated patients. An induction dose of 2mg/kg resulted in statistically significant decrease in systolic blood pressure of approximately 30%, the changes in heart rate was variable and insignificant. There was 22% - 25% decrease in the cardiac output, but the decrease (approximately 30%) was statistically significant in only two studies, and only during steady state of anaesthesia that is before surgical stimulation (Monk CR et al 1987, Coates et al 1987). In one of the studies, patient sustained a significant reduction in vascular resistance (21%). The stroke volume did not change significantly.

Claeys and Coworkers 1988 concluded that the major hemodynamic effect of Propofol was decrease in arterial pressure, and that blood pressure decreased because of lowered systemic vascular resistance and not because of reduced stroke volume or cardiac output.

These previous studies have all documented decrease in systemic arterial pressure (Van Aken et al 1988, Clays et

al 1988, Lepage et al 1988). However the reasons proposed as causes for this decrease in blood pressure vary from investigator to investigator. For example the reason for the decrease in systemic arterial pressure as suggested by Claeys et al was the decrease in systemic vascular resistance while cardiac output and stroke volume remained unchanged might have been influenced by other experimental condition such as presence of hypercarbia in spontaneously breathing subjects.

Ven Aken et al 1988 and Carlier et al 1989 ascribed, the decrease in systemic arterial pressure to significant decrease in Cardiac output and stroke volume without concomitant changes in systemic vascular resistance or in Pulmonary capillary wedge pressure, those authors suggested that a Negative inotropic action of Propofol is responsible for the decrease in cardiac output and systemic arterial pressure.

Lepage et al 1988 also found that the decrease in mean arterial pressure was related to a decrease in cardiac index. This decrease in cardiac index was associated with decrease in preload, they suggested that a decrease in venous return caused by an increase in venous capacitance may be responsible for the decrease in cardiac output and systemic arterial pressure. However whereas mean arterial pressure decreased significantly, end systolic volume remained unchanged in that study. therefore a reduction of

mean arterial pressure without a decrease in end systolic pressure suggest a negative inotropic effect as well.

Recently published results from animal studies provide evidence along the same lines. Pultick and Terar 1989 found a shortening of the action potential duration by Propofol indicating a reduction in Calcium entry and therefore a possible negative inotropic effect. The Peak negative inotropic effect of propofol occur 2 minutes after drug administration.

The effect of propofol on the baroreceptor reflex shows that propofol might indicate more pronounced baroreflex inhibition as described by Cuulen PM et al 1987. As the reflex tachycardia occurring during thiopental anaesthesia does not occur with propofol in the presence of similar reduction in blood pressure.

Heart rate changes in propofol anaesthesia is usually variable and not uniform (Grounds et al 1985, LT Fahy et al 1985). But vagotonic effects of propofol has been well documented (P.A. Guise 1991). When clinically significant cardiovascular depression occurs it is typically manifested by decrease in arterial blood pressure (MAP reduction of average 18mmHg) and cardiac index without significant change in Heart rate (Grounds et al 1985).

Most investigators seem to agree that the clinical significance of these hemodynamic changes in young healthy, normovolemic patient is negligible (B.V Wetchler 1991)

usually the hemodynamic changes are tolerated in healthy patients (Richard Johnston et al 1987). Nevertheless the induction dose of propofol should be individualized and titrated against the patient's response at an appropriate rate of 40mg every 10 seconds until clinical sign of anaesthesia appear, a lower rate of administration (approximately 20mg every 10s should be used in elderly, debilitated and hypovolemic patients.

The administration of Propofol to patients with good Left Ventricular function undergoing myocardial revascularization was reported to cause consistent and significant decrease in blood pressure, variable changes in heart rate, and no statistically significant changes in cardiac output and cardiac index (Patrick MR et al 1985, Stephen H et al 1986).

Although Patrick MR et al found significant rises in rate pressure product (RPP) after induction with Propofol, this index may be a poor approximation of myocardial oxygen demand in anaesthetised patients as no evidence of regional myocardial ischemia was noted by intraoperative ECG and pulmonary artery catheter findings (Vermeyen KM, Erpels FA - 1987).

Stephen et al 1986 measured myocardia blood flow and myocardial metabolism, a significant decrease 31% in left ventricular oxygen consumption and a corresponding 26% decrease in myocardial blood flow were found, but coronary

sinus lactate production was increased in two of twelve patients. Lactate production by myocardium reflects an imbalance of myocardial oxygen supply and demand indicating a degree of myocardial ischemia.

Although propofol can be administered to patients with coronary artery diseases it must be given with careful attention to hemodynamic changes. Administration of propofol in combination with potent opiods may constitute safer practise and more effective blunting of autonomic sympathetic responses (Stephen H, Sonntag H, Schence HD, et al 1986).

Larsen and Coworkers studied a geriatric population a subgroup, presumed to have dimished cardio vascular reserve (Larsen R, Rathgebar et al 1988). In these patients undergoing major upper abdominal surgery a significant decrease in myocardial oxygen consumption and myocardial blood flow were found, although two studies used the same technique to determine the degree of ischemia (including ECG, Pulmonary artery pressure, myocardia lactate production). Stephan et al found imbalance in myocardial oxygen supply and demand whereas Larsen et al did not (Larsen R, Rathgeber et al 1988). The differences between these two studies are probably related to the abscence of documented coronary artery disease in the elderly and to the use of lower dose (1.5mg/kg in Larsen study vs 2mg/kg.)

Induction of Anaesthesia with Propofol is not usually associated with disturbance of cardiac rhythm (Monk CR et al 1987, Cortes et al 1987). Although transient supraventricular tachycardia, ventricular ectopic beats and nodal rhythms have been noted during intubation (Harris CE, Murray AM et al 1988). Cardiac arrest after induction with Propofol has been reported (Henriksson BA et al 1985), (Guise PA 1991). This occurred after a period of bradycardia. The patient was resuscitated with atropine and external cardiac massage. Brandy cardia persisting into the postoperative period has also been reported (Thompson SJ, Yate PM - 1987).

When the hemodynamic effects of various induction agents are compared propofol appears to cause a greater reduction in blood pressure than most other agents (PS Sebel and JD Lowdon, 1989). In adults an induction dose of Propofol (2.5mg/Kg.) resulted in more significant decrease in arterial pressure than an equipotent dose of thiopental (4 - 5mg/kg) (Gronds RM, Twigky AJ et al 1985, Mackenzie N, Grants IS, 1985) O'Toole DP, Milligan KR, Dundee JW et al 1987), when compared with methohexitone 1.5 - 2.0mg/kg most investigations have found an induction dose of Propofol (2.0 - 2.5mg/kg) to results in greater decrease in arterial pressure (Doze Van Westphal LM, White PF 1986).

RESPONSE TO TRACHEAL INTUBATION

During general anaesthesia, the hemodynamic responses to tracheal intubation can be profound and deleterious with serious cardiovascular and cerebral effects (Fox EJ et al 1977). In the study examining cardiovascular and central nervous system effects the administration of an induction dose of Propofol resulted in a significant decrease ($P<0.05$) in systolic arterial pressure (greater than thiopentone or etomidate). After Laryngoscopy and intubation the arterial pressures of the patients who received propofol returned to approximately baseline values (Patrick MR et al 1985, Harris CE et al 1988). In contrast the arterial pressure of patients receiving thiopental exceeded baseline values after intubation. Although the induction dose of Propofol decreased arterial pressure the sympathetic stimulation of intubation reversed this decline, the net effect of these events being a return to preinduction haemodynamic status (PS Sebel and JD Lowdon 1989).

1.2.8. **RESPIRATORY EFFECTS:**

Most authors agree that Propofol is a profound respiratory depressant. After induction with propofol apnea of greater that 30 seconds duration has been reported in 13% up 80% of patients (Puralles et al 1987). Incidence of apnea is higher with propofol than methohexitone and

Pentothal (Richard Johnsten et al 1987, N Rest, F Traugott 1991) and patients become apneic for longer duration than did methohexitone or Ketamine, (Mackenzie N, Grant IS 1985, Sebel PS and JD Lowdon 1989).

Incidence of apnea induced by Propofol can be reduced to zero when the dose of propofol is reduced to 2.0mg/kg but at the expense of reporting higher number of induction failure which is unacceptable (Cummings GC et al 1984).

Huma Phares 1987 reports no incidence of apnea in his twenty six premedicated patients with Propofol dosage range of 2-2.5mg/kg. In his study apnea was defined as absence of spontaneous breathing for more than 20s.

Propofol was found to cause significant decrease in minute volume especially in the first 4 minutes after administration and in patient receiving an opiods premedication. Non invasive measurements of respiratory cycle (inductance plethysmography and pneumotachograph) have demonstrated that propofol causes significant decrease in tidal volume and mean inspiratory flow rate (Grounds RM et al 1987, Tailor M et al 1986). These changes in breathing pattern may suggest that the ventilatory depression of Propofol results from a decrease in central inspiratory drive as opposed to a change in central timing (Grounds RM et al 1987).

Ventilatory depression is reflected clinically by an increase in end - tidal carbon dioxide tension ($ETCO_2$)

Propofol increases $ETCo_2$, more profoundly after opiods premedication than without premedication (Johnston R, NoseWarthy et al 1987, Goodman NW et al 1987, Coates et al 1987, Monk et al 1987).

Goodman and Coworkers 1987 also found that Propofol blunted the ventilatory response to an increase inspired CO_2, but their patient had received a Subarachnoid block, painful surgical stimuli may counteract the ventilatory depressant effect of Propofol.

1.2.9. **EFFECT ON CEREBRAL BLOOD FLOW AND INTRACRANIAL PRESSURE**

The effects of Propofol in patients with elevated intracranial pressure have been studied with propofol (2mg/kg) administered to six Comatose patients with intracranial pressure greater than 25mmHg. In this group of patients the intracranial pressure decreased significantly. However the cerebral perfusion pressure also decreased in four of six patients below the minimum safe cerebral perfusion pressure of 50mmHg. This is all due to a decrease in arterial pressure (PS Sebel and JD Lowdon 1989)

In patients without intracranial pathology Propofol decreased cerebral blood flow (CBF) by 26% to 51% and increase cerebral vascular resistance (CVR) by 51% to 55%. Propofol was also found to decrease cerebral metabolic

requirement for Oxygen ($CMRO_2$) to a significant degree (36%). In one study but insignificantly (18%) in another study which combined a Propofol infusion with Nitrous Oxide, oxygen and enflurane (0.5%). The reactivity of cerebral vessels to changes in PCO_2 seems to be maintained during anaesthesia with Propofol (Stephen H, Sonntag et al 1987).

Although Propofol seems to be a reasonable agent for Neuro anaesthesia, its effects on Intracranial pressure and a cerebral blood flow are incompletely elucidated especially in patients with intracranial pathology, its therefore suggested that it should be used with caution in patients with increased intracranial pressure and unstable cardiovascular status.

1.2.10. **EFFECTS ON ADRENAL STEROIDOGENESIS**

On adrenal steroidogenesis effects of Propofol, thiopental, and etomidate were studied using in vitro model of isolated bovine adrenocortical cells. Etomidate was found to be a potent inhibitor of cortisol production, thiopental slightly reduced production, whereas propofol didn't affect production (Keryon CJ, McNeil LM, Fraser R, 1985). Thiopental appears like etomidate to inhibit the final enzymatic step of Cortisol synthesis 11 α Hydroxylase.

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In man when used as a single induction dose of 2.5mg/kg Propofol did not block Cortisol and aldosterone secretion in response to surgical stress or adrenal cortical trophic hormone (Fragen RJ, Weiss HW Molteni A 1987). In contrast using the same dose of Propofol for induction followed by a continuous infusion (4.4mg/kg/h) Kay NH & Colleagues 1985 found a transient decrease in plasma Cortisol concentration 30 minutes after induction of Anaesthesia. However by 3 hours after induction cortisol concentration was not significantly different from base line.

Studies on steroidogenesis have also been carried out following an 8 hours infusion for sedation in the intensive care unit. An infusion of 3mg/kg/h was given through a central vein and the infusion continued for 8 hours. Cortisol estimation were made at 4 and 8 hours then a synacthen test was performed. The synacthen test is a challenge with synthetic adrenocorticotrophic hormone which normally results in cortisol secretion, in this study propofol was found to have no effect on plasma cortisol concentration and response to the synacthen test was normal, with significant increase in cortisol concentration 30 and 120 minutes after synacthen administration. (Newman LH, Macdonald JC et al 1987).

Considering these studies, Propofol appears to have in vitro potential for affecting adreno steroidogenesis

however in clinical practise this doesn't appear to be a problem (Newman LH Macdonald JC at el 1987).

1.2.11: **EFFECTS ON HEPATIC AND RENAL FUNCTION**

Propofol seems to have minimal adverse effect on liver function, after reviewing a huge series of patients Stark et al 1985 found no patients to have elevated Aspartate Transaminase (AST) (128 patients tested) or Alanine Transaminase (ALT) (155 patients) greater than twice the upper limit of normal and less than 1% of patients to have similar elevations in bilirubin or alkaline phosphatase, and also propofol has not been reported to have adverse effects on renal function by test of creatinine and blood urea levels (Stark RD et al 1985).

1.2.12: **EFFECTS ON COAGULATION**

Propofol emulsion is quite similar to intralipid a product frequently used for intravenous hyperalimentation which has been associated with alteration of blood coagulation (Burnham WR et al 1982). But most studies have failed to show that propofol changes the coagulation profile as measured by thrombin time, Prothrombin time Partial thromboplastin time fibrinogen titres, fibrinogen degradation products and platelet counts (Kay NH et al 1985). The study that found an alteration in coagulation involved 8 hours infusion of Propofol for sedating

mechanically ventilated patients, most of whom had undergone surgery and had ongoing Pathophysiological processes to explain coagulopathy (Newmann LH et al 1987).

1.2.13: **ALLERGIC REACTIONS:**

Anaphylactoid reactions has been attributed to agents which had been dissolved in Cremophen EL (Dye D, Watkins J: 1980); Clark RSJ, Dundee JW et al 1975). The emulsion formulation of Propofol appear to be devoid of anaphylactoid side effects. The administration of Propofol did not cause significant increase in plasma histamine, immunoglobulin or complement C_3 level (Fahmy et al 1986).

1.2.14: **EFFECTS ON INTRAOCULAR PRESSURE**

Propofol causes a significant decrease in intraocular pressure ranging from 27% - 53%. Induction doses of propofol and thiopental results in similar decreases in intraocular pressure. Propofol was found to be superior in controlling intraocular pressure after rapid sequence induction than thiopental, but intraocular pressure was best controlled in those patients who received a second dose of propofol just prior to intubation and who were administered a non-depolarizing neuromuscular blocking agent to facilitate intubation) PS Sebel and J.D Lowdon 1989).

1.2.15: **EFFECTS AT SITE OF INJECTION:**

The incidence of pain on injection is significantly greater following Propofol, higher incidence is reported due to use of small veins or absence of a narcotic premedication. Incidence is variable 22 - 58% when veins on the dorsum of hand is used, in cases where the new preparation has been injected into a vein in antecubital fossa the incidence of pain is usually very low of about 3%. No local complication following injection of Propofol has been seen up to 72 hours after surgery, the incidence of thrombosis or thrombophlebitis after intravenous injection is less than 1% (LT Fahy et al 1985, Richard Johston et al 1987, Macntosh MJ and Lees NW 1985, Stark RD et al 1985).

1.3.0. SPECIAL SETTINGS

1.3.1. PROPOFOL IN PORPHYRIA AND MALIGNANT HYPERTHERMIA

Porphyrogenic nature of Propofol is not clearly known, it has been administered safely on two separate occasions to a patient known to have acute intermittent Porphyria (Mitterschiffthaler G et al 1988).

Preliminary studies on muscle biopsies suggested that propofol may be used in patients with malignant Hyperthermia, in one case report Propofol was used without incident during myocardial revascularization in patient with strong family history of malignant hyperthermia (PS Sebel and JD Lowdon 1989).

1.3.2: **PROPOFOL IN PREGNANCY AND PUERPERIUM**

Use of Propofol in pregnancy and puerperium has not been investigated closely. Preliminary studies showed that it crosses the placenta and may be associated with neonatal depression. Teratology studies in rats and rabbits showed no teratogenic effects. It has been used during termination of pregnancy in the first trimester. It should not be used in obstetric anaesthesia (Diprivan: Hospital formulary - Tanzania 1993).

A preliminary studies of women given Propofol in the puerperium showed that propofol was secreted in the colostrum with blood to colostrum ratio close to I (PS Sebel and JD Lowdon 1989). Safety to the neonates has not been established following the use of Diprivan in mothers who are breast feeding (Diprivan Hospital formulary - Tanzania 1993.

1.3.3. **PROPOFOL IN PAEDIATRIC POPULATION**

Propofol has not been extensively studied in the paediatric population. Purcell - Jones and coworkers compared Propofol (2.0 - 2.5mg/Kg) with thiopental (4 - 5mg/Kg) for induction in 60 children aged 3 - 16 years. All children were premedicated with papaveretum 0.4mg/kg and hyoscine 0.008mg/kg given intramuscular 90 minutes before operation, there was no statistical difference found between groups with respect to pain on

injection, induction times spontaneous movements or duration of apnea. Propofol caused greater decrease in systolic blood pressure but it was statistically significant only at 2 minutes after induction ($P<0.05$). Although a blinded independent assessor considered the quality of induction with thiopental good in all patients, quality of induction after Propofol was rated poor because of moderate pain on injection, apnea and occurance of involuntary movements (Purcell - Jones, Jates A Baker JR et al 1987).

When used to induce anaesthesia in children it is recommended that Propofol should be given slowly until the clinical signs show the onset of anaesthesia. The dose should be adjusted for age and or body weight. Most children over 8 years of age are likely to require approximately 2.5mg/kg of Propofol for induction of anaesthesia. Under this age the requirement may be more. Propofol is not recommended for use in children of less than 3 years of age (Diprivan - Hospital formulary - Tanzania 1993).

1.3.4: **PROPOFOL AND SEIZURES**

Initial animal studies have demonstrated that Propofol has neither convulsant nor anticonvulsant properties (Sutherland, P Burt 1994), but in present studies there is bulk of evidence that supports propofol is an anti

convulsant. Studies in mice suggest that propofol has comparable efficiency to thiopental in preventing experimentally induced seizures. Propofol has been used successfully to abort experimental status epilepticus in rabbits as well as to successfully treat status epilepticus in human (MJ Sutherland, P Burt - 1994) Other authors have pointed out that propofol in certain circumstances can be a pro-convulsant Spontaneous movements have long been recognized to be associated with propofol in animal as well as in humans, could it be that the wide variety of effects reported as convulsions or seizures (possibly due to propofol) are in fact the extreme end of a spectrum of effects beginning with "spontaneous movements"! Because there is little evidence to indicate EEG epileptiform activity in relation to propofol (Sunders PRI, Harris MNE 1990). Since Propofol causes marked cortical depression with isoelectric EEG in most cases, this suggest that what we are seeing with Propofol convulsions is drug induced decerebrate rigidity which could account for the opisthotonous and myoclonic manifestation with altered level of consciousness and a normal EEG. It is now clear that "seizure activity" excitatory phenomena and or a disorder of muscle tone are potential complication of the use of propofol. Whether this seizure activity is primary, secondary or not at all a cerebral cortical event is still to be elucidated. It would appear appropriate to recommend

to patients who experience apparent convulsive phenomena after Propofol that they should not be re-exposed to the drug (MJ Sutherland, P Burt 1994), and at present, Propofol should not be used in epileptic patients (Collier and K, Kelly 1991).

1.4 DRUG INTERACTIONS

1.4.1. INTERACTION WITH NEUROMUSCULAR BLOCKING AGENTS

Compatibility studies with mixture of Propofol in its emulsion form and the following muscle relaxants have been investigated: atracurium besylate, pancuronium bromide, Suxamethonium chloride and Vecuronium bromide. Stability data shows that propofol is stable in all mixture with exception of atracurium (Nightingalle P et al 1985, Diprivan hospital formulary - Tanzania 1993). However full compatibility studies have not been performed on the muscle relaxants so the use of these mixture cannot be recommended. Atracurium has been shown to have adverse effect on stability of diprivan emulsion. This incompatibility is probably due to a combination of the Low pH of atracurium and the Cationic properties of atracurium formulation. also the mildly alkaline pH of Propofol may inactivate atracurium. (Diprivan: Hospital formulary - Tanzania 1993).

1.4.2. INTERACTION WITH ANTICHOLINERGIC AGENTS.

Propofol has been shown to be stable in mixtures of Atropine or Hyoscine, the stability of the latter agents were not undertaken in these studies, therefore the use of such mixture cannot be recommended (Diprivan: Hospital formulary - Tanzania 1993).

1.4.3. INTERACTION WITH LIGNOCAINE INJECTION

20 parts Propofol 1% and up to 1 part of 0.5% or 1% lignocaine may be premixed. Mixture containing higher concentration of lignocaine have been shown to be unstable and are not recommended, Propofol/lignocaine mixture should be thoroughly mixed and used immediately after preparation. (Diprivan: Hospital formulary - Tanzania 1993.

1.4.4. INTERACTION WITH ALFENTANYL/FENTANYL

Alfentanyl is an opiod frequently used as an analgesic agent when propofol is being administered by infusion, the interaction of continuous infusion of propofol (6mg/kg/h) and alfentanyl have seen studied. The disposition kinetics of propofol was found to be unaffected by administration of alfentanyl. However the plasma alfentanyl concentration was significantly higher than expected values during infusion. The authors suggest co administration of Propofol with alfentanyl may affect alfentanyl kinetics either by a decrease in the volume of distribution or by decrease elimination (Gepts E, Jochkeer K et al 1988).

Mixture of Propofol with fentanyl have also been investigated. The result shows that Propofol is stable in the mixtures, however the stability of fentanyl was not assessed and recommendation on the use of Propofol and fentanyl mixed together cannot be made (Diprivan: Hospital formulary - Tanzania 1993).

1.4.5. DRUG - FOOD INTERACTION.

It is recommended that blood lipid level be monitored when propofol is being administered to patient thought to be at particular risk of fat overload. Administration of Propofol should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If patient is receiving other intravenous lipid concurrently a reduction in quantity should be made in order to take account of the amount of lipid infused as part of Propofol formulation 1.0ml of Propofol contains approximately 0.1g of fat. (Diprivan: Hospital formulary - Tanzania 1993.

1.4.6. INTERACTION WITH INFUSION FLUIDS

Propofol may be used for infusion diluted with 5% dextrose intravenous infusion only, dilutions must not exceed 2mg Propofol/ml and should be prepared aseptically and for compatibility reasons must be used within 6 hours of preparation.

Propofol may be administered with following infusion as Carrier fluids - Dextrose 5%, Nacl 0.9%, Dextrose 4% with Nacl 0.18%, 5% dextrose and 0.2% Nacl lactated Ringers and lactated ringers and 5% dextrose (Diprivan - hospital formulary - Tanzania 1993).

1.5. CLINICAL USES

1.5.1. INDUCTION AND MAINTENANCE OF ANAESTHESIA

Propofol is indicated for induction and maintenance of general anaesthesia in adults and children over 3 years.

The ideal intravenous induction agent posses characteristics which include rapidity of onset and recovery, reliability of action (smooth onset without excitatory effects or respiratory distress) water solubility, lack of allergic responses and tissue toxicity and stable hemodynamic effects (Dundee JW 1985). The suitability of Propofol as an induction agent has been assessed in different anaesthesia protocols, as bolus, as bolus followed by an infusion with oxygen and opiods as in total intravenous anaesthesia or supplemented with Nitrous oxide/oxygen mixtures.

Numerous studies have examined propofol as a single bolus (Cogan MR et al 1987) or as a bolus followed by maintenance anaesthesia with nitrous oxide and incremental doses of propofol (Robbinsol FP 1985) inductions was rapid with few excitatory effects such as Hypertonous, tremor or

hiccup (14%) or spontaneous movements (25%). (Cogan MR et al 1987 Appington J et al 1985).

After induction dose of (2-2.5mg/kg) when administered by repeated bolus injection, the timing of the repeat administration (25% to 50% of the induction dose) is determined by the anaesthesiologist and is based on the clinical signs of light anaesthesia (eg movements, tachycardia, Hypertension lacrimation). Clinically a repeat dose might be expected every 5 - 15 minutes depending on the previous dose, degree of surgical stimulation and patient variability of response (Bernard V Wetchler 1990).

Maintenance of anaesthesia by intravenous infusion of Propofol is generally smoother than with repeated bolus injections since continuous drug administration by infusion avoids the peak and ditches of blood level that are associated with changes in the depth of anaesthesia. Administration by continuous infusion produces an initial rapid increase in blood propofol concentrations followed by slow rise to a virtual steady state. When administering propofol by continuous infusion it is recommended that drop counters syringe pumps or volummetric pumps be used to provide controlled infusion rates. Although the rate of administration varies between patients and is somewhat dependent on the use of analgesics and muscle relaxants infusion rates of 0.1 to 0.2mg/kg per minute usually

provide satisfactory conditions. Some investigators advocate a slightly higher infusion rate of up to 0.3mg/kg per minute during the first few minutes following induction of anaesthesia. This is due to the extremely rapid redistribution of an induction dose of Propofol and attempts to ensure that initial blood levels do not fall too rapidly. In all cases the infusion rate should be adjusted during surgery according to the clinical response of the patient. A variable infusion technique rather than a fixed infusion regimen permits the rate of propofol to be precisely titrated to achieve the desired effect. Ease of control during maintenance of anaesthesia has been one of the frequently repeated advantages of Propofol infusion. (Bernard V Wetchler 1990).

Infusions of Propofol and an opiod (without nitrous oxide) have been combined in general anaesthesia. Combined infusions were first reported in 1985 by De Grood et al using fentanyl and propofol with good success at controlling anaesthetic depth and hemodynamic changes.

Because of their similar pharmacodynamic characteristics (rapid onset and short duration of action) it seems that propofol and alfentanyl would be ideal and complementary agents for total intravenous anaesthesia (TIVA). When these two agents were administered together for orthopedic and ENT procedures, anaesthesia proceeded smoothly with predictable changes in hemodynamic after

induction and intubation. Emergence from anaesthesia was rapid (time from end of infusion until patients being orientated 12.8 - 18.9 minutes). In the recovery room patients were described as fully alert and clear headed. (Meryne A et al 1988, Steegers PA Foster PA. 1988).

Comparisons of Propofol and inhalational techniques for maintenance of anaesthesia are limited, however preliminary investigations suggest that propofol may offer significant advantages when compared with a conventional thiopental, Isoflurane, Nitrous oxide oxygen technique in the management of anaesthesia for short ambulatory surgical procedures. The patients who received propofol demonstrated shorter stay in recovery room and faster times to independent standing, suggesting that the use of Propofol may provide faster patients turnover and less patient expense (Dose VA, White PF 1986, Cork RC et al 1988, Katillar K et al 1988).

CHARACTERISTICS OF ANAESTHETIC INDUCTION

Induction time is short with Propofol and comparable to other agents. There were no statistically significant differences, between Propofol and thiopental, etomidate or methohexitone when measuring the interval from beginning of injection to loss of eyelash reflex (Nightingalle et al 1985, Purcells Jones G et al 1987, Kay B, Healy TEJ 1985 De Grood et al 1987, Degrood PMRM, Mitsukuri et al 1987, Wells

JKG 1985) or to loss of counting (De Grood RMRM et al 1987, Rolly G, Versichelen L 1985, Fahy LT et al 1985). One exception is in a study done by Richard Johnstone et al 1987 who found the mean induction time was longer in the propofol group 35.7 ± 8.4 versus 26.3 ± 5.3 seconds in the thiopental group ($P<.0001$). Like thiopental, propofol in adequate doses will induce anaesthesia in one arm-brain circulation time. In one comparative study, propofol 2mg/kg resulted in loss of eyelash reflex in 30.5s compared with thiopental 4mg/kg which produced anaesthesia in 36.6s (Rolly G, Versichebn L 1985).

The induction of anaesthesia should not only be rapid but should also be smooth without excitatory phenomena such as myoclonia, hypertonous or involuntary movements. In this regard excitatory effects following propofol are relatively low in frequency ranging from 0-20 percent (Kay B, Heally TEJ 1985, De Grood PMRM et al 1987, Mackenzie N, Grants IS 1985). In comparison to other agents incidence of excitatory effects with thiopental range from 0 - 6.7% and methohexitone up to 90% of the patients (Mackenzie N, Grant IS 1985, De Grood RMRM et al 1987, Johnston R et al 1987).

RECOVERY CHARACTERISTICS

Many investigators have commented on the recovery aspects of Propofol, characterized by rapid emergence and minimal postoperative confusion (Mackenzie N Grant IS 1985, Johnston R et al 1987).

When compared to thiopental, propofol has been reported to have shorter recovery times by measurements such as time to open eyes on command, time to recall date of birth and time of orientation (Mackenzies N Grant IS 1985, Johnston R et al 1987) when Propofol and methohexitone were compared using similar methods of assessment results were inconsistent, mixed and without a clear trend (Mackenzie N Grant IS 1985, Wells JKG 1985, Jessop E et al 1985). Although Data is limited recovery characteristics of Propofol and etomidate appear to be similar (De Grood PMRM et al 1987, Wells JK 1985).

EFFECTS OF PREMEDICATION AND SPEED OF INJECTION

The effects of various premedication regimens on the characteristics of propofol have been evaluated in several studies. In one randomized study in gynaecological patients, Briggs and White gave an induction of 2.5mg/kg to patient who had received either no premedication, diazepam 10mg orally, or meperidine 50 -75mg intermuscular and atropine 0.6mg intramuscular approx 1 hour preoperatively. Anaesthesia was successfully induced in all patients with

mean induction times of less than 30s in all groups.

The systolic blood pressure decreased to a similar extent in all three groups. Premedication did not seem to affect the incidence of events such as spontaneous movement excitatory effects or respiratory upset (Briggs CP, White M 1985).

In another study in gynaecological patients, three premedications were compared; Lorazepam 1mg, 2 hours before surgery, papaveretum 10mg intramuscular with Hyoscine 0.2mg 1 hour before surgery; and no premedication. After a bolus of alfentanyl 250μg induction proceeded with propofol until the eyelash reflex was abolished. The induction dose did not correlate with either age or weight of the patients. The dose for induction was significantly higher in unpremedicated patients (126mg) than in premedicated patients (101mg) $P<0.01$. The incremental doses required for maintenance of anaesthesia however were not affected by different premedication regimens. Furthermore recovery time was related to the total dose of the Propofol, not premedication. Patients receiving an opiods premedication had more Nausea and vomiting (17.5%) compared to the other patients (2.6%) (Redferon N Stafford MA et al 1985) premedication seems to have few effects on the induction characteristics of Propofol. The addition of opiod to the premedication may decrease the induction dose of propofol. Various premedicants had little effects on time to

induction extent of hemodynamic changes and recovery (PS Sebel and J.D. Lowdon 1989).

Speed of injection may affect the induction of anaesthesia by changing the dose requirement and rapidity of onset (PS Sebel and JD Lowdon).

The administration of an induction dose of Propofol (2mg/kg) produced satisfactory level of anaesthesia more rapidly and more reliably if injected over a short time (5 seconds) than a longer time(s). Others have commented that the speed of injection had no effect on the degree to which arterial pressure declined or on the incidence or duration of apnea. (Rolly G, Versichelen L et al 1985).

1.5.2. SEDATION IN THE INTENSIVE CARE UNIT (ICU)

Sedation is required in many patients admitted to ICU for their comfort and safety, these patients are usually exposed to a number of noxious stimuli; they experience pain after trauma or surgery, distress and discomfort from presence of an endotracheal tube and mechanical ventilation, and anxiety from appreciation of the severity of their illness. In addition they are exposed to intermittent stimuli during physiotherapy, tracheal suction and nursing procedures such as turning and changing of dressings.

Etomidate was used by continuous infusion in the ICU particularly for its effects on intracranial pressure,

until reports of an associated increase in mortality in critically ill patients especially those associated with infective complications in trauma patients (Watts & Ledinghmous 1984). Further investigation revealed that this increase in mortality was related to suppression of the Neuro adrenal axis peripherally and possibly centrally too (Fugen RJ et al 1984, Grands RM & Lator JM et al 1987).

Newmans and Coworkers observed 10 patients being mechanically ventilated over an 8hour period. These patients required intensive care for various reasons including respiratory failure from chronic obstructive pulmonary disease, septic shock after bowel surgery; and postoperative chest or great vessel surgery.

Out of the 10 patients, 3 patients had initial bolus dose 1mg/kg of Propofol. Infusion were started in all patients at mean rate of 1.93mg/kg/h. The acceptable level of sedation was defined as that state where the patient remained comfortable without periods of agitation. An average of four changes were made in the infusion rate over the 8 hours period mainly for adjustments of the level of sedation, and control of continuing fall in the blood pressure of the three patients who received initial bolus dose of 1mg/kg of propofol. 2 patients exhibited marked decrease in mean arterial pressure of 40 and 53%. This decline appeared to improve after the infusion was discontinued. These researchers found propofol to be

suitable for infusion in critically ill patients but cautioned that the cardiovascular, respiratory and sedative effects must be carefully monitored in this sensitive group of patients (Newamans CH, et al 1987).

Grounds and Coworkers 1987, considered propofol by continuous infusion to be suitable in the postoperative cardiac intensive care and cited the rapid changes in level of sedation as an advantage, but they emphasized that propofol has no analgesic properties, a statement which is in conflict with the evidence from Briggs et al 1982 who found that the clemophor EL formulation of propofol had some analgesic properties in subhypnotic doses.

An interesting side effect of prolonged infusion of propofol was the report of green urine (PS Sebel and JD Lowdon) which clears rapidly after the infusion has been stopped, the urine when analysed was found to contain phenols which have been reported to cause green urine. The coloration did not affect renal function.

1.5.3. **SUPPLEMENTATION OF REGIONAL BLOCKADE**

Sedation during local and regional anaesthesia is often desirable to minimize the stress associated with the operating room environment in addition many patients have anxieties regarding recall of intraoperative events. Benzodiazepines are the drugs used most often.

Diazepam has a long elimination half life (24 - 48 hours) which is prolonged further in elderly patients (Klotz et al 1975), which is the population most likely to have regional anaesthesia.

Because of its pharmacokinetic and pharmacody namic profiles, propofol is a useful drug for intravenous sedation to supplement regional blockade. Propofol offers a smooth induction, satisfactory maintenance and rapid recovery with reliable amnestic properties. But it is not as potent an amnesic agent as Midazolam. But although the equipotent doses of propofol and midazolam have not been clearly defined recovery after propofol appears to be significantly more rapid than that after midazolam (Wilson E, Mackenzie N, Grant IS 1988, Dubris et al 1988, Jessop et al 1985)

1.5.4. **AS AN ANTIEMETIC AND ANTI PRURITIS**

Use of Propofol has been associated with reduced incidence of emetic sequelae and it has therefore been suggested that it has an antiemetic action (Maccollum JSC et al 1988, Gunawardena RD et al 1988). Apart from the reduced incidence of nausea and vomiting neither of the studies has demonstrated a true antiemetic effect of Propofol. Because antiemetics act at chemoreceptor trigger zone as dopamine antagonist, they bear structure similar to GABA and have a propylene chain with at least one tertiary

Nitrogen atom and an aromatic ring (Vickers et al 1984) Propofol is devoid of these structures.

Propofol in small doses - 10mg is being used in the management of nausea and vomiting in hyperemesis gravidarum and post labor.

Also it has been found to have anti pruritis action and being used in the management of pruritis associated with epidural narcotics. It is given in small dosage in a range of 10mg which can be repeated according to the clinical condition (Kelly Mc Queen 1995).

PART TWO - CLINICAL STUDY:

PROPOFOL ANAESTHESIA - A CLINICAL EXPERIENCE

2.1. INTRODUCTION:

Propofol (Diprivan), a new intravenous induction agent, introduced in the department of Anaesthesia Muhimbili Medical Centre in November 1994 was studied in one hundred and sixty healthy patients, to examine its anaesthetic properties as an induction agent and possible side effects in surgical procedures lasting less than one hour (60 minutes).

Induction and early recovery characteristics, haemodynamic changes after induction and responses to tracheal intubation, factors associated with prolonged recovery and immediate postoperative sequelae were determined.

2.2. ANAESTHETIC PROTOCOL, (MATERIALS AND METHODOLOGY):

A: **PATIENTS:**

One hundred and sixty patients of both sexes were randomly selected for the study. The age limits were put at 10 - 60 yrs.

Inclusion Criteria:

In this study patients scheduled for short surgical procedure lasting less than one hour, who were ASA physical status I & II with no previous history of adverse effects

with anesthetics, and with written informed consent for anesthesia and surgery were selected and included in the study.

Children below 10 years, elderly above 60 years, pregnant women and lactating mothers were excluded from the study.

B. **METHODOLOGY:**

Drug used was Propofol (Diprivan) 1% in a new oil-water emulsion form.

ANAESTHETIC PROCEDURE AND DATA COLLECTION:

Patients included in this study were unpremedicated. On arrival in operating room a peripheral intravenous cannula was inserted at any site which was found convenient. A routine blood pressure cuff was applied and baseline blood pressure and pulse were recorded. Patients were informed about the possibility of pain at the injection site, then they were preoxygenated for 2 minutes.

Patients were induced using propofol 2.5mg/kg at the rate of 20s. From the start of injection patients were asked to count slowly as anesthesia was being induced. Induction time was noted as the time from start of injection to cessation of counting. During the induction period pain at the site was assessed by either movement of the arm with the intravenous line and by looking at the

facial expression of the patient. Pain was graded as severe if there was screaming or difficulty in continuing counting during the induction.

Incidence of apnea was determined in those patients in which the procedures were done under mask without relaxant and that was defined as absence of spontaneous respiration lasting more than 15s after the induction dose of Propofol.

After induction anesthesia was maintained by O_2:N_2O (1:2) mixture (Total 6L/M) and halothane 1.5% for those breathing spontaneously or 0.5% for intubated patients. Atracurium besylate 0.5mg/kg was used to facilitate tracheal intubation. Supplemental opiod (Pethidine 1mg/kg) was given.

Hemodynamic changes after induction before surgical stimulation and tracheal intubation were noted within 2 minutes after induction. Blood Pressure (BP) and pulse rate (PR) was taken and compared with baseline readings. Next reading was taken at 5 minutes after induction in a group of patients who had been intubated (Group A) and those who had mask anaesthesia (Group B) and haemodynamic response to laryngoscopy and tracheal intubation assessed between these two groups. Then the BP & Pulse were checked every 5 minutes till the end of the procedure.

At the end of the procedure, all patients given atracurium to facilitate intubation were reversed with Atropine 0.02mg/kg and Neostigmine 0.07mg/kg, the time of

cutting off nitrous oxide and halothane was noted. Patients were then asked to open eyes on command every 30s and awakening time was defined as the time from cessation of anaesthetics to time the patient was able to open eyes on command.

Orientation time was defined as the time of cutting off anaesthetics to time when patients were able to answer questions like his/her age, place of residence, and name or where the patient was.

The occurrence of vomiting or retching during recovery was noted for, and also patients after being oriented were asked if they were feeling any discomfort which was noted. The site of injections were inspected for continuing pain and erythema, thrombophlebitis or thrombosis.

2.3. **STATISTICAL EVALUATION:**

The differences between Means were analysed by t - Tests to compare the mean values for continuous variables.

CHI-Square test was used to compare categoric variables.

Correlation between variables was determined by correlation analysis and use of t - Test for testing significance of correlation coefficient - "r".

2.4. **RESULTS:**

Out of 160 patients included in this study forty four (44) were males that is 27.5% and one hundred and sixteen (116) were females 72.5%. Preponderance of female patients was due to fact that they were usually the ones who were scheduled for short surgical procedures such as the dilatation of the cervix and curettage of the uterus, examination under anaesthesia, and laparascopies.

These patients had a mean age of 33 ± 11 years and the range was 12 - 60 yrs Fig. I. They had a mean weight of 58.7 ± 10 Kg, the weight ranged from
30 - 88 Kg. (Fig. II).

Out of 160 patients, one hundred and twenty were ASA 1 (75%) and forty patient were classified as ASA II (25%), This reflects the fact that, this study was carried out in relatively healthy and fit patients.

SURGICAL PROCEDURES:

The bulk of the surgical procedures carried out were minor gynecological procedures (58%), such as laparascopies and dilatation of the cervix and curretage of uterus and others which explain the high proportion of females in the study group. Other surgical procedures included in the study were minor orthopaedics and trauma surgical operations such as implants removal and bone saucerization. Also included were urological diagnostic procedures such as

cystoscopies and urethral Bouginage, and minor general surgical operations. Table I.

The mean duration of anaesthesia during these surgical procedures was 30.1 ± 12 minutes with a range of 10 - 60 minutes.

Induction Characteristics:

In the operating room after applying blood pressure cuff for indirect blood pressure monitoring peripheral intravenous cannulation was performed in all cases at the site where a vein could be easily identified depending on individual case. Table II shows distribution of the site of intravenous cannulation.

At that predetermined dose based on body weight (2.5mg/kg); and at the rate of administering of 20s, no induction failure was encountered by the author.

Propofol was found to produce rapid onset of anaesthesia with mean induction time of 27.7 ± 6 seconds in males and 25.9 ± 7 seconds in females (Table III). The difference between induction time with regards to sex was not statistically significant.

Induction was generally smooth in most of the patients studied, 7 patients (4.3%) (all males) developed spontaneous movements of the arms and face at induction which was not associated with light anaesthesia or pain at the injection site, and 3 patients (1.9%) (2 females and

one male) had hiccup at induction.

There were a total of 84 patients (males and females included) whose procedures were done under facemask with spontaneous breathing. In this subgroup occurrence of apnea after induction was noted. Out of 84 patients, 36 developed transient apnea at induction (42.8%). This has been defined in the protocol as absence of spontaneous breathing for more than 15 seconds. Ventilation was then assisted till spontaneous breathing was established.

Major adverse effect which was noted at induction was the pain on injection site. Out of the 160 patients 55 patients experienced pain, that constituted 34.4% (Table IV). In 5 cases, (9%) (4 females and 1 male) the pain was graded as severe, but didn't necessitate discontinuation of administration of the drug.

Most of the patients who experienced pain had their intravenous cannulation done on small veins on the dorsum of hand, out of 44 cases who had intravenous line on the dorsum of the hand, 26 (59.1%) cases experienced pain on injection, including 3 cases who had very severe pain. In 87 cases who had intravenous line at the wrist, 27 (31%) had similar experience of pain at the site. In contrast no pain was experienced by patients who had intravenous line at the antecubital fossa (17 cases). The difference in the proportion of patient experiencing pain on injection at different sites is statistically significant. (Table V).

HAEMODYNAMIC CHANGES:

Haemodynamic effects of Propofol as an induction agent and response to tracheal intubation were studied with one hundred and sixty patients in this clinical study, parameters of interest in this study which was possible to be measured indirectly was blood pressure and Heart Rate.

Pulse Rate:

There was a basal mean pulse rate of 86.4/m before induction of anaesthesia and a range of 69 - 120 beats/minute, median 86/m.

2 minutes after induction at the steady state of anaesthesia before tracheal intubation there was a mean change of pulse rate of -0.5 ± 1. The mean change was statistically not significant $P > 0.1$ (Table VI).

After 5 minutes of induction there was a mean change of pulse rate of 6.03 in the group of patients with endotracheal tube (Group A) and a mean change of 2.64 in the group of patients with mask (Group B). These changes were statistically significant $P < 0.05$ (Table IX).

A significant fall in heart rate to 50 beats/m was noticed in 3 patients, all were female, ASAI. Two patients aged 25 years were both undergoing laparoscopies and dye insufflation for primary infertility, the other was a 50 years old woman undergoing a diagnostic D & C all were treated with atropine 1mg intravenously.

BLOOD PRESSURE

There was a mean change of systolic blood pressure of -15.8 ± 0.7 mmHg and diastolic blood pressure of -7.6 ± 0.6mmHg from baseline to 2 minutes after induction at steady state of anaesthesia and before endotracheal intubation, changes which were statistically significant P < 0.001 (Table VI).

And after 5 minutes of induction there was a mean change of systolic blood pressure of 7.11mmHg and diastolic blood pressure of 2.11mmHg in the group of patients with endotracheal tube (Group A) and in the group of patients with mask (Group B) there was a mean change of systolic blood pressure of 2.14mmHg and diastolic blood pressure of 0.6mmHg. Statistically significant differences in systolic blood pressure changes between these two groups were seen (P <0.001) (Table VII).

Mean changes of diastolic blood pressure was not statistically significant (P > 0.05) (Table VIII). (for details of haemodynamic changes see appendix I)

RECOVERY:

In this study 51 (31.9%) patients were given intraoperative pethidine 1mg/kg as the adjuvant therapy for analgesia.

Awakening time was assessed in all patients. Mean awakening time for entire population was 6.4 minutes ± 1.9.

In the patients who had Pethidine intraoperatively the mean awakening time was 7.7 minutes ± 2 and the group of patients who had no Pethidine intraoperatively the mean awakening time was 5.8 minutes ± 1.5 (Table X).

The mean orientation time for the entire population was found to be 9.2 minutes $^{\pm 2.9}$.

In the proportion of the patients who had Pethidine intraoperatively, they had a mean orientation time of $11.4^{+3.1}_{-}$ minutes and in proportion of patient without narcotics had mean orientation time of 8.1 ± 2.2 minutes.(Table XI).

When correlation was sought between orientation time and body weight on which the dose of the drug administered was determined it was found that there was no statistical evidence of a linear correlation between these two variables ($P>0.05$).

But there was evidence of a positive linear correlation between the orientation time with the age of the patients ($P < 0.05$).

And strong evidence of a positive linear correlation was determined between both awakening and orientation time and the duration of anaesthesia $P<0.001$.

Adverse Effects at Recovery.

Three (3) patients (0.9%) vomited at recovery room this happened in 2 females who had laparoscopy and tubal

dye insufflation done on them. They both had no intraoperative pethidine. The other was a young boy of 22 years old who underwent an open reduction and internal fixation of the left radius with pethidine 50mg added for intraoperative analgesia.

There was no erythema or thrombophlebitis or continuing pain on the site of intravenous line through which the drug was injected.

TABLES AND FIGURES

Fig I: Showing Number of Patients Against Age Group (both sexes put together.

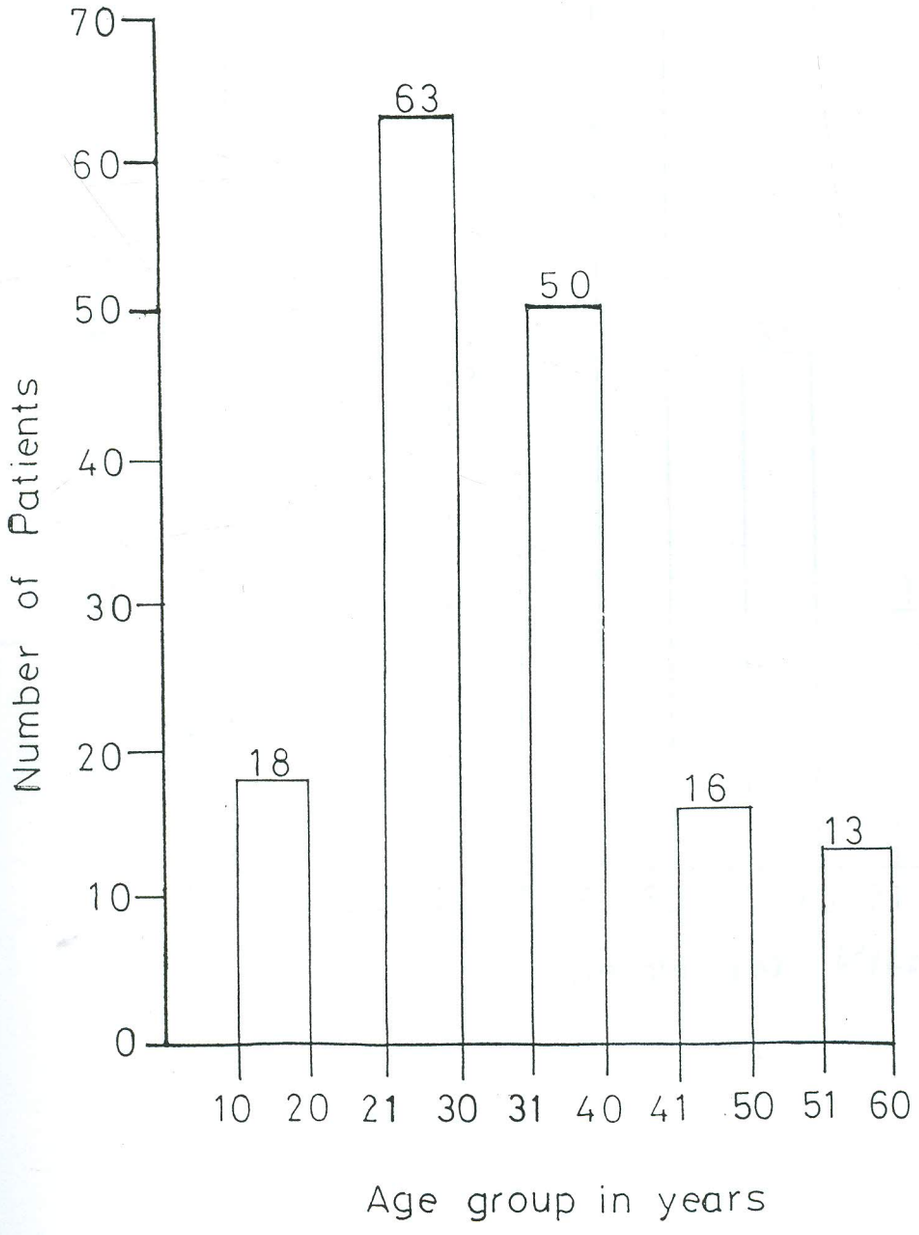


Fig II: Number of patients against weight (both sexes included)

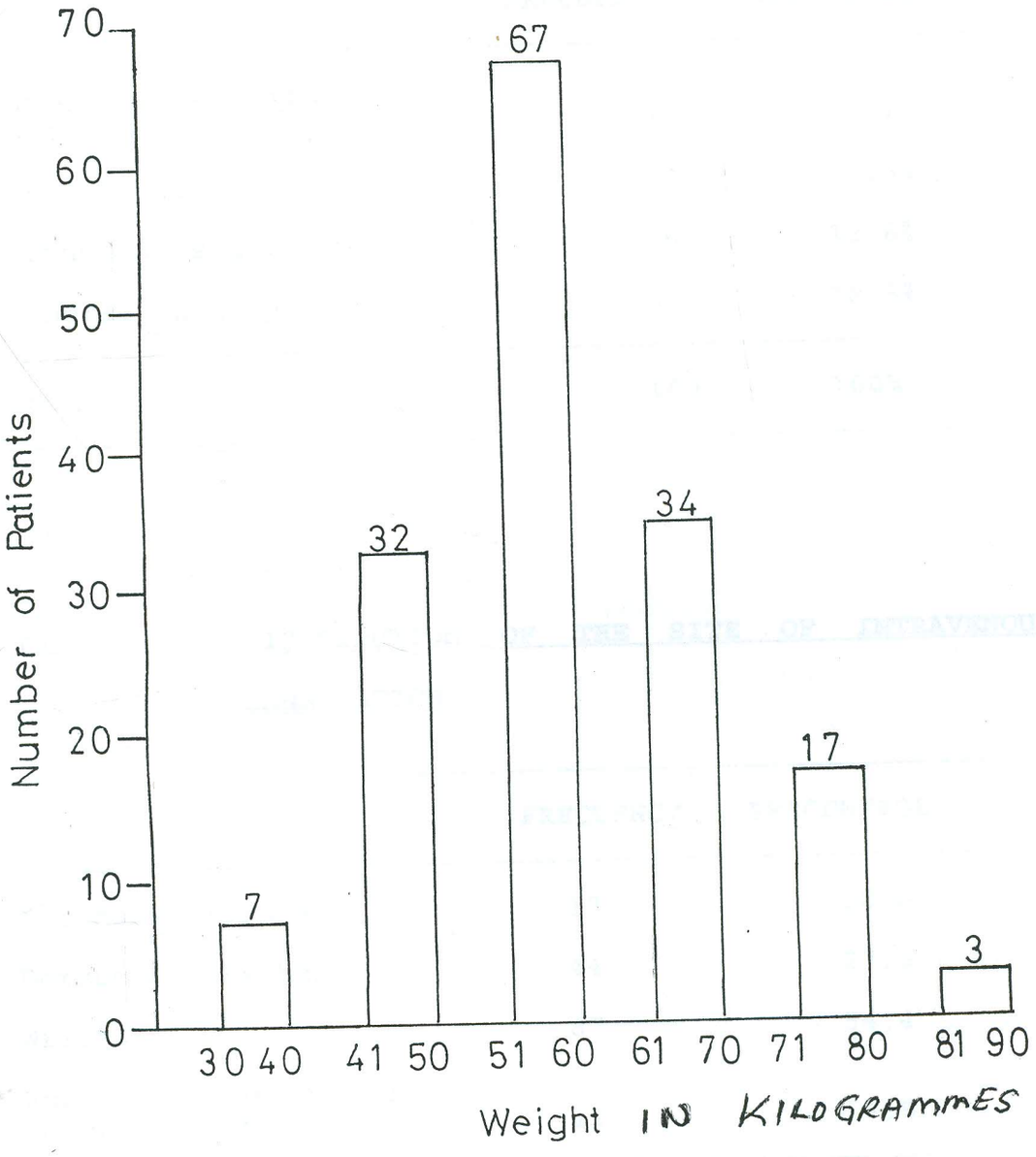


Table I: DISTRIBUTION OF MINOR SURGICAL PROCEDURES

	FREQUENCY	PERCENTAGE
Minor Gynaecological procedure	93	58.1%
Urological	12	7.5%
Orthopedics & Trauma	25	15.6%
General Surgery	30	18.8%
TOTAL	**160**	**100%**

Table II: **DISTRIBUTION OF THE SITE OF INTRAVENOUS CANNULATION**

	FREQUENCY	PERCENTAGE
Antecubital Fossa	17	10.6
Dorsum of the hand	44	27.5
Wrist	87	54.4
Forearm (Between wrist joint - Elbow joint)	12	7.5
TOTAL	**160**	**100%**

Table III: DISTRIBUTION OF MEAN INDUCTION TIMES (SECONDS)

	MEAN	STD DEV	CASES
Male	27.7	6.1	44
Female	25.9	7.0	116
TOTAL			160

Range for the entire population 28 - 43 seconds.

Table IV: **OCCURANCE OF PAIN ON INJECTION SITE**

PAIN	FREQUENCY	PERCENTAGE
Yes	55	34.4%
No	105	65.6%
TOTAL	**160**	**100%**

Table V: **SHOWS ASSOCIATION BETWEEN INCIDENCE OF PAIN ON INJECTION AND SITE OF INTRAVENOUS CANNULATION**

	PAIN		
	YES	**NO**	**ROW-TOTAL**
Antecubital Fossa	0	17	17
		100%	
		16.2%	
Dorsum of the hand	26	18	44
	59.1%	40.9%	
	47.3%	17.1%	
Wrist	27	60	87
	31%	69.0%	
	49.1%	57.1	
Forearm	2	10	12
	16.7%	83.3%	
	3.6%	9.5%	

CHi-Square = 22.9 on 3 degree of freedom p = 0.0004

Table VI: **STATISTICAL ANALYSIS OF HAEMODYNAMIC CHANGES 2 MINUTES AFTER INDUCTION DOSE OF PROPOFOL (2.5MG/KG) ADMINISTERED TO 160 PATIENTS AT STEADY STATE OF ANAESTHESIA AND BEFORE TRACHEAL INTUBATION.**

	Mean at Baseline	Mean at 2M	d = (X_2 - X_1) mean change	t	df	PValue
Systolic Blood Pressure	128.4	112.6	-15.8±0.7	-24.2	159	P<0.001
Diastolic Blood Pressure	82.1	74.5	-7.6±0.6	-12.6	159	P<0.001
Pulse Rate	86.5	86.0	-0.5±1	-0.47	159	P>0.1

Table VII: **ANALYSIS OF SYSTOLIC BLOOD PRESSURE CHANGES AT 5 MINUTES IN INTUBATED PATIENTS AND PATIENTS WITH MASK ANAESTHESIA: ASSESSMENT OF RESPONSE TO TRACHEAL INTUBATION**

	Mean at 2 minutes	Mean at 5 minutes	$d = (X_2 - X_1)$ mean change	Sample size (N)
Group A	112.9	119.60	7.11	76
Group B	113.10	115.24	2.14	84

t value = 3.7 $P < 0.001$

Table VIII: **ANALYSIS OF DIASTOLIC BLOOD PRESSURE CHANGES AT 5 MINUTES IN INTUBATED PATIENTS AND PATIENTS WITH MASK ANAESTHESIA: ASSESSMENT OF RESPONSE TO TRACHEAL INTUBATION.**

	Mean at 2 minutes	Mean at 5 minutes	$d = (X_2 - X_1)$ mean change	Sample size (N)
Group A	74.60	76.71	2.11	76
Group B	73.57	74.17	0.6	84

t value = 1.7 P > 0.05

Table IX: **ANALYSIS OF PULSE RATE CHANGES AT 5 MINUTES IN INTUBATED PATIENTS AND PATIENTS WITH MASK ANAESTHESIA: ASSESSMENT OF RESPONSE TO TRACHEAL INTUBATION**

	Mean at 2 minutes	Mean at 5 minutes	$d = (X_2 - X_1)$ Mean change		Sample size (N)
Group A	85.36	91.39	6.03	104.37	76
Group B	84.95	87.59	2.64	66.23	84

t value = 2.33 $P < 0.05$

Table X: **DISTRIBUTION OF MEAN AWAKENING TIME IN MINUTES BETWEEN PATIENTS WHO HAD INTRAOPERATIVE NARCOTIC AND THOSE WHO HAD NOT IN THE STUDY POPULATION**

	Mean	Std error of Mean	Cases
Patient with Narcotics	7.7m	2.0	51(31.9%0)
Patient without Narcotics	5.8m	1.5	109(68.1)
TOTAL(for entire population)	**6.4**	**1.9**	**160**

Table XI: DISTRIBUTION OF MEAN ORIENTATION TIME IN MINUTES BETWEEN PATIENTS WHO HAD INTRAOPERATIVE NARCOTIC AND THOSE WHO HAD NOT IN THE STUDY POPULATION

	Mean	Std error	Cases
Patient with Narcotics	11.4	3.1	51
Patient without Narcotic	8.1	2.2	109
TOTAL(For entire population)	9.2	2.9	160

2.5 **DISCUSSION**

In the present study which involved one hundred and sixty patients, Propofol as an induction agent at the dose of 2.5mg/kg produced rapid and smooth onset of anaesthesia with a mean induction time of 27.7± 6 seconds in males and 25.9± 7 seconds in females (Table III). This is comparable to other authors who defined induction time as an interval from beginning of injection to loss of counting (De Grood Panrar et al 1987), Rolly G. Versichellen 1985). Fahy LT et al 1985 found longer induction time of 36 ± 9 seconds but they used a induction dose of 2mg/kg.

Other authors compared induction time of Propofol with other orthodox induction agents using either interval between injection and loss of eye lash reflex or loss of counting as an indicator of induction time. They found no statistically significant difference comparing Propofol to thiopental, etomidate, or methohexitone (Nightngalle et al 1985, Wells JKG 1985, De good PMRM, Mitsukari et al 1987). Generally induction of anaesthesia is considered to be rapid if there is induction of anaesthesia in one arm - brain circulation time (< 60s). Differences in a few seconds within that time might not be of any clinical significance.

Apart from rapidity of action, the induction generally in this study was smooth in most patients with incidence of excitatory effects of 4.3% and hiccups 1.9% which is

relatively low, this low incidence is in keeping with the reports of other workers (Kay B, Heally TEJ 1985, De groom PMRM et al 1987, Phares 1987). It has been reported earlier that the occurrence of true excitatory effects such as tremor twitching and rigidity is not a significant feature of Propofol but spontaneous movements at induction do occur (Fahy L.T et al 1985).

Other authors found higher incidence of excitatory effects of up to 20% (Mackenzie N, Grant IS 1985). But in their study patients had not received supplemental inhalational anaesthetics and probably most of the movements they were seeing was because the patients were recovering from the induction dose of Propofol because of its rapid elimination.

When compared with other induction agents the incidence of excitatory effects with thiopental range from 0 - 6.7% and methohexitone up to 90% of the patients (Mackenzie N Grant IS 1985, De groom RMRM et al 1987, Johston R et al 1987). In this aspect Propofol has an advantage over Methohexitone for induction of anaesthesia.

Incidence of transient apnea at induction in this series was found to be 42.8%, other workers have reported that apnea occurs in both premedicated and unpremedicated in 35 - 50% of patients (Billane et al 1985, Brigg P and White M 1985). Others have reported higher incidence up to 80% (Puraulles et al 1987). In one study by Huma Phares

1987 he reports no incidence of apnea with the use of Propofol. This great variability in reporting can be explained by variability of definition of apnea in anaesthetic protocols which vary from author to author, and the rate of administering the drug. Although previous investigators have reported that the speed of injection has no effect on incidence or duration of apnea (Rolly G Versichelean et al 1985), it has been noted that the degree of respiratory depression produced by Propofol is reduced when the induction dose is administered over 40 - 60 seconds (compared to 15 - 30 seconds) (Van A Doze et al 1986). This rate of administering the drug is a better way of reducing the incidence of transient apnea associated with propofol as opposed to reduction of the induction dose to 2mg/kg as suggested by other authors (Calmin et al 1984), as this is associated with a higher number of induction failures.

Apnea of 42.8% found in this series is of concern and it is suggested that Propofol be administered by those trained in anaesthesia and at a place where facilities for artificial ventilation are available. It sounds logical to advocate administering at the rate of 40 - 60 seconds as suggested by Van a Dose et al 1986 rather than using the speed of administering of 20 seconds used in the present study when it is intended that the case is to be done under mask anaesthesia, this will improve safety in the hands of

all cadres Practicing Anaesthesia.

In this present study incidence of pain was found to be 34.4% (Table IV) this compared favourably with the work of W.M. Weightman & M Zacharias 1987, LT Fahy et al 1985, Macntosh MJ Lees NW 1985 and Richard Johston et al 1987).

It must be remembered that site of injection and size of vein are major determinant of pain on injection with many intravenous anaesthetics (Kawar, Dundee JW 1982). Even with Propofol the incidence of pain on injection appear to be related to the size of vein into which the drug is injected. Veins on the dorsum of the hand are associated with a higher incidence of pain during induction (Van A Doze et al 1986, Richard Joston et al 1987, Macntosh MJ, Lees NW 1985). In present study 44 patients (27.5%) had an intravenous line on the dosurm of the hand. Out of these 26 patients (59.1%) experienced pain on injection including three (3) cases who had very severe pain. This may contribute to generally high incidence of pain reported in this study.

In contrast no pain was experienced by 17 patients (10.6%) who had intravenous lines at the antecubital fossa. This same experience has been reported by other workers (Cammings GS et al 1984, N Rest, F Trangott 1991).

The difference in Proportion of patients experiencing pain on injection at different site are statistically significant (P = 0.0004) (Table V.)

As seen in this study pain on injection pose a great disadvantage on the use of propofol and should always be taken into consideration when using the drug to smoothen an induction. Apart from injecting the drug into a larger vein, other strategies have been used to minimize pain, including concurrent administration of lignocaine Hydrochloride (STARK RD et al 1985) and rapid use of an opiod premedication (Frogen RJ et al 1982). This may decrease the incidence of pain and induction time but it may also increase the duration and incidence of apnea (Briggs P et al 1982).

Another strategy includes adding a drug to a fast running infusion (Rocky G. Versichelen L 1985) either of the strategy suggested should be used routinely.

When used for induction of Anaesthesia Propofol has been reported to produce a significant greater reductions in blood pressure than thiopental, methohexitone or etomidate (Mackenzie N Grant IS 1985, Wells JKg 1985, Noceten SM et al 1985). Quite in keeping with these studies, in present study there was a significant fall of both systolic and diastolic blood pressure at two minutes after induction at steady state of anaesthesia before endotracheal intubation which was statistically significant ($P<0.01$) (Table VI). A mean change which is less than what has been reported by others. This may be attributed to the fitness of patients used in this series, all were

ASA physical status I and II. This Risk of Hypotension increases when you administer Propofol to severally ill (ASA physical status III or higher). This finding is again in agreement with what has been published in the literature that black patients tended to have a lower risk of hypotension than patients of other races (Hug et al 1993).

After 5 minutes of induction despite having supplemental halothane there was a mean change of systolic blood pressure of 7.11 mmHg in group of patients who had laryngoscopy and endotracheal intubation (Group A) and 2.14mmHg in the group which was not intubated (group B), the difference which was statistically significant, the mean change of diastolic blood pressure between two groups were not statistically significant. comparing this values with initial value at baseline to 2 minutes, it indicates that although induction dose of propofol decreased both systolic and diastolic blood pressure significantly, the sympathetic stimulation of laryngoscopy and intubation tend to reverse this decline especially with reference to systolic blood pressure.

The finding of significant fall of both systolic and diastolic blood pressure at 2 minutes after induction is expected and predictable from the pharmacology of Propofol, that the Peak negative inotropic effect of Propofol occur 2 minutes after drug administration. This compares well with the study done by LT Fahy GA et al 1985 who also used

supplemental halothane for maintenance.

It is suggested that although the changes in systemic arterial pressure was tolerable in this series of patients, thus no patient required treatment with vaso pressor drugs, patients should be carefully monitored especially for the first 5 minutes of induction which is the critical time as indicated in this study. Indirect blood pressure monitoring as used in this study is sufficient to ensure safety. Equally important for safety is that the dose should be carefully titrated against the response.

It must be remembered that patients in this series were healthy with good resting cardio circulatory state. The pattern of blood pressure changes depicted may therefore be risky in severely ill and Hypovolemic patients.

There was no significant changes in pulse rate at 2 minutes ($P>0.1$) (Table VI), after induction and during steady state of anaesthesia which is in agreement with the study done by Grounds et al 1985. Some have documented a decrease in Pulse rate after induction (Richard Johnston et al 1987). But the heart rate changes in Propofol anaesthesia in usually variable and not uniform (Grounds et al 1985, LT Fahy 1985), No change at all in the pulse rate, a decrease and an increase have all been reported (P.A. Guise et al 1991).

At 5 minutes after induction there was a relative increase in Heart rate, a mean change of 6.03 in group of patients who had laryngoscopy and endotracheal intubation and a mean change of 2.64 in group of patient with mask, a difference which was statistically significant ($P<0.05$), this again can be explained by sympathetic stimulation of laryngoscopy and endotracheal intubation. This reflex response should be borne in mind especially in patients with limited cardiovascular reserve.

Three patients in this study developed Bradycardia which was defined in the protocol as decrease in Heart rate to below or equal to 50 beats/minute. Episodic severe fall of pulse rate sometime culminating into cardiac arrest has been reported by some workers (Sebel PS and JD Lowdon, P.A. Guise et al 1991, Baraka A, 1988). These have been explained as being due to the central vagotonic and sympatholytic effects of Propofol. No arrest occurred in this series. All three patients responded to Intravenous Atropine.

Since the possible potential danger of severe bradycardia has been noted in this study, it is advised, as suggested by P.A. Guise et al 1991 that Prophylactic intravenous atropine should be used in procedures which potentiate vagal activity such as in anal rectal procedures and dilatation of the cervix, and in anxious patients, and in concomitant use of Vagotonic drugs like fentanyl and

suxamethonium. And again close monitoring of the radial pulse during induction is emphasized.

The early recovery phase was assessed in this study by looking at the mean awakening and orientation times (Table X and XI respectively). A mean awakening time of 5.8 ± 1.5 minutes and orientation time of 8.1 ± 2.2 minutes is reported in the group of patients who had no intraoperative Pethidine and mean awakening time of 7.7m ± 2.0 minutes and orientation time of 11.4 ± 3.1 minutes in patients who had intraoperative Pethidine.

When duration of Anaesthesia, awakening and orientation times were analysed there was a strong evidence of a positive linear correlation ($P<0.001$) between duration of anaesthesia, and awakening and orientation times. This shows that with the technique used in this study the longer the duration of anaesthesia, the longer the awakening and orientation time. This means the greatest advantage of Propofol, that is the rapid recovery from anaesthesia can only be appreciated, in short surgical procedure with mean duration of anaesthesia of 30 minutes ± 12. In the Present Study this is evidenced by the fact that the results of this study on the group of patient who had no intraoperative Pethidine compared well with the study done by Richard Johston et al 1987, and WM Weightman & M Zacharias 1987. In former reports awakening time was 5.8 ± 2.8 and orientation time of 7.8 ± 3 minutes. In latter

reports the awakening time was 7.3 ± 2.1 minutes and orientation time of 8.9 ± 2.1 minutes. In both occasions they were using a similar technique of intermittent bolus of Propofol and Nitrous oxide and oxygen without supplemental volatile anaesthetics.

The mean duration of anaesthesia in the former study was 10 ± 2.1 minutes and in the latter study was 9.1 ± 3.4 minutes while in the present study it was 30.1 ± 12 showing that in short surgical procedures with mean duration of anaesthesia of 30 ± 12 the additional of Volatile anaesthetic may add little difference with regards to awakening and orientation time. This has also been commented upon by Carter JA et al 1985 saying that the use of supplemental Isoflurane makes difference in recovery although this would seem unlikely as recovery from isoflurane is also generally rapid.

White et al 1993, concluded with regards to isoflurane that the use of isoflurane to supplement Propofol Nitrous oxide anaesthesia for short (<60m) surgical procedures increased the time of emergence however, the average difference in these emergence time are of little if any clinical significance because it does not increase the discharge times or the incidence of side effects.

Looking at the study of other workers comparing propofol and Pentothal without supplemental volatile anaesthetics, the mean times to initial recovery as tested

by the subjects response to questions and ability to give correct answers to questions are approximately twice as fast in propofol group than thiopentone group. Thus there is an advantage in using the technique used in the study rather than thiopental Nitrous oxide and supplemental halothane for short surgical procedures with regards to short stay in recovery room and discharge.

Opiods (Pethidine) 1 mg/kg used intraoperatively in 51 patients (31.9%) in this study caused both prolonged time to awakening and orientation and this has also been reported by AP Felbaum et al 1993 that there is a statistically significant relationship between a prolonged time to awakening and orientation and the Concomitant use of opiods. It has however been said by other workers that opiods used as premedicant reduce the requirement for sedative hypnotics and inhalational anaesthetics there by decreasing emergence time after an outpatient procedure (Horigan et al 1980, White and Chang 1984). Pethidine used in this series was given intraoperatively and although pethidine may be used in short surgical procedures, it is not as popular as the more potent but rapid and short acting opioids like Fentanyl and alfentanyl. Fentanyl remain the most widely used analgesic in procedures done on day case basis.

Statistically in this study there was no correlation between weight of the patients and orientation time, this

observation compares well with that of WM Weightman and M Zacharias 1987 who also found no significant correlation between the dose and the subjects weight, the height and recovery. The result from the two studies differ in relating the age of the patients and recovery. In this series there was evidence of positive linear correlation between orientation time and age of the patients ($P < 0.05$).

There was incidences of postoperative vomiting in 3 patients (0.9%). Two of these were females who had laparoscopy and dye insufflation procedures which are known to have increased incidences of nausea and vomiting of up to 30 -40% (N,N Campbell and AD Thomas). They had no intraoperative opiod. Another was a young boy who had open reduction and internal fixation of the left radius with 50 mg of Pethidine intraoperatively. Though a low incidence of nausea and vomiting associated with Propofol has also been reported by others, it is not surprising in this series because the overall incidence of post operative nausea and vomiting in our community, though not documented, is relatively low, so it cannot be substantiated if it is really due to antiemetic effect of Propofol which is documented in literature (Macoullen JSC et al 1988), or because of the smoothness of Propofol induction. Smoothness of induction is associated with least incidence of emetic Sequelae (Semu 1983). These

findings suggest that antiemetic should not be used routinely in Propofol anaesthesia.

In the immediate Post operative period there was no evidence of erythema or continuing pain at the site of injection even in a group of patient who had experienced pain at induction, no other worker has reported adverse venous sequelae in the short periods of postoperative observation.

No other postoperative complication is reported during this short period of Postoperative observation in this series.

CONCLUSION:

From the present Study, Propofol is a smooth and rapid acting intravenous agent, with significant cardiorespiratory depressant properties. Its use entails a vigilant monitoring of cardio-respiratory functions and care with regards to pain on injection which is a significant side effect.

It's potential advantage is rapid and early recovery from anaesthesia with minimal emetic sequelae.

It is recommended that since its acquisition cost is high, 4680/= per 200mg ampoule, it should be stocked in small amount and incorporated into the routine anaesthetic practise of the department for use in short surgical procedures. Because of its impact on less stay in the

recovery room with less staffing and less time to discharge this will ultimately improve patient flow in the recovery room. When the price of the drug becomes cheaper, we can think of using the drug for both induction and maintenance of anaesthesia as an infusion for maximal utilization of its advantages.

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