MIDAZOLAM (DORMICUM) AS AN INTRAVENOUS INDUCTION AGENT, A CLINICAL EXPERIENCE AT MUHIMBILI MEDICAL CENTER

BY

DR. EDWIN RWEBUGISA LUGAZIA, MD (DAR)

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS OF MEDICINE (M.MED) ANAESTHESIOLOGY OF THE UNIVERSITY OF DAR ES SALAAM, 2000

CERTIFICATION

The undersigned certify that he has read and hereby recommend for acceptance by the University of Dar es salaam a dissertation entitled: *Midazolam (Dormicum) As an Intravenous Induction Agent, A Clinical Experience At Muhimbili Medical Center,* in partial fulfilment of the requirements for the degree of Masters of Medicine (M.MED).

.....

DR. V. MWAFONGO, MD, MMED.
(SUPERVISOR)

DATE: 18/4/2012

DECLARATION AND COPYRIGHT

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

Signature: _____

This dissertation is copyright material protected under the Berne Convention, the Copyright Act 1966 and other international and national enactments, in that behalf, on intelletual property. It may not be rproduced by any means, in full or in part, except for short extracts in fair dealing, for research or private study, critical scholarly review or discourse with an acknowlegement, without written permission of the Directorete of Postgraduate Studies, on behalf of both the author and the University of Dar es Salaam.

ACKNOWLEDGEMENT

I would like to give my sincere thanks to my teachers Dr. V.V. Mwafongo, Head of Department, Dr. F.Mbanga and Dr. N.J.Matekere for their endeavor in imparting to me the knowledge pertaining to the practice of anaesthesia.

Special thanks go to my supervisor Dr.V.Mwafongo for his invaluable assistance throughout the preparation of this work. I am also grateful to Dr. F. Mbanga, who read the manuscript and offered constructive criticism and suggestions, which made this dissertation possible.

My special thanks goes to Prof. Massele and Dr. Rimoy of the Department of Pharmacology for their tireless assistance offered to during the preparation of this work.

I am indebted to Roche Pharmaceutical for the provision of the drug Midazolam (Dormicum) used in this study.

I am also grateful to Mr. C. K. Makwaiya and M's. Moshillo of the department of Epidemiology/Biostatistics for their guidence in the statistical part of this study. I am also indebted to Prof. A.B.M Swai for his helpful sugestions during the proposal development

I would like to extend my appreciation to the staff department of anaesthesia, surgeons, theater personnel, recovery nurses and all others who contributed in one way or another to the success of this study.

I would also like to express my gratitude to Monica and Specy the Directors of LANDCARE LTD & INAMULLA HOLDINGS LTD respectively for provision of their computers and other office facilities during the preparation of this work.

Lastly but not the least, special thanks and appreciation are due to my family especially my son Edwin Jr. and his Mom Dr. Azma Simba who provided a conducive environment that enabled me to accomplish this work.

DEDICATION

This work is dedicated to my late father Peter.M.Lugazia, my mother Blandina Lugazia and my son Edwin Kalinjuma Lugazia, Jr.

ABSTRACT

Midazolam a new intravenous induction agent of the benzodiazepine class was studied in 120 healthy unpremedicated patients. These patients were undergoing short diagnostic and therapeutic procedures lasting less than one hour. The mean duration of Anaesthesia was 22.63minutes. Rapid smooth induction of anaesthesia was attained with an induction dose of 0.3mg/kg. with the mean induction time of 67.82 seconds. Characteristics of concern were transient apnoea 25.84%, incidence of side effects which was found to be low and changes in the systolic and diastolic blood pressure which were found to be significant, but well torelated by these healthy patients. Haemoglobin levels as well as serum albumin levels were not shown to have any effect on the induction characteristics of midazolam. Induction was also associated with short recovery and orientation time. These were found to have a positive correlation to the duration of anaesthesia.

TABLE OF CONTENTS

CERTIFICATION ii

DECLARATION AND COPYRIGHT iii

ACKNOWLEDGEMENT iv

DEDICATION vi

ABSTRACT vii

TABLE OF CONTENTS viii

PART ONE 1

INTRODUCTION AND LITERATURE REVIEW: 1

PHARMACOLOGY OF MIDAZOLAM 6

Physical and chemical properties: - 8

Mechanism of Action: - 9

Pharmacokinetics and pharmacodynamics: 11

Toxicity: - 20

Effects of Midazolam on organ systems:- 21

Clinical uses and dosage of Midazolam: 28

Warnings and precautions: 58

Contraindications: 65

Drug Interactions: 66

Adverse reactions: 68

PART TWO. **77**

CLINICAL STUDY 77

Introduction: 77

Objectives: 77

Rationale of the study: 79

Anaesthetic protocol, (materials, patients and methodology) 81

Results: 89

TABLES OF RESULTS 98

Discussion: 109

Summary: 121

REFERENCES: 123

APPENDIX I: QUESTIONNAIRE 139

PART ONE

INTRODUCTION AND LITERATURE REVIEW:

In the history of medicine and health care provision, lots of changes have occurred and are still taking place. The practice of surgery and its dynamic changes necessitate changes in the practice of anesthesia, indeed improvement in this field of anesthesia has made possible attempts and practice of many surgical procedures that would have otherwise been impossible. Over the years anaesthetists have endeavored to improve the quality of anesthesia by aiming at improving the safety of the patient and minimizing anaesthetic complications as well as creating favorable conditions for surgery. Various techniques have evolved as a result of these efforts. The search for anaesthetic agents capable of providing rapid and smooth onset of action, intraoperative amnesia and analgesia, good surgical condition, as well as short recovery period with minimal side effects has been the interest of anaesthetists in their efforts to improve the practice of anesthesia.

The growing number of surgical cases and the cost involved as well as the inability of most of the patients and the governments to meet these costs has necessitated the practice of daycare surgery where the operations are performed on an outpatient basis. This requires the use of induction agents with less peri-operative complications i.e. prolonged

emergence, nausea and vomiting, dizziness and headache which may delay discharge thus increasing the cost as well as the likelihood of acquiring nosocomial infections especially in children, elderly and the immunocompromised which are costly to treat[1]. Daycare surgery or surgery performed on an outpatient basis has been shown to decrease hospital costs by 40-80% for most procedures[1,2]. However this requires the use of an induction agent capable of smooth, rapid onset of anesthesia coupled with optimal surgical conditions and short recovery accompanied with minimal emergence sequelae.

Intravenous anaesthetics have gained a prominent position in the practice of anesthesia especially induction of anesthesia mainly due to their fast onset of action, reliability and their good acceptance by the patients. The properties of an ideal intravenous agent in a nutshell can be expressed as follows; solubility in water so that properties of the solvent can be ignored, stability in solution and on exposure to light over long periods of time. Also it should be able to induce sleep in one arm brain circulation time, with short duration of action, no cumulative properties, and inactivation by metabolism with inactive, nontoxic metabolites, minimal cardiorespiratory effects, analgesic properties and no histamine release[3]. The anaesthetic should provide fast induction of smooth comfortable anesthesia without excitation, moreover maintenance of anesthesia by repeated injection or infusions should be

possible. It should cause minimal local toxicity and no acute or retarded systemic toxicity. Preferably it should not be contra indicated in pathological conditions (emergencies, hypovolemia, cardiovascular disease, renal and/or hepatic insufficiency) or in specific groups for example pediatric, elderly or obstetric patients. Lastly increased cost awareness in the health sector means that the cost benefit of a drug should be given the appropriate consideration.

Among anaesthetic techniques, total intravenous anesthesia (TIVA) is a novel and very interesting approach and one of the main reasons for developing this method is the long term toxicity observed in personnel working in operating theater as a result of repeated exposure to volatile anaesthetic agents. This concept of intravenous anesthesia was known to Sir Christopher Wren since 1665, but it first became established in 1920's with the use of intravenous alcohol tribromoethanol and the barbiturate pernoston. It was later popularized by a German obstetrician Bumm, the name pernoston being adopted in 1935 for the 10% aqueous solution of this barbiturate.[4,5]

However the first drug capable of producing sleep in one arm brain circulation time was a hexobarbiturate produced in the laboratories of Helmet Weese in 1932. Despite the fact that it causes muscle movements hexobarbitone enjoyed popularity in the1930's and 40's, an estimated number of about ten million patients were

possible. It should cause minimal local toxicity and no acute or retarded systemic toxicity. Preferably it should not be contra indicated in pathological conditions (emergencies, hypovolemia, cardiovascular disease, renal and/or hepatic insufficiency) or in specific groups for example pediatric, elderly or obstetric patients. Lastly increased cost awareness in the health sector means that the cost benefit of a drug should be given the appropriate consideration.

Among anaesthetic techniques, total intravenous anesthesia (TIVA) is a novel and very interesting approach and one of the main reasons for developing this method is the long term toxicity observed in personnel working in operating theater as a result of repeated exposure to volatile anaesthetic agents. This concept of intravenous anesthesia was known to Sir Christopher Wren since 1665, but it first became established in 1920's with the use of intravenous alcohol tribromoethanol and the barbiturate pernoston. It was later popularized by a German obstetrician Bumm, the name pernoston being adopted in 1935 for the 10% aqueous solution of this barbiturate.[4,5]

However the first drug capable of producing sleep in one arm brain circulation time was a hexobarbiturate produced in the laboratories of Helmet Weese in 1932. Despite the fact that it causes muscle movements hexobarbitone enjoyed popularity in the1930's and 40's, an estimated number of about ten million patients were

anaesthetized using it, in the first decade post its introduction[5]. Other agents like thiamylal, methohexitone, thiopentone, etomidate, propanidid, althesin, ketamine and propofol were discovered and have been used. The hypnotic effect of thio-barbiturates has been appreciated and this has conferred to them an advantage for use as intravenous anaesthetic agents. Clinical trials carried out on thiopental sodium a thiobarbiturate at Mayo clinic in Minnesota, demonstrated its ability to provide smoother induction of anesthesia and shorter duration of action compared to hexobabitone.[4,5] Hexobabitone was gradually displaced and thiopentone has remained the most popular intravenous anaesthetic agent, despite the presence of other barbiturates in clinical use with many similarities to thiopentone like thiamylal (sulphurated barbiturate) and methohexitone (oxybarbiturate).

Ketamine holds a unique position among intravenous anaesthetic agents due to its amnesic, analgesic and cardiovascular system effects in addition to its hypnotic effects, which makes it popular for use in high-risk patients.

Etomidate, a carboxylated imidazole derivative was found to be more potent than thiopentone and methohexitone but caused pain on induction (propylene glycol vehicle), and it was associated with higher incidences of tremor, hypertonia, muscle movements, hiccups, nausea and vomiting compared to barbiturates. These side effects have limited

its usefulness.[4,5] Similarly another agent gamma aminobutyric acid introduced in anesthesia in 1960 became unpopular due to its slow onset of action and associated extrapyramidal motor activities.

Other promising anaesthetic agents like propanidid and Althesin - a mixture of two water insoluble steroids alphadrone and alphaxalone solubilized in cremophol EL have also been withdrawn from the market because of adverse anaphylactic reaction and depression of the adrenal cortical function.

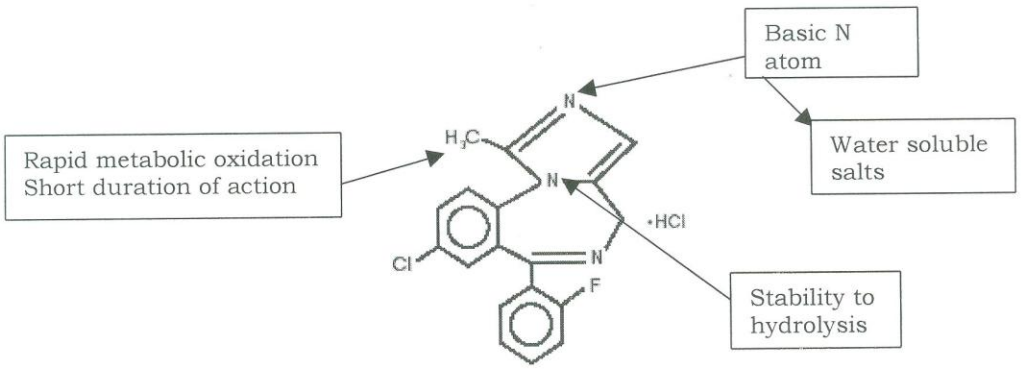
In 1977 a phenolic compound propofol was introduced in anesthesia and like althesin and Propanidid was also formulated in cremorphol EL a vehicle that causes allergic reactions. This necessitated reformulation in fat emulsion in 1983. This emulsion form is still in use providing a greater challenge to thiopental with regards to rapid and smooth induction of anesthesia, non-cumulative effects and rapid clear-headed recovery.

The search for ideal intravenous agents capable of meeting the requirements of modern anesthesia still continues and various drug groups including benzodiazepines have been and are still being studied.

PHARMACOLOGY OF MIDAZOLAM

Midazolam is a white to light yellow crystalline compound, insoluble in water. The hydrochloride salt of Midazolam, which is formed in situ, is soluble in aqueous solutions. This water-soluble benzodiazepine is available as a sterile, nonpyrogenic parenteral dosage form for intravenous or intramuscular injection. Each mL contains Midazolam hydrochloride equivalent to 1 mg or 5 mg Midazolam compounded with 0.8% sodium chloride and 0.01% edetate disodium, with 1% benzyl alcohol as preservative; the pH is adjusted to approximately 3 with hydrochloric acid and, if necessary, sodium hydroxide.

Chemical structure of midazolam:



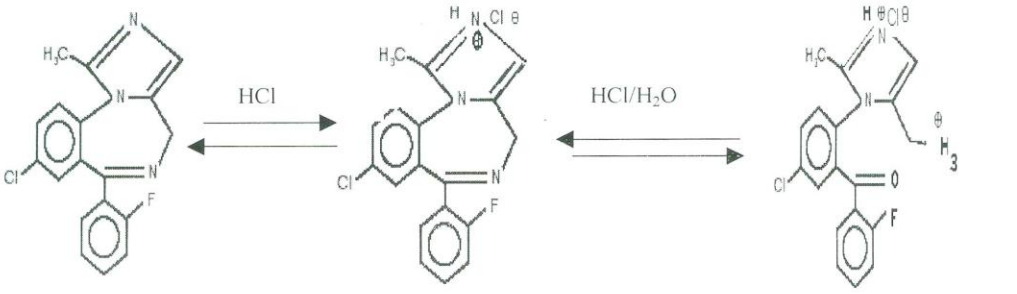
Midazolam belongs, to the family of benzodiazepines known as Imidazo benzodiazepines. Its chemical name is 8-chloro-6- (2fluorophenyl)-1

methyl - 4H imidazo [1, 5-a] [1,4] benzodiazepine. Chemically Midazolam hydrochloride has the empirical formula C18H13ClFN3.HCl, a calculated molecular weight of 362.25 and the above-depicted structural formula.

The presence of imidazole rings in positions 1 & 2 confers to Midazolam properties that are not typical of classic benzodiazepines in three respects i.e. it has a basic pH, stability in aqueous solution and has a very rapid metabolism in the body compared to the other benzodiazepines.

The basic Nitrogen in position 2 with a pKa of 6.15 enables Midazolam to form water-soluble salts of monohydrochloride. At a pH of approximately 3.5 purely aqueous solutions can be produced which are well tolerated on intravenous or intramuscular injection.

The hydrochloride solution used in clinical medicine, which has a pH of about 3.3, contains 80-85% of the closed and 15-20% of the open form. The open form is usually neutralized immediately following injection and it is converted to the closed form.



Midazolam: formation of a soluble salt (eg hydrochloride) and reversible opening of the seven-ring molecule

Physical and chemical properties: -

The free base of Midazolam is a lipophilic substance with low solubility in water. But the presence of Nitrogen in position 2 (with pka. 6.15) of the imidazo benzodiazepine ring system enables this active ingredient to form water-soluble salts with acids. The aqueous solution formed is colourless, and stable and suitable for intramuscular administration, with good tolerance. It does not require organic solvents as aqueous vehicle thus its injection solution is well tolerated and compatible with blood. The pH of the solution used in clinical medicine is about 3.3-3.5. This is very important since Midazolam is characterized by a pH dependent ring-opening phenomenon in which

the ring remains open at pH values below 4 thus maintaining water solubility of the drug. The ring closes on exposure to physiological pH i.e. >4, converting Midazolam to a highly lipid soluble ring.

Mechanism of Action: -

As with all classic benzodiazepines, the mechanism of action of Midazolam is through the modulation of the central GABA receptors. GABA is the most important inhibitory neurotransmitter in the central nervous system. Benzodiazepines have been shown to augment the GABAergic synaptic inhibition in the central nervous systems by increasing the sensitivity of GABA receptors to GABA[6,7].

Conceptually there are separate benzodiazepine and GABA receptors coupled to a common chloride channel. Chloride ions normally pass through these channels and inhibit conduction of nerve impulses. In this scheme, benzodiazepine receptors are a regulatory mechanism for the activity of GABA receptors. When the GABA receptors are occupied, the chloride channel is activated and chloride ions flow across the membrane. The increased chloride permeability stabilizes the membrane potential at a level (equilibrium potential of chloride) which is well below the threshold at which action potentials

can be fired. GABAergic neurotransmission is therefore inhibitory, and counteracts excitatory influences.

On the other hand the occupation of benzodiazepines receptors by an endogenous inhibitor e.g. peptides, reduces the affinity of GABA receptors for their inhibitory neurotransmitter GABA. Conversely, the occupation of these receptors by benzodiazepines enhances the affinity of GABA for its receptors with resulting inhibition of nerve conduction that manifests as the observed pharmacological effects of benzodiazepines[6].

The GABA receptors with the chloride ions channel and binding sites for GABA and benzodiazepines are found throughout the CNS, in particularly in large numbers in the neocortex, the limbic system and the cerebellum. The benzodiazepine receptors occur almost exclusively on postsynaptic nerve endings in the central nervous system. This anatomical distribution of receptors is consistent with the minimal effect of these drugs outside the central nervous system (CNS) example minimal circulatory effects.

Pharmacokinetics and pharmacodynamics:

Absorption:

Absorption of Midazolam following intramuscular administration is rapid and complete and maximum plasma concentrations comparable to those obtained after intravenous injections are reached within 30 minutes. The plasma concentrations about one and a half hours after intramuscular injection are virtually the same as after intravenous administration, the absorption half life is about ten minutes, in other words twenty minutes after the intramuscular injection, three quarters of the dose has already been absorbed. Usually peak plasma concentration (Cp*max*) is reached within about twenty minutes. The bioavailability following intramuscular administration is over 90%.

After oral administration Midazolam undergoes rapid absorption from the gastrointestinal tract and prompt passage across the blood brain barrier. Only about 50% of an orally administered dose of Midazolam reachs the circulation, this reflects a substantial hepatic first pass effect. Following rectal administration, Midazolam is quickly absorbed and the area under the plasma concentration time curve (AUC) in children is comparable to that of adults after intravenous administration. The Cp*max* is achieved within 9-29minutes, like the oral route, the bioavailability here is also 50% this suggest an analogous

hepatic first pass effect; in this case it can be postulated that the absorption takes place through the upper rectal veins which have connection to the portal circulation.

Protein binding:

Similar to most benzodiazepines Midazolam is extensively bound to plasma proteins, various studies show binding to proteins of 96-98% particularly albumin. This binding is independent of the plasma concentration of Midazolam.

Distribution:

When Midazolam is injected intravenously the plasma concentration time curve shows two distinct phases of distribution, the volume of distribution calculated under steady state condition is 50 – 60 liters in a 70Kg man, generally the volume of distribution (Vd) ranges between 1-3L/Kg.

Distribution processes rather than the elimination rates determine the onset and the duration of action after a single intravenous administration of benzodiazepines, however after repeated doses, the elimination half life of a derivative will determine the duration of drug action.

In the case of Midazolam, its high lipid solubility accounts for its ability to readily cross the blood brain barrier and rapidly exert its action on the central nervous system (CNS). This lipid solubility also cause rapid redistribution from the brain to inactive tissue sites as well as rapid clearance.

Metabolism:

Midazolam is completely and rapidly metabolized in the body. It undergoes hydroxylation by hepatic microsomal oxidative mechanism. This biotransformation is mediated principally by the cytochrome P450 3A4, which appear to be present in the liver as well as in the gastrointestinal tract mucosa. The biotransformation products are 1-hydroxy-Midazolam also termed alpha hydroxy midazolam (60-79% of the biotransformation products) and smaller amounts of 4 hydroxy-midazolam (<%5 of biotransformation products) are formed in parallel. Small amounts of dihydroxy derivatives have also been detected but not quantified. These products are subsequently glucuronized i.e. conjugated with glucuronic acid and eliminated, via the renal system. The fraction extracted by the liver is around 40-50% of the dose administered. Drugs that inhibit the activity of cytochrome P450 3A4

like cimetidine, verapamil, erythromycin etc may inhibit midazolam clearance and elevate steady state Midazolam concentrations.

Elimination:

In healthy subjects the elimination half life of Midazolam is very short compared to other benzodiazepines and it is between 1.5 - 3hours whereas that of diazepam is between 21 - 37hours, Lorazepam 10 - 20hours. Thus the Central Nervous System effects of Midazolam are short lived compared to those of the others.

The plasma clearance of Midazolam is in the range of 300-400mls/min., with total clearance (Cl) of 0.25 to 0.54L/hr/kg. It has been observed that there was no difference in the clearance, in subjects administered 0.15 mg/kg and 0.30 mg/kg) IV doses indicating linear kinetics. However the clearance was successively reduced by approximately 30% at doses of 0.45 mg/kg and 0.6 mg/kg indicating non-linear kinetics in this dose range. When given by intravenous infusions its elimination kinetics do not differ from those following bolus injections. The elimination half life of the main metabolite $\propto$ hydroxy-Midazolam is shorter than that of the parent substance. Immediately after its formation it is conjugated with glucoronic acid (inactivated) and 50-70% of the dose is then eliminated by the kidneys. Usually following

a rapid intravenous administration of Midazolam, the plasma concentration falls within the first quarter of an hour to 10-20% of the original value. After two hours, almost 5% of the original plasma concentration is present.

The excretion of Midazolam is reduced in association with old age, congestive heart failure, liver disease (cirrhosis) or conditions which diminish cardiac output and hepatic blood flow.

Pharmacokinetics in special clinical situation: -

Elderly patients:

The increased sensitivity of the elderly to the benzodiazapines was explained by Klotz and colleagues, as follows; since all benzodiazapines elimination from the body depends on hepatic metabolism, impairment in liver function or changes in distribution pattern will affect the pharmacokinetics of these drugs. Such alterations have been documented in old age especially for long acting benzodiazepine like Diazepam, Flurazepam and nitrazepam[8,9]. Old age is usually associated with prolonged elimination half-life, increased volume of distribution, reduced total clearance and less extensive plasma protein binding of long acting derivatives. Greenblatt et al in 1982 pointed out that the

elimination half life may be doubled in elderly patients reflecting age related reduction in hepatic blood flow and enzyme activity[10].

The kinetic alterations and increased sensitivity to the benzodiazepines in the elderly attributable to changes at the receptor level in the brain was also cited by Casteleden et al in 1977[11].

In elderly patients receiving Midazolam by Intravenous infusion for long term sedation e.g. in some intensive care patients the elimination half life may be prolonged from three to six times the normal. In these patients infusion at an unchanged rate results in higher plasma level at steady state. Consequently the infusion rate should be adjusted according to the patients clinical response.

Pediatrics and Neonates:

In pediatric patients aged 1 year and older, the pharmacokinetic properties following a single dose of Midazolam reported in 10 separate studies of midazolam are similar to those in adults. Weight-normalized clearance is similar or higher (0.19 to 0.80 L/hr/kg) than in adults and the terminal elimination half-life (0.78 to 3.3 hours) is similar to or shorter than in adults. The pharmacokinetic properties during and following continuous intravenous infusion in pediatric patients in the

operating room as an adjunct to general anaesthesia and in the intensive care environment are similar to those in adults.

In seriously ill neonates, however, the terminal elimination half-life of midazolam is substantially prolonged (6.5 to 12.0 hours) and the clearance reduced (0.07 to 0.12 L/hr/kg) compared to healthy adults or other groups of pediatric patients. It cannot be determined if these differences are due to age, immature organ function or metabolic pathways, underlying illness or debility.[12]

Renal failure:

Patients with renal impairment may have longer elimination half-lives for midazolam and its metabolites, which may result in slower recovery. Patients with acute renal failure appear to have a longer elimination half-life for midazolam and may experience delayed recovery.

Midazolam and 1-hydroxy-midazolam pharmacokinetics in 6 ICU patients who developed acute renal failure (ARF) were compared with a normal renal function control group. Midazolam was administered as an infusion (5 to 15 mg/hr). Midazolam clearance was reduced (1.9 vs 2.8 mL/min/kg) and the half-life was prolonged (7.6 vs 13 hours) in the ARF patients. The renal clearance of the 1-hydroxy-midazolam glucuronide was prolonged in the ARF group (4 Vs 136 mL/min) and the half-life was

prolonged (12 Vs >25 hours). Plasma levels of metabolites accumulated in all ARF patients to about ten times that of the parent drug. The relationship between accumulating metabolite levels and prolonged sedation is unclear.

In a study of chronic renal failure patients (n=15) receiving a single IV dose, there was a two-fold increase in the clearance and volume of distribution but the half-life remained unchanged. Metabolite levels were not studied.

Congestive Heart Failure:

In patients suffering from congestive heart failure, there appeared to be a two-fold increase in the elimination half-life, a 25% decrease in the plasma clearance and a 40% increase in the volume of distribution of midazolam.

Hepatic insufficiency:

Midazolam pharmacokinetics were studied after an IV single dose (0.075 mg/kg) was administered to 7 patients with biopsy proven alcoholic cirrhosis and 8 control patients. The mean half-life of midazolam increased 2.5-fold in the alcoholic patients. Clearance was reduced by 50% and the Volume of distribution increased by 20%. In

another study in 21 male patients with cirrhosis, without ascites and with normal kidney function as determined by creatinine clearance, no changes in the pharmacokinetics of midazolam or 1-hydroxy-midazolam were observed when compared to healthy individuals.

Obesity:

Morbidly obese patients have an increased volume of distribution of Midazolam resulting from enhanced distribution of the drug into peripheral adipose tissues. This increase has been observed to be as high as approximately 50% of the Volume of distribution corrected for total body weight. The mean half-life of Midazolam observed in these morbidly obese patients is greater compared to that observed in normal subjects. However the clearance is not significantly different between these two groups.

Pharmacokinetics-Continuous Infusion:

The pharmacokinetic profile of midazolam following continuous infusion, based on 282 adult subjects, has been shown to be similar to that following single-dose administration for subjects of comparable age, gender, body habitus and health status. However, midazolam can accumulate in peripheral tissues with continuous infusion. The effects

of accumulation are greater after long-term infusions than after short-term infusions. Maintaining the lowest Midazolam infusion rate that produces satisfactory sedation can reduce the effects of accumulation. Infrequent hypotensive episodes have occurred during continuous infusion; however, neither the time to onset nor the duration of the episode, appeared to be related to plasma concentrations of midazolam or alpha-hydroxy-midazolam. Further, there does not appear to be an increased chance of occurrence of a hypotensive episode with increased loading doses.

Toxicity: -

Extensive animal toxicological studies were carried out to determine the acute, sub acute and chronic toxicity associated with the use of Midazolam. The scope of these studies included the determination of the presence of any reproductive toxicity, mutagenic effect or any carcinogenic effect attributable to the use of Midazolam. Throughout these studies, Midazolam was found in terms of acute, sub acute and chronic toxicity to be very well tolerated with a wide therapeutic margin. It is particularly well tolerated on parenteral (Intramuscular & intravenous) administration. No evidence of embryotoxic, teratogenic or mutagenic effects have been found.

Effects of Midazolam on organ systems:-

A number of studies have been carried out to assess the suitability of Midazolam as an induction agent of anesthesia for surgery of different systems and its effects on various body systems evaluated. Most of these results showed comparable results to those obtained with other induction agents.

Cardiovascular system:

In cardiac hemodynamic studies in adults, intravenous induction of general anaesthesia with Midazolam was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 85/minute) tended to slow slightly. In pediatric patients, a comparison of IV Midazolam (500 µg/kg) with propofol (2.5 mg/kg) revealed a mean 15% decrease in systolic blood pressure in patients who had received IV Midazolam vs a mean 25% decrease in systolic blood pressure following propofol. Other rare (<1%) incidences of cardiovascular effects of Midazolam like Bigeminy, premature ventricular contractions, vasovagal episode,

bradycardia, tachycardia, and nodal rhythm have been observed as adverse experiences following intravenous injection as a single dose.

Foster et al studied the cardiovascular effects of Midazolam in unpremedicated volunteers given 0.15mg/ kg by intravenous injection within 15 seconds. The systolic and diastolic arterial blood pressure fell from 121 ± 2 to 115 ± 2 mmHg and 78 ± 2 to 70 ± 2 mmHg respectively three minutes after the injection. These decrease in pressure remained constant for at least 25 minutes. The heart rate increased one minute after administration of the drug from 77 ± 4 to 90 ± 3 beats/min ($p<0.05$) and lasted for five minutes[13]. Midazolam like other benzodiazepines e.g. Diazepam, produces a transient depression of baroreceptor mediated heart rate responses following Intravenous administration in doses appropriate for induction of anaesthesia. The administration of Midazolam in patients with hypovolaemia results in enhanced blood pressure lowering effects similar in magnitude to those produced by other induction agents. However Midazolam does not prevent the cardiovascular responses to intubation.[14,15] Reflex responses to laryngoscopy and tracheal intubation are frequently minor but may be serious. Sympathetic responses (sympathetic reflex) are hypertension, tachycardia, and tachyarrhythmias. Vagal responses are laryngospasm, bradycardia, hypotension, cardiac arrest and apnoea.

The vagal responses are usually blocked by the preadministered vagolytic dose of atropine. These reflexes are most likely during light levels of anaesthesia and in association with hypoxia, during periods of hypercarbia and acidosis. These reflexes may be diminished by pretreatment with Lidocaine (intravenous or topical administration), narcotics, or b-adrenergic receptor blocking drugs; and by ensuring an adequate depth of anaesthesia at the time of laryngoscopy.

Respiratory effects:

Serious respiratory adverse events have occurred after administration of Midazolam. These have included respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest leading to cardiac arrest, sometimes resulting in death or permanent neurologic injury. These occur at an increased incidence in patients premedicated with an opioid. Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect

Higher risk adult and pediatric surgical patients, elderly patients and debilitated adult and pediatric patients require lower dosages, whether or not concomitant sedating medications have been

administered. Adult or pediatric patients with Chronic Obstructive Pulmonary Diseases (COPD) are unusually sensitive to the respiratory depressant effect of Midazolam. Pediatric and adult patients undergoing procedures involving the upper airway such as upper endoscopy or dental care are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction.

The usual recommended intramuscular premedicating doses of Midazolam do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent in adults. Intravenous induction doses of Midazolam depress the ventilatory response to carbon dioxide stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental in adults. Impairment of ventilatory response to carbon dioxide is more marked in adult patients with chronic obstructive pulmonary disease (COPD).

Sedation with IV Midazolam does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (Vmax) increase. In one study of pediatric patients under general anaesthesia, intramuscular Midazolam 100 or 200 μg/kg) was shown to depress the response to carbon dioxide in a dose-related manner.[12]

Other rare observed respiratory effects of the drug include laryngospasm, bronchospasm, dyspnea, hyperventilation and wheezing.

Foster et al in 1980 performed studies to determine the effect of intravenously administered benzodiazapines Diazepam and Midazolam on respiration especially the extent of depression produced in the respiratory center by administration of these drugs. The study results suggests that administration of these drugs through the intravenous route cause direct depression of the respiratory center,although in view of the muscle relaxant effects of these drugs, a certain impairment of the respiratory musculature may well be involved in the overall effect[16].

Gross et al in 1983 showed that the depression caused by Midazolam is slower in onset and more prolonged than that produced by another Intravenous induction agent, thiopental at a dose of 3.5mg /kg. Gross et al also described respiratory depression due to Midazolam following intravenous injection. The respiratory rate was not significantly affected but the minute volume decreased. [17] Kanto and co workers also pointed out the occurrence of transient apnea following rapid administration of high doses of Midazolam (> 0.15mg/kg.) intravenously especially in subjects premeditated with opiods[8].

Generally it has been confirmed that the use of Midazolam may be accompanied by depression of the respiratory center. Patients with

chronic obstructive airway disease experience even greater Midazolam induced depression of ventilation.

Central Nervous System (CNS):

The central Nervous System effects of Midazolam range from mild sedation to deep levels of sedation virtually equivalent to a state of general anaesthesia, anxiolysis amnesia as well as adverse drug effects like, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation and prolonged emergence from anaesthesia. Use of concomitant medications capable of depressing the CNS pontentiate the central nervous system effects of this drug.

Effects on cerebral blood flow and intracranial pressure.

In patients without intracranial lesions, induction of general anaesthesia with IV Midazolam is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that observed following IV thiopental. Preliminary data in neurosurgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with Midazolam and with thiopental

during intubation. No similar studies have been reported in pediatric patients.[17] Griffin and co workers found out that Midazolam like Thiopentone when used in induction of anaesthesia does not prevent increase in intracranial pressure associated with direct laryngoscopy for intubation of the trachea[20,19]

Midazolam has been found to produce dose related reduction in cerebral blood flow and cerebral oxygen utilization. Cottrell et al in 1982 observed that a dose of Midazolam of 0.1 mg kg^{-1} used to induce sleep causes a 39% reduction in cerebral blood flow as well as an increase in cerebral vascular resistance of about 52%[18]. Also patients with decreased intracranial compliance showed little or no change in intracranial compliance when given Midazolam in intravenous doses of 0.15 - 0.27mg $kg.^{-1}$. Thus Midazolam can serve as a safe alternative to barbiturates in the induction of anaesthesia in patients with intracranial pathology. Massei et al also had findings supporting the use of Midazolam as an alternative to Thiopentone in induction of anaesthesia in patients with raised intracranial pressure.[19]

Effects on intra ocular pressure:

Studies done to evaluate the pattern of intraocular pressures following induction of anaesthesia with Midazolam, Diazepam and

etomidate showed that intraocular pressure dropped to the same extent after induction using these agents. However none of them prevented a rise in intraocular pressure after administration of suxamethonium and tracheal intubation[22,23].

Clinical uses and dosage of Midazolam:

Clinical uses of Midazolam include:-

- Preoperative medication (premedication).
- Conscious sedation.
- Induction and maintenance of anaesthesia.
- Continuous intravenous infusion for sedation in intensive care settings.
- Anticonvulsant effect/activity.
- Provision of complete anaesthesia for short procedures such as cardioversion requiring minimal analgesia.
- Treatment of delirium.
- Production of skeletal muscle relaxation, for the management of lumbar disc disease and diseases such as tetanus.

Preoperative medication:

As a drug for premedication Midazolam produces anxiolysis, soothing drowsiness and relaxation as well as amnesia, all of these are very important for the subsequent conduct of smooth anaesthesia. The amnesic effect of an intravenous dose of Midazolam 5 mg, ranges from 20-32 minutes and may be even longer with intramuscular injection. The anti anxiety and amnesic effect of Midazolam are enhanced by concomitant administration of scopolamine. Midazolam like other benzodiazepines has been shown to reduce the occurrence of preoperative insomnia through reduction of anxiety and stress. Thus the physiological pattern of sleep is hardly affected. However premedication on the eve of surgery should not be taken as a substitute for premedication on the day of surgery itself. Thus necessary drugs to achieve other goals of premedication not covered by Midazolam or benzodiazepines in that matter like analgesia if the patient is already in pain, toning down of reflexes in particular vagal reflexes, prevention of vomiting and inhibition of salivation and bronchial secretions; should be administered.

Various clinical trials were carried out by different scientist to evaluate its suitability as a drug for premedication in various forms of surgical procedures. It was compared to other drugs used in

premedication like Pethidine, Promethazine, Droperidol, Diazepam, Fentanyl etc. Midazolam proved to be an alternative to premedication with a combination of two or more of the above drugs.[24,25,26,27,28,29] Midazolam given intramuscularly was compared to drugs like diazepam and pethidine with respect to the following parameters:- Quality of premedication, anterograde amnesia, local tolerance, side effects and effect on the cardiovascular system and respiration. Midazolam proved to be a good alternative to conventional premedication. However it was found to have the following additional advantages:-

- Rapid onset of action with regards to sedation, anterograde amnesia and reduction and relief of anxiety.
- High degree of bioavailability i.e. more than 90% of the administered dose.
- Short duration of action with the effects not prolonged or spilling over into the post off period.
- Virtually no impairment of respiratory or cardiovascular parameters if the recommended dosages are adhered to.
- The use of Midazolam in premedication has been associated with excellent local tolerance and few or even no side effects.

Compared to a combination of Pethidine and promethazine for intramuscular premedication; Midazolam was found to have more

marked anxiolytic effect. Also no side effects or stress symptoms like increased anxiety, palpitations, dryness of mouth, dizziness, nausea and a feeling that the heart was stopping, were seen in those premedicated with Midazolam[24]. In a study done by Batch et al, Midazolam was proved to be superior to droperidol in premedication; with regards to sedation, perioperative amnesia, emotional state, psychomotor function and perioperative somatic symptoms and side effect as well as recovery after surgery[25]. The authors are of the opinion that Midazolam is the drug of choice in premedication for out patient gynecological surgery. This outcome is comparable to the conclusion given after the study done by Shefer et al, in patients under going brief gynecological procedures. These patients had less anxiety, a reduction in recall and in psychomotor function and better sedation after intramuscular premedication with 5mg Midazolam than the control group which received 1ml of physiological saline as placebo[23]. In another study, McAteer et al found that premedication with 0.1mg of Midazolam per kg intramuscularly had anxiolytic and sedative effects comparable to the combination of papaveretam 0.24mg/kg and hyoscine 0.048mg/kg. However the amnesic effect prior to induction was significantly more marked with Midazolam than with the two combined drugs.[27] Van Wijhe and coworkers in 1985 compared Midazolam with a combination of fentanyl and Droperidol or placebo in premedication. They found out

that Midazolam produced better results than Fentanyl plus Droperidol or placebo with respect to anxiolytic action, sedation and amnesia on transfer to the Operation Theater (OT), venepuncture, and also general assessment by doctors and patients.[28] When compared to other benzodiazepine like Diazepam, flunitrazepam and lorazepum it displayed most marked amnesia, good sedation and anxiolytic action[29].

Various pharmacokinetics and clinical studies have shown that four different routes i.e. intravenous, intramuscular, oral or rectal can be used to administer Midazolam in the premedication period. Several workers compared the effectiveness of rectal and intramuscular routes in the administration of Midazolam in premedication.[26,29,30,31,32,33,34] In almost all these studies the rectal route is given preference because it causes no pain or undue anxiety. Various dose-searching studies were carried out and the recommended dose for premedication in adults is 0.07-0.1 mg/kg. depending on age and general condition of the patient, given intramuscularly about half an hour before anaesthesia. Children require higher doses in terms of weight when compared to adults (0.15-0.2mg/kg) for intramuscular injection whereas for rectal administration a dose of 0.35-0.45 mg /kg 20-30 minutes before induction of anaesthesia is required.[30, 32,33,34,35]

Midazolam has also been used to provide it's anti anxiety and sedative effects in children. The intramuscular route has been used with good results. Rita et al carried out a study to ascertain the ideal dose for premedication in the group age 1-15 ASA I or II and found out that an intramuscular injection of 0.8mg/ kg of Midazolam is the ideal dose of premedication especially 30-90minutes before induction. This dose was associated with drowsiness or being asleep in the pre operating room. Also induction was found to be smooth and better tolerated (mask induction). The recovery or awakening after surgery was calm.[35]

Other studies showed lower doses of Midazolam to be effective in premedication for older children, whereas young ones required increasing higher doses. Most authors recommends dosages of 0.1-0.2mg/kg for effective premedication in children aged two to ten years. All these studies demonstrate the need to adjust the dosage to the age of the child.

When administered rectally for premedication in children a dose ranging from 0.3 to 0.5mg /kg rectally produce excellent sedation and relief of anxiety and the children are found to have better acceptance of the mask during induction and they tolerate the anaesthetic gases well.

De jong .P and Co-worker Verburg carried out a study to compare the rectal and intramuscular routes of administration of Midazolam in

premedication in young children. The sedative effect, tolerance of induction as well as intraoperative & postoperative salivary secretion was comparable in both groups. Regarding the side effects of premedication i.e. hiccup loss of coordination diplopia, cough, regurgitation and laryngospasms, the authors report that these were mild and rare. However the authors noted that rectal administration caused more frequent peristalsis. Despite this they found the rectal route to be as effective as the intramuscular route in premedication. They give preference to the rectal variant since it causes no pain or anxiety in the children.[36]

Midazolam ampoule solution when mixed with an appropriately prepared taste improving solution can be used orally for premedication. However despite the fact that orally administered Midazolam does not have an effect on gastric secretion or acidity of the gastric juices, it is necessary to administer atropine intramuscularly in addition to oral Midazolam in premedication. This is based on the observation of frequent pronounced salivation, which hinders smooth course of anaesthesia, in particular during extubation. Meursing et al found that doses of Midazolam ranging from 3.75mg to 7.5mg given orally produced good results[37]. When compared to diazepam in oil for intramuscular premedication Midazolam was found to provide better sedation, rapid onset of action, reliability as well as good local tolerance.[28]

Thus when compared to other benzodiazepines like Diazepam, Flunitrazepam, & Lorazepam in premedication, Midazolam has a superior role in the place of benzodiazepines in premedication.

For Midazolam given preoperatively for sedation, anxiolysis, and amnesia through the intramuscular route, it should be injected deep in a large muscle mass. The recommended premedication dose of Midazolam for good risk (ASA Physical Status I & II) adult patients below the age of 60 years is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM) administered up to 1 hour before surgery. The dose must be individualized and reduced when IM Midazolam is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant narcotics or other CNS depressants. In a study of patients 60 years or older, who did not receive concomitant administration of narcotics, 2 to 3 mg (0.02 to 0.05 mg/kg) of Midazolam produced adequate sedation during the preoperative period. The dose of 1 mg IM Midazolam may suffice for some older patients if the anticipated intensity and duration of sedation is less critical. As with any potential respiratory depressant, these patients require observation for signs of cardiorespiratory depression after receiving IM midazolam. Onset is within 15 minutes, peaking at 30 to 60 minutes.

It can be administered concomitantly with atropine sulfate or scopolamine hydrochloride and reduced doses of narcotics.

For paediatric patients doses of 0.1 to 0.15 mg/kg are usually effective and do not prolong emergence from general anaesthesia. For more anxious patients, doses up to 0.5 mg/kg have been used. Although not systematically studied, the total dose usually does not exceed 10 mg. If Midazolam is given with an opioid, the initial dose of each must be reduced.

Conscious sedation:

Consious sedation means a minimally depressed level of consiousness that retains the patient's ability to independently and continuously maintain an airway and respond appropriately to physical stimulation or verbal command. It is produced by a pharmacological or non-pharmacologica method or a combination thereof. The drugs and/or techniques used should carry a margin of safety wide enough to render unintended loss of consciousness unlikely. Further, patients whose only response is reflex withdrawal from repeated painful stimuli would not be considered to be in a state of conscious sedation.

Midazolam has shown to be invaluable in the provision of conscious sedation in painful medical or surgical procedures performed for either therapeutic or diagnostic purposes. An ideal sedative in painful diagnostic procedures should posses the following characteristic i.e.

- It should induce or have adequate amnesic and analgesic effects
- It should have short lasting effect of about 5-15 minutes
- It should not depress the respiratory or cardiovascular system.
- It should be able to provide dose dependent sedation till light sleep is attained.
- It should not require to be complemented by other drugs i.e. no need for anaesthesia.

Despite the fact that Midazolam does not fulfil all the above characteristic of an ideal sedative for painful procedures, it nevertheless comes closest at present to satisfying the above condition.

Indeed Midazolam has played a greater role in modern practice of conscious sedation in painful or unpleasant procedures, this is due to its ability to remove the anxiety, induce amnesia as well as its ability to calmly sedate these patient thus facilitating the performance of the required procedure.

The scope of Midazolam in conscious sedation is very wide and its areas of use include Gastroenterology, Gynaecology, urology,

Pulmonology, Cardiology, orthopedics, Radiology, ENT, Plastic surgery and minor surgical procedures.

Various studies have been carried out in different specialties or areas to find out which situation and at which dosage is Midazolam used as a sedative. Midazolam has been used to provide basal sedation before diagnostic or surgical interventions performed under local anaesthesia as well as those performed under regional anaesthesia. Salehi in 1986 showed that most patients undergoing surgery under regional anaesthesia nevertheless wished to sleep during the procedure despite adequate analgesia[38]. The induction of sleep in these patients is not desired since the anaesthetist depends on the patient's cooperation especially those under local or regional anaesthesia so as to be able to monitor the progress as well as the patient well being. Mild sedation on the other hand is advantageous to both the patient and doctor since the patient is calm and tolerates the intervention well thus allowing the doctor to work better. Midazolam like the other benzodiazepines has proved itself to be a better adjunct to local or regional anaesthesia because of its rapid onset of action, smooth sedation, with reliable anterograde amnesia and anxiolytic effect. Its good side effect profile, ease of management and short elimination half life with no long acting active metabolites has further increased its desirability as an adjunct to local anaesthesia and or regional anaesthesia.

The combination of Midazolam with regional or local anaesthesia has proved very useful in various specialties example in gynaecology the combination of Midazolam and paracervical blockade provided an ideal environment or condition for performing curettage and termination of pregnancy comparable to the one obtained when general anaesthesia is used. The author Nielsel & Co workers, 1987 in fact advocate the use of this technique in patient with lung condition, since it has less impairment of the respiratory function and compared to the general anaesthesia[39]. However the combination of Midazolam and regional anaesthesia in caesarian section has been shown to have a depressant effects on the child's vital functions attributable to Midazolam. Thus Bland et al suggests that it should not be used in caesarian section[40,41].

Although Gitsch et al pointed out that administration of Midazolam before delivery facilitated delivery by the relief of anxiety and tension and thus reduced the use of analgesics causing respiratory depression[42], other workers refute these findings [43,44,]. They expressed a degree of skepticism about the administration of Midazolam before delivery. They are of the opinion that the amnesia caused by the drug prevents the mother from directly experiencing birth of the child.

The use of Midazolam in urology in combination with regional anaesthesia as a sedative has proved to be very useful and desirable by both the surgeons and patients. Sedation with Midazolam in those

patients undergoing cystoscopy under eurethral analgesia was found to be better, with adequate amnesia and they rated the procedure as painless and the postoperative recovery is better compared to those who receive Diazepam. In fact Birch and miller, suggests that Midazolam is a safer sedative which can be used to increase the number of patient with urological problems treated on an outpatient basis by some 25-50%.[46]

In the field of gastroentorology Midazolam due to its short duration of action, marked anterograde amnesia and excellent local tolerance has won a place in conscious sedation especially in those undergoing endoscopy. It helps alleviate the discomfort and stress by its anxiolytic calming and amnesic effect, while maintaining or preserving the patient's co-operation, which is highly needed in those procedures. Midazolam has also been shown to be superior to other benzodiazepines like Diazepam in sedation of patient undergoing oesophagogastroscopy and colonoscopy. Those sedated with Midazolam required less Pethidine compared to those sedated with Diazepam. Majorities of the patients sedated with Midazolam were willing to undergo the procedures again showing a greater degree of acceptance.[47].

In the performance of some special investigation like Liver biopsy, Endoscopic retrograde pancreatography Midazolam does offer distinct advantages in these fields. It reduces the anxiety and discomfort felt by

the patient, and its amnesic effect extinguishes all recollection of the procedure. In the case of liver biopsies these two advantages increases greatly the chances of the patients to undergo further clinically indicated biopsies and other investigations willingly[48].

In patients undergoing cardiac catheterization and angiography, conscious sedation with Midazolam, makes the procedure successful and acceptable to both patient and physician[49]. In angiography procedures the good sedation provided by Midazolam while the patient is awake and co-operative is very important, moreover, Midazolam does allow deep sedation in the initial phase when the catheter is being introduced into the blood vessels. Towards the end of this procedure the patient must be able to hold his/her breath when instructed to do so, in order to ensure good quality angiography.

For children undergoing invasive radiological studies or investigations like angiography, needle biopsy, myelography, arthrography and sialography an addition of analgesics like Pethidine makes the sedation provided by Midazolam excellent. However children must be under constant monitoring of their respiratory function and oxygen saturation by a trained personnel.

Intravenous access is not thought to be necessary for all pediatric patients sedated for a diagnostic or therapeutic procedure because in some cases the difficulty of gaining IV access would defeat the purpose

of sedating the child. Rather, emphasis should be placed upon having the intravenous equipment available and a practitioner skilled in establishing vascular access in pediatric patients immediately available.

Conscious sedation with Midazolam has made dental surgery, plastic surgery and opthalmological procedures performed under local analgesia acceptable an enjoyable by the patients.

When used for conscious sedation, with anxiolysis and amnesia for therapeutic or diagnostic procedures, narcotic premedication results in less variability in patient response and a reduction in dosage of Midazolam used. For peroral procedures, the use of an appropriate topical anaesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.

Sedation guidelines recommend a careful presedation history to determine how a patient's underlying medical conditions or concomitant medications might affect their response to sedation/analgesia as well as a physical examination including a focused examination of the airway for abnormalities. Further recommendations include appropriate presedation fasting.

The dosage must be individualized and titrated. Midazolam should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. Individual response will vary with age, physical status and concomitant

medications, but may also vary independent of these factors, slower injection is recommended. For healthy adults below the Age of 60 titrate slowly to the desired effect (e.g. the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 2.5 mg should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If further titration is necessary, continue to titrate, using small increments, to the appropriate level of sedation. Wait an additional 2 or more minutes after each increment to fully evaluate the sedative effect. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint. If narcotic premedication or other CNS depressants are used, young healthy patients will require approximately 30% less Midazolam than unpremedicated patients, while elderly or debilitateed patients will require at least 50% less Midazolam than healthy young unpremedicated patients.

For patients aged 60 or older, and debilitated or chronically ill the danger of hypoventilation, airway obstruction, or apnea is greater and because the peak effect may take longer in these patients, increments should be smaller and the rate of injection slower,titrated to the desired effect. No more than 1.5 mg should be given over a period of no less than 2 minutes. Wait an additional 2 or more minutes to fully

evaluate the sedative effect. If additional titration is necessary, it should be given at a rate of no more than 1 mg over a period of 2 minutes, waiting an additional 2 or more minutes each time to fully evaluate the sedative effect. Total doses greater than 3.5 mg are not usually necessary. Additional doses to maintain the desired level of sedation may be given in increments of 25% of the dose used to first reach the sedative endpoint, but again only by slow titration, especially in the elderly and chronically ill or debilitated patient. These additional doses should be given only after a thorough clinical evaluation clearly indicates the need for additional sedation.

Intensive care setting:

In the management of patients in the intensive care setting, sedation plays a special role, the patients are sedated to support long term mechanical ventilation, or to facilitate the procedures e.g. cardioversion, endoscopy and change of dressings especially in burn cases as well as to provide post operative sedation. Midazolam has been found to be very useful in attaining these goals either administered as continuous infusion or intermittent bolus injections.[50,51,52,53,54,55,56]

It has been observed that sedation with Midazolam instead of Diazepam, necessitated addition of lower amounts of opiods like

Fentanyl or Pethidine thus implying better sedation. Its use has also an advantage of early recovery after withdrawal of the sedative.

Midazolam when used for conscious sedation given by the intravenous route, it should not be administered rapidly as a bolus, but it should be titrated. The drug can be diluted in aqueous Nacl and dextrose solution to allow for gradual titration. Since the individual response to effect of the drug varies according to age, concomitant medication and the state of health of the individual, the drug should be titrated slowly against effect. In healthy adults up to 60 years of age the initial dose administered over a period of at least 2 minutes should not exceed 2.5mg, in case addition sedation is required further sub doses usually a quarterly initial dose is titrated after two minutes. Usually desired sedation is achieved with a total dose of less than 5mg of Midazolam. For patients over 60years of age, debilitated and chronically ill patients the sub doses should be smaller and the rate of injection slower.

For continuous infusion, Midazolam 5 mg/mL formulation is recommended diluted to a concentration of 0.5 mg/mL with 0.9% sodium chloride or 5% dextrose in water. Usual adult dose, if a loading dose is necessary to rapidly initiate sedation, 0.01 to 0.05 mg/kg (approximately 0.5 to 4.0 mg for a typical adult) may be given slowly or infused over several minutes. This dose may be repeated at 10 to 15

minute intervals until adequate sedation is achieved. For maintenance of sedation, the usual initial infusion rate is 0.02 to 0.10 mg/kg/hr (1 to 7 mg/hr). Higher loading or maintenance infusion rates may occasionally be required in some patients. The lowest recommended doses should be used in patients with residual effects from anaesthetic drugs, or in those concurrently receiving other sedatives or opioids. In general, Midazolam should be infused at lowest rate that produces the desired level of sedation in the patient.

Assessment of sedation should be performed at regular intervals and the Midazolam infusion rates adjusted up or down by 25% to 50% of the initial infusion rate so as to assure adequate titration of sedation level. Larger adjustments or even a small incremental dose may be necessary if rapid changes in the level of sedation are indicated. In addition, the infusion rate should be decreased by 10% to 25% every few hours to find the minimum effective infusion rate. Finding the minimum effective infusion rate decreases the potential accumulation of Midazolam and provides for the most rapid recovery once the infusion is terminated.

As a group, pediatric patients generally require higher dosages of Midazolam (mg/kg) than do adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require close monitoring. In obese pediatric

patients, the dose should be calculated based on ideal body weight. To initiate sedation, an intravenous loading dose of 0.05 to 0.2 mg/kg administered over at least 2 to 3 minutes can be used to establish the desired clinical effect, it should not be administered as a rapid intravenous dose. This loading dose may be followed by a continuous intravenous infusion to maintain the effect. An infusion of Midazolam has been used in patients whose trachea was intubated but who were allowed to breathe spontaneously. assisted ventilation is recommended for pediatric patients who are receiving other central nervous system depressant medications such as opioids. Based on pharmacokinetic parameters and reported clinical experience, continuous intravenous infusions of Midazolam should be initiated at a rate of 0.06 to 0.12 mg/kg/hr (1 to 2 μg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required or supplemental intravenous doses of Midazolam can be administered to increase or maintain the desired effect.

Pediatric patients unlike adult patients, generally receive increments of midazolam on a mg/kg basis.

Frequent assessment at regular intervals using standard pain/sedation scales is recommended. Based on pharmacokinetic parameters and reported clinical experience in preterm and term neonates whose trachea was intubated, continuous intravenous

infusions of Midazolam should be initiated at a rate of 0.03 mg/kg/hr (0.5 μg/kg/min) in neonates <32 weeks and 0.06 mg/kg/hr (1 μg/kg/min) in neonates >32 weeks. Intravenous loading doses should not be used in neonates, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. This is particularly important because of the potential for adverse effects related to metabolism of the benzyl alcohol. Hypotension may be observed in patients who are critically ill and in preterm and term infants, particularly those receiving Fentanyl and/or when Midazolam is administered rapidly. Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm patients whose trachea is not intubated.

Patients who exhibit agitation, hypertension, or tachycardia in response to noxious stimulation, but who are otherwise adequately sedated, may benefit from concurrent administration of an opioid analgesic. Addition of an opioid will generally reduce the minimum effective Midazolam infusion rate required.

Induction and maintenance of anaesthesia

Benzodiazepines in the past had limited use as induction agents Diazepam being the only one with appreciable effects as documented by various workers.[5,57,58,59.] However its use as an induction agent was limited by its slow onset of action and prolonged recovery, potential to produce recurrent sedation, and potential risks of developing thrombophlebitis following intravenous administration, thus it offered no challenge to thiopentone. In 1982 Kanto and co-workers suggested benzodiazepine derivatives suitable for induction of anesthesia (GA) should possess a fairly short onset of action. The clinically acceptable induction time being not more than 2minutes, this is true for Diazepam, Flunitrazepam and Midazolam. But the slow onset of action of Lorazepam with maximum effect 20-45 minutes after administration limits its use as an induction agent[60]. Benzodiazepines in general do not produce the desired level of anesthesia in one arm brain circulation time[61]. This and great inter-individual variation in drug response to benzodiazepines as well as long acting residual effects might be the reasons why Benzodiazepines could not replace the conventional orthodox drugs in induction of anaesthesia[62]. The high dose required in some cases doesn't favor the benzodiazepines e.g. diazepam up to 40mg

and flunitrazepam 6mg were not sufficient to ensure induction of anesthesia in patients on central nervous system depressant drugs.[17] Midazolam an imidazole benzodiazepine, has all the qualities of the benzodiazepines, with other superior qualities like rapid onset with short duration of action devoid of severe adverse effects, very little cardiopulmonary depressant effects and less risks of thrombophlebits. These and the ability to induce sleep in one arm brain circulation time with pronounced intensity makes it comparable to other induction agents. Indeed Midazolam has been used for induction of anesthesia in other parts of the world with good results [11,63,64,65]. Induction doses at which response to commands and eyelid reflex disappear are stated in the literature as 0.1-0.4mg/kg of Midazolam [65,66,67,68,69]. The dosage varies depending on age, sex, premedication, state of health, rate of induction and serum albumin concentration. Patients over the age of 60 are more sensitive to Midazolam and induction takes less time in these, the dose needed in patients aged between 18-30 years were twice as high as those required in elderly patients [70]. In the elderly a dose of 0.15mg/kg given intravenously resulted in smooth induction though the time needed for induction was rather long and a sudden but transient fall in blood pressure was found in a significant number of patients[71]. However those patients were pre-medicated with either Diazepam, Pethidine, and Atropine or Dixyrazin. Care should be exercised when

used in combination with an opioid, particularly in the elderly although all ages are at risk of respiratory depression.

In a study done to determine the induction dose of Midazolam in children undergoing elective surgery, different doses ranging from 0.075-0.6mg/kg were used. But even an induction dose of 0.6mg/kg was found to be unreliable in children but effective enough to cause significant fall in systolic blood pressure after induction, though it failed to induce sleep in a considerable fraction of the children even at this highest dose employed[73]. However in another study done by Otte et al it was found that for induction of sleep Midazolam in a dose of 0.3mg/kg was needed for children >6 years and 0.4mg/kg for those <6years. The maximum dose was 15mg and all the patients fell asleep and did not remember anything about the procedure and no side effects were observed[68].

Onset of anesthesia is quicker with rapid intravenous (I.V) administration than with slow I.V administration of Midazolam. It also proved to be shorter (mean 77secs) in those with lower albumin concentration in blood[63]. Certain pathological processes such as renal failure may accelerate induction and prolong the duration of anesthesia[72].

In a study done by Jensen and colleagues the induction time ranged from 50-110 seconds with mean induction time of

77±15.3seconds (mean±SD), assuming a normal distribution the expected mean in this study was 80 seconds. This range in the induction time is comparable to the results observed in other studies[74,75,76,77,78]. In a study by Driessen et al it was found that premedication with droperidol and fentanyl shortly before induction shortens the induction time i.e. time taken for the eyelash reflex to disappear. The mean induction time being as short as 37.5seconds while in the non premedicated patients the mean induction time ranged from 50-110seconds.[66,67,75,76]

With the use of narcotic premedication, induction of anaesthesia with midazolam can be attained within a relatively narrow dose range and in a short period of time. Induction of Anaesthesia in unpremedicated patients or before administration of other anaesthetic agents has been associated with variable individual response to the drug. The dosage should be titrated to the desired effect according to the patient's age and clinical status.

In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3 to 0.35 mg/kg for induction, administered over 20 to 30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used; induction may instead be completed with inhalational anaesthetics. In resistant cases, up to 0.6

mg/kg total dose may be used for induction, but such larger doses may prolong recovery.

Unpremedicated patients over the age of 55 years usually require less Midazolam for induction; an initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less Midazolam for induction. An initial dose of 0.2 to 0.25 mg/kg will usually suffice; in some cases, as little as 0.15 mg/kg may suffice.

When the patient has received sedative or narcotic premedication, particularly narcotic premedication, the range of recommended doses is 0.15 to 0.35 mg/kg. In average adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice. The initial dose of 0.2 mg/kg is recommended for good risk (ASA I & II) surgical patients over the age of 55 years. In some patients with severe systemic disease or debilitation, as little as 0.15 mg/kg may suffice.

Narcotic premedication frequently used before induction with Midazolam Fentanyl (1.5 to 2 μg/kg IV, administered 5 minutes before induction), Morphine (dosage individualized, up to 0.15 mg/kg IM), and Meperidine (dosage individualized, up to 1 mg/kg IM). Except for intravenous Fentanyl, administered 5 minutes before induction, all other

premedications should be administered approximately 1 hour prior to the time anticipated for Midazolam induction.

In the practice of anaesthesia Midazolam has been established not only as an induction agent in inhalational anaesthesia or a sleep-inducing component in combined anaesthesia, including total intravenous anaesthesia but also as an agent for maintenance of anaesthesia. Midazolam has proved to be very useful in maintenance of anaesthesia, where it is administered as intermittent injections or continuous infusion, with the rate being adjusted according to the level of anaesthesia required[51,61]. Intravenously Midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen for provision of a balanced anaesthesia .

To maintain anesthesia after induction with midazolam, fewer additional doses and analgesics are necessary compared to thiopentone, also amnesia is more pronounced with Midazolam and better accepted by both the patients and doctors.[76,77,78]

When injectable Midazolam is used during maintenance of anaesthesia, for surgical procedures, as a component of balanced anaesthesia, effective narcotic premedication is recommended. Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anaesthesia and repeated as necessary.

Modern anaesthetic techniques have embraced the concept of co-induction, this is the concurrent administration of two or more drugs to induce anaesthesia with greater ease, improved safety and cost effectiveness. The aim is to make use of the desirable characteristics of each agent administered in combination while minimizing the undesired effects associated with the individual drugs. The concept is based on the existence of synergistic drug interaction between agents when used in combination. A number of studies were carried out on co-induction between Midazolam and opioids or Midazolam and thiopental, or Midazolam and propofol or combination of Midazolam, propofol and alfentanil. These studies demonstrated the following advantages of co-induction: - increased efficacy i.e. better induction due to synergistic interactions of the drugs, improved predictability of the agents, calmness and amnesia at induction (Midazolam), reduced total doses of combined anaesthetics therefore reduced side effects and lower costs [1, 8,77,82,83,84,85,86]

When Midazolam is used before other intravenous agents for induction of anaesthesia, or in co-induction, the initial dose of each agent may be significantly reduced at times, to as low as 25% of the usual initial dose of the individual agents[83].

It also plays an important part in combination with Ketamine (I.M administration) in ataralgesia in children[87,88,89,90]. The term ataralgesia

(ATA) denotes the combination of a benzodiazepine and a potent opioid and/or ketmine.

Neurolepto analgesia and its variants had for a longer time assumed a form of anaesthesia known as the intravenous anaesthesia. Neurolepto agents e.g. droperidol and a narcotic analgesic agent of the opiod class usually Fentanyl provided the backbone of this type of anaesthesia supplemented by other drugs usually gases such as Nitrous oxide. With the continued search for better anaesthetics new substances with ability to provide balanced anaesthesia without certain untoward effects of neuroleptics were discovered. Most of these agents belongs to the benzodiazepines groups, De castro coined the term ataralgesia (ATA) for the combination of a benzodiazepine and a potent opioid and /or ketamine[91] .

The analgesics commonly used are Fentanyl, Alfentanyl and ketamine. In a special form of ataralgesia known as Total Intaravenous Anaesthesia (TIVA) the use of anaesthesia gases is totally dispensed with. Midazolam has found an unsurpassed role in the practice of TIVA in combination with muscle relaxants.

In Nilsson's technique, steady state concentrations of Midazolam achieved through continuos infusion are employed, this is particularly useful for prolonged interventions[92] . De Castro pointed out that continuous infusion of Midazolam at a rate of 0.020mg/kg/ min

together with Alfentanyl 0.001mg /kg/min and atracurium 0.006mg/kg/min was enough to maintain anaesthesia for major surgery lasting more than 2 hours. Good result ranging from satisfactory to very good when using intravenous anaesthesia with Midazolam have been expressed by several other workers[87,91,94,95,96]. The recommended dosage with ketamine is 0.03-0.1mg/kg/hr and with narcotics 0.03-0.3mg/kg/hr reduced according to the patients status, elderly, debilitated and high-risk surgical patients. However in this technique patients particularly those undergoing longer procedure the major problem is postoperative sedation, but this can be resolved by administering the specific benzodiazepine antagonist Flumazenil[66].

Monitoring:

Because serious and life-threatening cardiorespiratory adverse events have been reported, provision for monitoring, detection and correction of these reactions must be made for every patient to whom midazolam injection is administered, regardless of age or health status. Patient response to sedative agents, and resultant respiratory status, is variable. Regardless of the intended level of sedation or route of administration, sedation is a continuum; a patient may move easily from light to deep sedation, with potential loss of protective reflexes. This is especially true in pediatric patients. Sedative doses should be

individually titrated, taking into account patient age, clinical status and concomitant use of other CNS depressants. Continuous monitoring of respiratory and cardiac function is required (i.e., pulse oximetry ECG).

Immediate availability of resuscitative drugs and age and size-appropriate equipment and personnel trained in their use and skilled in airway management should be assured.

For deeply sedated pediatric patients a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Warnings and precautions:

Midazolam should only be administered IM or IV. Midazolam Injection may be mixed in the same syringe with the following frequently used premedications: morphine sulfate, pethidine, atropine sulfate or scopolamine. Midazolam, at a concentration of 0.5 mg/mL, is compatible with 5% dextrose in water and 0.9% sodium chloride for up to 24 hours and with lactated Ringer's solution for up to 4 hours. Both the 1 mg/mL and 5 mg/mL formulations of Midazolam may be diluted with 0.9% sodium chloride or 5% dextrose in water.

Midazolam is a potent sedative agent that requires slow administration and individualization of dosage. Clinical experience has shown Midazolam to be 4 times as potent per mg as diazepam.

Excessive single doses or rapid intravenous administration may result in respiratory depression, airway obstruction and/or arrest. The potential for these latter effects is increased in debilitated patients, those receiving concomitant medications capable of depressing the CNS, and patients without an endotracheal tube but undergoing a procedure involving the upper airway such as endoscopy or dental

Midazolam must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression. Prior to the intravenous administration of Midazolam in any dose, the immediate availability of oxygen, resuscitative drugs, age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, or apnea, i.e., pulse oximetry. Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures are taken immediately.

The immediate availability of specific reversal agents (flumazenil) is highly recommended.

Vital signs should continue to be monitored during the recovery period. Because intravenous Midazolam depresses respiration and because opioid agonists and other sedatives can add to this depression,

Midazolam should be administered as an induction agent only by a person trained in general anaesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway and supporting ventilation. When used for sedation/anxiolysis/amnesia, Midazolam should always be titrated slowly in adult or pediatric patients. Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid intravenous administration should also be avoided in this population

Serious cardiorespiratory adverse events have occurred after administration of Midazolam. These have included respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death or permanent neurologic injury. There have also been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations particularly in adult or pediatric patients with

hemodynamic instability. Hypotension occurred more frequently in the sedation studies in patients premedicated with a narcotic.

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect.

Higher risk adult and pediatric surgical patients, elderly patients and debilitated adult and pediatric patients require lower dosages, whether or not concomitant sedating medications have been administered. Adult or pediatric patients with COPD are unusually sensitive to the respiratory depressant effect of Midazolam. Pediatric and adult patients undergoing procedures involving the upper airway such as upper endoscopy or dental care are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction. Adult and pediatric patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems and because dosage requirements have been shown to decrease with age, reduced initial dosage of Midazolam is recommended, and the possibility of profound and/or prolonged effect should be considered.

Injectable Midazolam should not be administered to adult or pediatric patients in shock or coma, or in acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of intravenous Midazolam in adult or pediatric patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

There have been limited reports of intra-arterial injection of Midazolam. Adverse events have included local reactions, as well as isolated reports of seizure activity in which no clear causal relationship was established. Precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

The decision as to when patients who have received injectable Midazolam, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of Midazolam cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until one full day after anaesthesia and surgery, whichever is longer. For pediatric patients, particular care should be taken to assure safe ambulation.

Usage in Pregnancy:

An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several studies. Although studies on midazolam showed no evidence of these, if it is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines.

Usage In Preterm Infants and Neonates:

Rapid injection should be avoided in the neonatal population. Midazolam administered rapidly as an intravenous injection (less than 2 minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid intravenous injection of fentanyl. Seizures have been reported in several neonates following rapid intravenous administration.

The neonate also has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of Midazolam.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including Midazolam) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of Midazolam for preterm and term infants includes amounts of benzyl alcohol well below that associated with toxicity; however, the amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources.

Use with other CNS depressants:

The efficacy and safety of Midazolam in clinical use are functions of the dose administered, the clinical status of the individual patient,and

the use of concomitant medications capable of depressing the CNS. Anticipated effects range from mild sedation to deep levels of sedation virtually equivalent to a state of general anaesthesia where the patient may require external support of vital functions. Care must be taken to individualize and carefully titrate the dose of Midazolam to the patient's underlying medical/surgical conditions. It should be administered to the desired effect being certain to wait an adequate time for peak CNS effects of both Midazolam and concomitant medications, and have the personnel and size-appropriate equipment and facilities available for monitoring and intervention. Practitioners administering Midazolam must have the skills necessary to manage reasonably foreseeable adverse effects, particularly skills in airway management.

Contraindications:

Injectable Midazolam is contraindicated in patients with a known hypersensitivity to the drug or other benzodiazepines. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma. Benzodiazepines may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate

lowering following induction with Midazolam; patients with glaucoma have not been studied.

Midazolam is not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form.

Drug Interactions:

The sedative effect of intravenous Midazolam is accentuated by any concomitantly administered medication, which depresses the central nervous system, particularly narcotics (eg, morphine, meperidine and fentanyl) and also secobarbital and droperidol. Consequently, the dosage of Midazolam should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450 3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. These drug interactions may result in prolonged sedation due to a decrease in plasma clearance of midazolam.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular Midazolam for premedication in adults.

The intravenous administration of Midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anaesthesia. This decrease correlates with the dose of Midazolam administered; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

Although the possibility of minor interactive effects has not been fully studied, Midazolam and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration in adults. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of succinylcholine. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

No significant adverse interactions with commonly used premedications or drugs used during anaesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and other nondepolarizing muscle relaxants) or topical local anaesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of midazolam.

Drug/Laboratory Test Interactions: Midazolam has not been shown to interfere with results obtained in clinical laboratory tests

Adverse reactions:

Midazolam has been shown to be relatively free of side effects when used alone and offers several advantages over traditional pharmacological agents such as chloral hydrate and the combination of pethidine, chlorpromazine, and promethazine. However, Hiccups, cough, nausea and vomiting are the most commonly reported adverse effects.[63] Serious cardiorespiratory events and possible paradoxical

reactions have been observed following the use of midazolam. The variation in vital signs were the most frequently seen findings following parenteral administration of Midazolam in adults. This included decreased tidal volume and/or respiratory rate (23.3% of patients following IV and 10.8% of patients following IM administration), apnea (15.4% of patients following IV administration) as well as variations in blood pressure and pulse rate. The majority of serious adverse effects, particularly those associated with oxygenation and ventilation, have been reported when Midazolam is administered with other medications capable of depressing the central nervous system. The incidence of such events is higher in patients undergoing procedures involving the airway without the protective effect of an endotracheal tube (e.g., upper endoscopy and dental procedures).

In adults the following additional adverse reactions were reported after intramuscular administration:- Headache (1.3%), Local effects at IM Injection site including:- pain (3.7%), induration (0.5%),redness (0.5%),muscle stiffness (0.3%)

Administration of IM Midazolam to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics

The following additional adverse reactions were reported subsequent to intravenous administration as a single sedative/anxiolytic/amnestic agent in adult patients:-
hiccoughs (3.9%),nausea (2.8%),vomiting (2.6%),coughing (1.3%), headache (1.5%) ,drowsiness (1.2%) , Local effects at the IV site:- tenderness (5.6%),pain during injection (5.0%),redness (2.6%),induration (1.7%)and phlebitis (0.4%)

In pediatric patients, the following adverse events related to the use of IV Midazolam in pediatric patients were reported in the medical literature: desaturation 4.6%, apnea 2.8%, hypotension 2.7%, paradoxical reactions 2.0%, hiccough 1.2%, seizure-like activity 1.1% and nystagmus 1.1%. The majority of airway-related events occurred in patients receiving other Central Nervous System (CNS) depressing medications and in patients where Midazolam was not used as a single sedating agent.

In preterm infants and neonates, Midazolam administered rapidly as an intravenous injection (less than 2 minutes) has been associated with severe hypotension, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam, who then receive a rapid intravenous injection of fentanyl. Seizures have been reported in several neonates following rapid intravenous administration. The neonate also

has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of Midazolam.
Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol.

Other adverse experiences:

These were observed mainly following IV injection as a single sedative/anxiolytic/amnesia agent and occurring at an incidence of <1.0% in adult and pediatric patients; based on the affected system they are as follows:

- -Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea
- -Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm
- -Gastrointestinal: Acid taste, excessive salivation, retching
- -CNS/Neuromuscular: Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess,

restlessness, emergence delirium or agitation, prolonged emergence from anaesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia

- -Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness
- -Integumentary: Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site
- -Hypersensitivity: Allergic reactions including anaphylactoid reactions, hives, rash, pruritus

-Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug abuse and dependence:

Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs. Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of

midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, hallucinations, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuation of benzodiazepines, including midazolam.

Abdominal distention, nausea, vomiting, and tachycardia are prominent symptoms of withdrawal in infants. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage-tapering schedule followed. There is no consensus in the medical literature regarding tapering schedules; therefore, practitioners are advised to individualize therapy to meet patient's needs. In some case reports, patients who have had severe withdrawal reactions due to abrupt discontinuation of high-dose long-term midazolam, have been successfully weaned off of midazolam over a period of several days.

Overdosage:

The manifestations of Midazolam overdosage reported are similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity from Midazolam overdosage has been reported. However reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported in both adult and pediatric patients. These reactions may be due to inadequate or excessive dosing or improper administration of Midazolam; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. Should such reactions occur, the response to each dose of Midazolam and all other drugs, including local anaesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in pediatric patients.

Treatment of Overdosage:

Treatment of injectable Midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive

measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation, including administration of oxygen. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of midazolam overdosage.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. There are anecdotal reports of reversal of adverse hemodynamic responses associated with Midazolam following administration of Flumazenil to pediatric patients. Prior to the administration of Flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. Flumazenil will only reverse

benzodiazepine-induced effects but will not reverse the effects of other concomitant medications. The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.

PART TWO.

CLINICAL STUDY

Introduction:

Midazolam a new induction agent of the benzodiazepine family of drugs, was introduced in the Department of anaesthesiology of the Muhimbili Medical Center in 1998. The drug was studied in 120 healthy patients undergoing surgical and diagnostic procedure lasting less than one hour. The study evaluated the suitability of Midazolam for use as an induction agent by looking at its induction characteristics which included the time taken for induction of anaesthesia, smoothness of induction of anaesthesia, the accompanying haemodynamic changes after induction; adverse effect of the drug as well as the recovery characteristics. The study also evaluated the effect of the level of hemoglobin and serum albumin level on the induction characteristic of this drug.

Objectives:

The main objective of the study was to evaluate Midazolam (Dormicum®) as an intravenous induction agent.

SPECIFIC OBJECTIVES:

The specific objectives of this study were: -

- To determine the mean induction time.

- To determine the incidences of smooth and disturbed induction of anaesthesia.
- To determine the average Hemoglobin (Hb) level of the patients induced with Midazolam.
- To determine the average serum albumin levels of the patients induced with Midazolam.
- To compare the mean induction time between those with normal Hemoglobin levels (above average) and those with low Hemoglobin levels (below average).
- To compare the mean induction time between those with low serum albumin levels (below average) and those with normal serum albumin levels (above average).
- To compare the haemodynamic changes associated with the induction of anaesthesia with Midazolam among those with normal Hemoglobin and those with low Hemoglobin levels.
- To compare the haemodynamic changes associated with the induction of anaesthesia with Midazolam among those with normal serum albumin levels and those with low serum albumin levels.
- To determine the haemodynamic changes associated with intubation in patients induced with Midazolam.

- To compare the incidence of side effects during induction of anaesthesia with Midazolam between those with normal serum albumin levels and those with low serum albumin levels.
- To compare the mean awakening time between those with Normal Hemoglobin levels and those with low Hemoglobin levels.
- To compare the mean awakening time between those with low serum albumin levels and those with Normal serum albumin levels.
- To compare the mean orientation time between those with low Hemoglobin levels and those with normal Hemoglobin levels.
- To compare the mean orientation time between those with low serum albumin levels and those with normal serum albumin levels.

Rationale of the study:

In most developing countries the health sector has undergone drastic changes as a result of dwindling ability of these governments to provide free health services. These changes in most cases have embraced the concept of cost sharing where the patients or their relatives shoulder the cost of health services provided partially or in total.

However the increase in patient load due to improved capacity to perform complicated surgeries, result in escalating costs of hospitalization. This in most cases is out of proportion with the financial capacity of the people (patients) and in most instances the health service providing institutions lack the necessary facilities to cope with the patient load. The practice of anaesthesia thus, needs to be well planned in such a way as to ensure maximum patient turnover at minimal cost.

Anaesthetic agents do prolong the hospital stay thus limiting maximal utilization of the meager facilities available as well as increasing the cost. It has been observed that perioperative complications of induction agents i.e. prolonged emergence, nausea and vomiting, headache and dizziness play a major role in delaying patients discharge.

The ideal induction agent should be capable of producing rapid smooth induction coupled with optimal surgical conditions, short recovery time and minimal perioperative complications.

Midazolam (Dormicum®) has all the qualities of benzodiazepines including anxiolysis, sedation muscle relaxation and short anterograde amnesia. The presence of Anexate (Flumazenil) a benzodiazepine antagonist capable of reversing the effects of Midazolam makes it possible to have smooth and rapid induction of anaesthesia with

minimal perioperative complications and shortest possible recovery time. However no study has been done in Africa South of the Sahara to evaluate the use of Midazolam as an induction agent. Moreover the fact that most of our patients are of low social status with low income, the possibility of these patients being malnourished with low Haemoglobin and low serum albumin levels is high. Thus there was a need in this study to evaluate the effects of Haemoglobin level and serum albumin levels on the quality of induction of anaesthesia with Midazolam.

It's a fact that in our medical institutions Midazolam has not been used for induction of anaesthesia. There is a need to carry out a study in our center to evaluate its effectiveness and suitability as an induction agent especially in daycare surgery so as to increase the patient turnover as well as reducing the total cost involved.

Anaesthetic protocol, (materials, patients and methodology)

Patients:

One hundred and twenty patients of both sexes were randomly selected and included in this study. Due to unpredictable responses of children and eldery to the drug cited in the literature, only patients within the age limit of 15-75 years were eligible for inclusion in the study.

Sample size:

The minimum calculated sample size required for this study was 105 patients as calculated using the formula:-

Sample size $n=4r^2/\varepsilon^2$

Where r^2 is the expected variance (r is the standard deviation)

and ε is the margin of error, that is expected mean induction time minus the estimated mean induction time (μ-x)seconds.

Sample size n= 4x 15.3x15.3/(3x3)

= 105.

This was calculated using the available data in the literature, the range of induction time being 50-110seconds with mean of 80 seconds assuming normal distribution, with a standard deviation of 15.3 seconds and an average induction time of 77 seconds.

The inclusion criteria:

The study involved patients within the above age limit with American Society of Anaesthesiologists (ASA) physical status I and II. These patients were unpremedicated and with no previous history of adverse effects with anaesthetics. All the patients had written informed consent for anaesthesia and surgery and were scheduled to undergo short surgical and or diagnostic procedures lasting less than

one hour, mainly Examination Under Anaesthesia (EUAs), Dilatation & Curettage (D&C) of the uterus, evacuations, Manual Vacuum Aspirations (MVAs) , cystoscopies, reduction and immobilization of fractured and /dislocated limbs and others like laparatomies for ectopic pregancies, pelvic abscess drainage and diagnostic exploration which where expected to last within one hour.

Exclusion criteria

All patients with ASA class III and IV, previous adverse reaction to anaesthetics and those whose operations were expected to last longer than one hour were excluded from this study Pregnant women, breast feeding mothers as well as children were also excluded in this study.

Materials:

Drugs: The principal drugs used in this study were Midazolam (Roche) and Atropine.

Monitor: HP Viridia automated monitor model 24/24c/24CT Manufactured by Hewlett- Packard was used in the monitoring of patients and measurement of the haemodynamic parameters mainly

systolic blood pressure, Diastolic Blood pressure and pulse rate which were of interest in this study.

Methodology

Anaesthetic procedure and data collection:

On arrival in the operating theatre the patient's age, sex and weight were documented on the study questionnaire. A peripheral intravenous line was established using a cannula at a site, which was convenient preferably the dorsum of the hand the wrist, forehand or the antecubital fossa. Blood samples were obtained for hemoglobin and serum albumin evaluation.

Blood pressure cuff and electrodes for the monitor were applied and baseline blood pressure and pulse rate were recorded. In order to have consistency of the results the same monitor was used through out the study. All patients received intravenous Atropine 0.07mg/kg to reduce secretions, and were pre-oxygenated before induction of anaesthesia, during the whole procedure oxygen supplementation was given.

Patients were induced using Midazolam 0.3mg/kg intravenously, given over a period of 15-20 seconds, for the elderly patient the calculated dose was titrated till induction of anaesthesia i.e. loss of

eyelid reflex was attained. Additional amounts of Midazolam 0.15mg/kg were given intra operatively depending on the individual patients reaction or needs. The induction time was noted as the time taken from start of injection to the time the eyelid reflex disappeared.

During the induction period pain at the site of injection was evaluated by either movement of the arm with the intravenous line and by looking at the patients face for changes in expression indicating pain sensation.

The occurrence of apnoea was determined only in those patients undergoing procedures lasting less than half an hour done under mask anaesthesia as absence of spontaneous respiration lasting more than 15 seconds after induction of anaesthesia with Midazolam.

The quality of induction that is smooth induction of anaesthesia was determined by the absence of respiratory upsets (cough and hiccups), excitatory phenomenon, involuntary muscle movement or activities.

Haemodynamic changes following induction of anaesthesia with Midazolam were evaluated in the various subgroups of the study population. The subgroups were obtained on the basis of the Hemoglobin level, serum albumin levels and intubation. Those with haemoglobin levels below the average obtained in the study were regarded as having low haemoglobin while those with haemoglobin

level above this average (12g/dl) were regarded as having normal haemoglobin. Similarly for those with serum albumin levels below the average obtained in the study (38g/l) were regarded as having low serum albumin level and those above this level were regarded as having normal serum albumin levels.

The study concentrated on the pulse rate and blood pressure that was measured indirectly using non-invasive procedure with the aid of using the automated monitor and documented. The blood pressure and pulse rate at baseline, 5 minutes after induction and at the end of the procedure were measured and recorded in the study questionnaire for use in the evaluation. However these parameters were continuously monitored after every 5 minutes through out the procedure and during the recovery period.

Patients undergoing short procedures lasting less than half an hour were given mask anaesthesia with oxygen and halothane 1.5-2.5% and whenever deemed necessary a supplementary dose of Midazolam was given.

Those undergoing procedures lasting more than half an hour or with higher risk of aspiration or poor control of airway were intubated. Suxamethonium 1mg/kg was given intravenously to facilitate intubation. The patients were maintained with halothane 0.5-1%, a narcotic mainly pethidine and where profound muscle

relaxation was needed for better surgical access for example in laparatomies for diagnostic exploration. A non-depolarizing muscle relaxant Pancuronium 0.1mg/kg was administered (after second readings of vital signs) and reversed at the end of procedure with Atropine 0.01mg/kg and Neostigmine 0.04mg/kg and a nerve stimulator was used to ensure complete reversal.

Pethidine like most opioids reduces sympathetic and enhances vagal and parasympathetic tone, particularly when administered in a large bolus dose. If not countered by indirect effects (e.g catecholamine release) or the coadministration of drugs with anticholinergic or sympathetic activity (e.g atropine or Pancuronium), pethidine can result in hypotension. Other specific cardiovascular effects of pethidine are histamine release and venodilatation, which further enhance its hypotensive effect. Pethidine can also cause tachycardia perharps because of its structural similarity to atropine.

To avoid the interference of these effects on the assessment of the haemodynamic changes following induction of anaesthesia with Midazolam, Pethidine 1mg/kg was administered after the second readings of vital signs were obtained.

The mean duration of anaesthesia was calculated from the time of induction of anaesthesia to the time the patient woke up. The

awakening time was determined as the time from the cutting off of the inhalational agent (halothane) to the time the patient was able to open his or her eyes on command. Patients were asked to open their eyes on command every 30 seconds.

The orientation time was taken as the time from the end of anaesthesia to the time the patient was able to answer questions like what is his or her name, age or place of domicile or residence.

The occurrences of vomiting or retching during recovery, apnoea or cardiac arrest were noted. Patients were asked about being nauseated or feeling dizziness or having a headache. The presence of any of these was recorded in the questionnaire.

Statistical evaluation:

The data collected was computerized from the questionnaire. EPI INFO 6 was used in the analysis of the results obtained in this study. The differences between means were analyzed by t tests to compare the mean values for continuous variables. Chi square test was used to compare categorical variables, Correlation between variables was determined by correlation analysis and use of t-Test for testing significance of correlation coefficient "r". For highly skewed data transformation to logarithmic scale was done to facilitate the analysis.

Results:

Out of the 120 patients involved in this study 76 (63.3%) were females and 44 (36.7%) were males. The proportion of females in the study group is higher compared to males. This is inherent in the fact that, majority of the procedures were gynaecological both elective or emergency cases for therapeutic or diagnostic purposes such as Examination under anaesthesia (EUA), Dilatation and Curettage of the uterus (D&C), laparascopies and evacuations.

The distribution of the studied patients according to their age, weight and sex is illustrated in Tables I and II.

Surgical procedures:

The majority of the surgical procedures performed where gynaecological procedures that accounted for 50.83% of the total procedures performed. These ranged from evacuation, D & C, laparascopies and laparatomies for ectopic pregnancies and drainage of pelvic abscesses. This is reflected in the high proportion of females in the study population or group. The other major category of surgical procedures is made by general surgical operations, which contributed 30.83% of the total procedures performed. These included surgical toilets for stab wounds, lacerations, incision and drainage, biopsies,

exploratory laparatomies, sloughectomy and others. Urological procedures like Direct Vision Urethroscopy (DVU), Cystoscopies, and others contributed 10.83% of all the procedures done in this study. The last portion is contributed by minor orthopedic and trauma surgical operation such as reduction and immobilization of fractured/dislocated limbs and surgical toilet, Table III.

The mean duration of anaesthesia during these surgical and diagnostic procedures was 22.6±15.9 minutes with a range from 5minutes to 60 minutes.

The average Hemoglobin level of the subjects involved in this study was 12.0±1.2g/dl, with a range from9.5g/dl to 14.5g/dl.

The average serum albumin level of the subjects in the study was 38.2± 3.1g/l with a range from 26g/l to 45g/l.

Induction characteristics

In this study; the predetermined dose of induction based on body weight of 0.3mg/kg of Midazolam given intravenously over a period of 15–20 seconds was found to be sufficient to induce sleep.

The mean induction time in this study was found to be 69.04±15.00 seconds in males and 69.14±14.60 seconds. In females. The induction time for the whole study group was 67.85±14.20 seconds with a range

being from 39 seconds to 106 seconds. The difference in induction time between the sexes was not statistically significant, P>0.05; Table IV. The difference in the mean induction time for those with Hemoglobin levels above the average haemoglobin of the study group (12g/dl) and those below the average haemoglobin level was not statistically significant, P.>0.05 Table IX.

The difference in the mean induction time between those with serum albumin levels below the average levels of the study group and those above the average serum albumin level was not statistically significant, P>0.05; Table X.

Induction was found to be generally smooth in majority of the patients (87.5%), while 8 (6.67%) developed respiratory upset-cough or hiccup and 7 (5.83%) developed spontaneous movements of the arms and face which was not related to pain at site of injection or light anaesthesia. Tables XIII and XIX.

Out of the 120 patients in the study 89 (74.2%) had their procedures done without the need for tracheal intubation and the patients were under face mask with spontaneous breathing. The rest 31 (25.8%) required intubation. The incidence of apnoea in this study group was found to be 25.8% that is 23 patients out of 89 patients under mask anaesthesia developed transient apnoea at

induction. These patients were assisted in ventilation till they resumed adequate spontaneous breathing.

Pain at the injection site was not noted in any of the patients involved in this study.

Cardiac arrest (was not noted or) did not occur in this study group of patients who were induced with Midazolam.

Haemodynamic changes

Pulse rate changes

The mean basal pulse rate of the study group was 90.6±12.88 before induction of anaesthesia with a range from 66 to 120 beats/minute, and median of 89.5 beats/minute.

The mean pulse rate at 5 minutes after induction of anaesthesia with Midazolam was 109.58±11.26 beats/min. with a median of 110beats/minutes and ranged from 70 to 130 beats/minute.

The change in pulse rate mean between basal and 5min after induction of anaesthesia was 18.95 which is statistically significant, p-value<0.05. Table V

The mean change in pulse rate for those with low Haemoglobin levels was 18.60 compared to 19.14 for those with Haemoglobin level above average. This change was not statistically significant , P>0.05 Table VI

The mean change in pulse rate in those with serum albumin levels above average when compared to the mean change in pulse rate in those with serum albumin levels below average was not statistically significant, P>0.05; TableVII.

On the other hand the mean change in pulse rate between those who were intubated when compared to the mean change in those who were not intubated, the changes are statistically significant, P<0.05; Table VIII.

The change in pulse rates mean between baseline and at the end of procedure was statistically significant, P<0.05; Table XI.

Blood pressure

The mean systolic blood pressure at base line and at 5minutes following induction of anaesthesia with Midazolam, shows a mean change of systolic Blood Pressure which was statistically significant, P>0.05; Table V.

The mean Diastolic Blood Pressure at baseline and at 5 minutes after induction with Midazolam, shows a mean change which was Statistically significant, P<0.05; Table V.

The mean change in systolic blood pressure and diastolic blood pressure in those with hemoglobin level below average when compared to the mean change in those with hemoglobin levels above

average, the change was not statistically significant, P>0.05; Table VI.

The mean change of Systolic Blood Pressure and Diastolic Blood Pressure from baseline to 5 minutes after induction of anaesthesia with Midazolam, in those with serum albumin levels below average was not statistically significant when compared to the mean change observed in those with serum albumin levels above average , P>0.05; Table VII.

However the mean change in Systolic Blood Pressure and Diastolic Blood Pressure observed in patients who were intubated when compared to mean change in observed in those who were not intubated, the change was statistically significant, P<0.05; Table VIII.

The change in mean Systolic Blood Pressure and Diastolic Blood Pressure between baseline and end of procedure readings was not statistically significant, P>0.05; Table XI.

Recovery:

In this study a total of 31 patients were intubated and required addition of an inhalational agent halothane and a muscle relaxant and an opioid to facilitate provision of good condition for surgery as well as adequate air way protection against aspiration in those with full stomach. Whereas a total of 89 patients had their procedures

performed under Midazolam and oxygen supplement with or without halothane given by facemask. The mean awakening time for the entire study group was 11.8±6.27minutes. The range was from 5minutes to 30 minutes.

The mean awakening time was shorter for those who were intubated and given halothane, oxygen and muscle relaxant, compared to those who received mask anaesthesia with oxygen and halothane. This difference is statistically significant, $P<0.05$; Table XX.

The difference in the mean awakening time of those who had low Hemoglobin and those with Hemoglobin above the average level was not statistically significant, $P>0.05$; Table XV.

The difference in the mean awakening time between those with serum albumin level above the average and those with serum albumin level below average was not statistically significant, $P>0.05$; Table XVI.

The mean orientation time for the entire study group of patients was 18.38±7.06 minutes. The range for the orientation time was from 8 to 36 minutes for the study population.

The difference in the mean orientation time between those with Hemoglobin levels above average and those with Hemoglobin level below average was not statistically significant, P>0.05; Table XVII.

The difference in the mean orientation time between those with serum albumin levels below average and those with serum albumin levels above average was not statistically significant, P>0.05; Table XVIII.

Correlation between the awakening time and orientation time with the duration of anaesthesia was determined and found to be statistically significant. With the respective correlation coefficients r and F statistics being r=-0.56, F=53.28 for awakening time and r=-0.48, F=35.97 for orientation time.

The incidence of adverse effects observed during induction or the recovery period was 13.3% for headache & dizziness, 13.3% for nausea and vomiting or retching, 25.8% for apnoea, 6.7% for respiratory upsets and 5.8% for excitatory phenomenon, Table XIII.

The proportion of these incidences in those with low serum albumin levels were headache and dizziness 20% (56.25%), nausea, retching or vomiting 22.2% (62.5%), apnoea 42.9% (65.2%) respiratory upsets 6.67% (37.5%) and excitatory phenomenon 11.11% (71.43%). The number in brackets represents the contribution of those with low serum albumin level to the total

occurrence of these incidences in the study group. These results show a higher incidence of these side effects in those with serum albumin levels below the average value of the study population. However only the proportion of apnoea, nausea and vomiting in those with low serum albumin levels was statistically significant when compared to that in those with normal serum albumin levels, $P<0.05$; Table XIII.

TABLES OF RESULTS

TABLE. I. PATIENTS AGE AND SEX DISTRIBUTION:

AGE GROUP	MALE	FEMALE	TOTAL
16 – 25	7 (21.9%)	25(78.1%)	32 (26.7%)
26 –35	8 (20.0%)	32 (80.0%)	40 (33.3%)
36 – 45	12(70.6%)	5 (29.4%)	17 (14.2%)
46 – 55	6 (66.7%)	3 (33.3%)	9 (7.5%)
56 – 65	9 (47.4%)	10 (52.6%)	19 (15.8%)
66 – 75	2 (66.7%)	1 (33.3%)	3 (2.5%)
TOTAL	44 (36.7%)	76 (63.3%)	120 (100%)

Mean age=36±14 years; Range 16 to 68 years.

TABLE. II. NUMBER OF PATIENTS AGAINST WEIGHT BOTH SEXES:

WEIGHT (KG)	NO	%
40 – 50	8	6.7
51 – 60	41	34.2
61 – 70	70	58.3
71 – 80	1	0.8
TOTAL	120	100

Mean Weight 62.6 ± 6.1Kg.; Range 45 to 75 Kg.

TABLE.III. DISTRIBUTION OF SURGICAL PROCEDURES:

PROCEDURE	FREQUENCY	%
GYNAECOLOGICAL	61	50.83
GENERAL SURGICAL	37	30.83
UROLOGICAL	13	10.84
ORTHOPAEDIC & TRAUMA	9	7.50
TOTAL	120	100

TABLE. IV. DISTRIBUTION OF MEAN INDUCTION TIME (SECONDS):

	MEAN	STD DEV.	CASES
MALE	69.14	14.60	44
FEMALE	67.04	14.00	75
TOTAL	67.815	14.198	119

F statistics=0.00; P=0.97

TABLE.III. DISTRIBUTION OF SURGICAL PROCEDURES:

PROCEDURE	FREQUENCY	%
GYNAECOLOGICAL	61	50.83
GENERAL SURGICAL	37	30.83
UROLOGICAL	13	10.84
ORTHOPAEDIC & TRAUMA	9	7.50
TOTAL	120	100

TABLE. IV. DISTRIBUTION OF MEAN INDUCTION TIME (SECONDS):

	MEAN	STD DEV.	CASES
MALE	69.14	14.60	44
FEMALE	67.04	14.00	75
TOTAL	67.815	14.198	119

F statistics=0.00; P=0.97

TABLE. V. HAEMODYNAMIC CHANGES AT 5. MINUTES AFTER INDUCTION WITH 0.3Mg/Kg OF MIDAZOLAM.

	MEAN AT BASE LINE	MEAN AT 5.MINUTES	MEAN CHANGE $d= (X_2 - X_1)$	p-value & T statistic
SBP	119.75±8.19	118.08±10.17	-1.67	P=0.04 T=2.11
DBP	78.29±5.92	76.50±7.12	-1.79	P=0.00 T=3.06
PR	90.63±12.88	109.58±11.26	18.95	P=0.00 T=8.32

TABLE. VI. HAEMODYNAMIC CHANGES AT 5. MINUTES AFTER INDUCTION IN THOSE WITH HB LEVELS ABOVE & BELOW AVERAGE.

GROUP A LOW HB LEVEL (<12) N=42	MEAN AT BASE LINE	MEAN AT 5.MIN	MEAN CHANGE $d= (X_2 - X_1)$
SBP	119.40±9.77	117.27±9.25	-2.14
DBP	78.33±6.78	76.31±6.15	-2.02
PR	92.74±12.91	11.33±11.24	18.60
GROUP B NORMAL B.LEVEL (≥12) N=78			
SBP	119.94±7.27	118.53±10.66	-1.41
DBP	78.27±5.45	76.603±6.03	-1.67
PR	89.5±12.80	108.64±11.23	19.14

SBP; F statistics=0.11; P=0.74
DBP; F statistics=0.02; P=0.89
PR; F statistics=0.17; P=0.67

TABLE. VII. HAEMODYNAMIC CHANGES AT 5. MINUTES AFTER INDUCTION IN THOSE WITH SERUM ALBUMIN LEVEL BELOW AND ABOVE AVARAGE.

SERUM ALBUMIN BELOW AVARAGE N=45	MEAN AT BASE LINE	MEAN AT 5.MIN	MEAN CHANGE $d = (X_2 - X_1)$
SBP	122.11±8.83	119.34±10.47	-2.44
DBP	79.74±6.87	76.58±7.63	-3.11
PR	90.53±9.95	110.24±9.37	19.67
SERUM ALBUMIN ABOVE AVARAGE N=75			
SBP	118.66±7.7	117.5±10.04	-1.20
DBP	77.62±5.34	76.46±6.92	-1.00
PR	90.68±14.09	109.28±12.08	18.52

SBP; F statistics=0.45; P=0.50
DBP; Fstatistics=2.49; P=0.12
PR; Fstatistics=0.53; P=0.47

TABLE. VIII. HAEMODYNAMIC CHANGES IN PATIENTS INTUBATED AND THOSE NOT INTUBATED 5. MINUTES AFTER INDUCTION WITH MIDAZOLAM: ASSESMENT OF RESPONSE TO TRACHEAL INTUBATION

INTUBATED n=31	MEAN AT BASE LINE	MEAN AT 5.MIN	MEAN CHANGE $d = (X_2 - X_1)$
SBP	116.61±6.38	123.55±10.42	6.94
DBP	77.10±4.79	81.13±6.80	4.03
PR	92.81±14.96	111.23±14.15	18.48
NOT INTUBATED			
SBP	120.84±8.50	116.18±9.42	-4.66
DBP	78.71±6.24	74.88±6.53	-3.82
PR	89.88±12.07	108.99±10.09	19.11

FOR SBP: χ^2=21; P=0.01

FOR DBP: χ^2 =18.14; P=0.01

FOR PR: χ^2=64; P=0.00

TABLE IX. MEAN INDUCTION TIME IN THOSE WITH LOW HEMOGLOBIN AND THOSE WITH NORMAL HEMOGLOBIN LEVELS.

	MEAN	STD DEV.(VAR.)	CASES
LOW HB	67	13.52(177.82)	42
NORMAL HB	68.26	14.62(213.59)	77
TOTAL	67.85	14.20	119

F statistic 0.21; P=0.64

TABLE. X. MEAN INDUCTION TIME IN THOSE WITH LOW SERUM ALBUMIN LEVELS AND THOSE WITH NORMAL SERUM ALBUMIN LEVELS.

	MEAN	STD DEV.	CASES
LOW SERUM ALBUMIN (<38)	68.5	17.10	44
NORMAL SERUM ALBUMIN(≥38)	67.43	12.30	75

F statistic=0.16; P= 0.69

TABLE. XI. HAEMODYNAMIC CHANGE AT THE END OF THE PROCEDURE.

	MEAN AT BASE LINE	MEAN AT END OF PROCEDURE	MEAN CHANGE $d=(x_2 - x_1)$
SBP	119.75±8.20	120.54±6.88	0.79
DBP	78.29±5.92	78.37±8.00	0.08
PR	90.63±12.88	100.86±11.65	10.23

FOR SBP: T STATISTICS 1.31; P=0.19;
FOR DBP: T STATISTICS 0.13; P=0.90;
FOR PR: T STATISTICS 12.61; P=0.00;

TABLE .XII MEAN AWAKENING TIME WITH RESPECT TO DURATION OF ANAESTHESIA

	MEAN AWAKENING TIME	STD. DEV	CASES
DURATION <30 MIN.	13.86	6.23	86
DURATION >30 MIN.	6.588	1.60	34
TOTAL	11.8	6.27	120

F statistic=44.90; P=0.00,

TABLE. XIII. INCIDENCES OF SIDE EFFECTS DURING INDUCTION OF ANAESTHESIA WITH MIDAZOLAM IN PATIENTS WITH NORMAL & LOW SERUM ALBUMIN LEVEL

SIDE EFFECT	SERUM ALBUMIN LEVELS		TOTAL	P-VALUE Chi^2
	LOW N=45 (N=35)	NORMAL N=75 (N=54)		P=0.00
APNOEA	15 (42.86%)	8 (14.81%)	23 (25.84%)	Chi^2=9.33
RESPIRATORY UP SETS	3 (6.67%)	5 (6.67%)	8(6.67%)	P=0.71 Chi^2=0.14
HEADACHE & DIZZINES	9 (20%)	7 (9.33%)	16(13.33%)	P=0.10 Chi^2=2.77
NAUSEA & VOMITING	10 (22.22%)	6 (8%)	16(13.33%)	P=0.03 Chi^2=4.92
CARDIAC ARREST	0	0	0	
PAIN	0	0	0	
EXCITATORY PHENOMENON	5 (11.11%)	2 (2.68)	7(5.83%)	P=0.13 Chi^2=2.28

TABLE XIV. MEAN ORIENTATION TIME WITH RESPECT TO DURATION OF ANAESTHESIA.

DURATION	MEAN ORIENTATION TIMES	STD. DEV	CASES
<30MIN.	20.37	7.25	86
>30MIN.	13.32	2.74	34

Mean for the whole study group 11.8±6.26minutes.
F statistics=30.28; P=0.00

TABLE XV. THE MEAN AWAKENING TIME IN THOSE WITH LOW HEMOGLOBIN & THOSE WITH NORMAL HEMOGLOBIN LEVELS.

	MEAN AWAKENING TIME	STD DEV	CASES
LOW HB	12.83	5.98	42
NORMAL HB	11.22	6.39	78
TOTAL	11.8	6.27	120

F statistic 1.81; P=0.18

TABLE.XVI. THE MEAN AWAKENING TIME IN PATIENTS WITH LOW SERUM ALBUMIN LEVELS & THOSE WITH NORMAL SERUM ALBUMIN.

	MEAN AWAKENING TIME	STD. DEV	CASES
LOW SERUM ALBUMIN	12.36	6.28	45
NORMAL SERUM ALBUMIN	11.47	6.39	75
TOTAL	11.8	6.27	120

F statistic =0.57; P=0.45

TABLE. XVII. MEAN ORIENTATION TIME IN PATIENTS WITH LOW & NORMAL HEMOGLOBIN

	MEAN	STD. DEV	CASES
LOW HB (<12)	19.667	6.99	42
NORMAL HB (≥12)	17.679	7.011	78
TOTAL	18.375	7.058	120

F statistic =2.20; P= 0.14

TABLE. XVIII. MEAN ORIENTATION TIME IN PATIENTS WITH LOW SERUM ALBUMIN & NORMAL SERUM ALBUMIN LEVELS.

	MEAN	STD. DEV	CASES
LOW ALBUMIN	18.82	6.99	45
NORMAL ALBUMIN	18.111	7.14	75
TOTAL	8.38	7.06	120

F statistic=0.29; P=0.59

TABLE. XIX. INCIDENCE OF SMOOTH AND DISTURBED INDUCTION OF ANAESTHESIA.

	NO.	%
SMOOTH INDUCTION	105	87.5
DISTURBED INDUCTION	15	12.5
TOTAL	120	100

Chi^2=135; P=0.00

TABLE. XX. MEAN AWAKENING TIME WITH RESPECT TO INTUBATION.

	MEAN	STD. DEV	CASES
INTUBATED	8.23	5.54	31
NOT INTUBATED	13.05	6.05	89
TOTAL	11.80	6.27	120

Chi^2=17.19; P=0.00,

TABLE. XXI. MEAN ORIENTATION TIME WITH RESPECT TO INTUBATION.

	MEAN	STD. DEV	CASES
INTUBATED	14.90	6.03	31
NOT INTUBATED	19.58	7.02	89
TOTAL	18.38	7.06	120

Chi^2=10.60; P=0.00

Discussion:

In this study which involved 120 healthy patients, Midazolam (Dormicum®) was used as an induction agent at the dose of 0.3mg/kg. The induction of anaesthesia had a mean induction time of 67.82 ±14.20 seconds for the whole study group. This is comparable to the results obtained by other authors who defined induction time as the time taken from injection of the drug to loss of eyelid reflex [2,43,44,68,77,106]. Saarnivaara and coworkers had slightly longer induction time of 85 seconds at a dose of 0.34mg/kg , but it is within the range obtained in this study[96]. Premedication has been shown to reduce the induction time, in a study done by Verma et al, patients were premedicated with papaveretum, scopolamine and Fentanyl and had a lower induction time of 36 seconds[97]. Salonen and coworkers had longer induction time 122± 135, but these had used smaller dose of Midazolam[73]. In a study done by holloway et al also using a lower induction dose of 0.15mg/kg of Midazolam the induction time was similarly prolonged and ranged from 30 seconds to 220 seconds[2]

In general, induction of anaesthesia is considered to be rapid if the induction of anaesthesia occurs within one arm-brain circulation time (<60sec). Differences of few seconds within that time might not be

of any clinical significance. Thus the mean induction time of 67.815 seconds obtained in this study shows that Midazolam is accepted as rapid induction agent. This induction time is considered long when Midazolam is compared to other commonly used intravenous induction agents[40,79,96,97,98,99,106]. However the induction was gradual, calm and associated with less side effects.

When compared to the other benzodiazepines used for induction of anaesthesia like Diazepam and Flunitrazepam, Midazolam proved to be superior as far as its rapidity of induction, short duration of action as well as the relatively low dose required for induction of anaesthesia is concerned [100,101,102].

In this study the induction of anaesthesia was generally found to be smooth in majority of the patients with the incidence of disturbed induction of anaesthesia being 12.5%, the incidence of respiratory upsets i.e. cough and hiccups was 6.67% While the incidence of excitatory phenomenon was 5.83%. This incidence of cough and hiccups is higher when compared to 3.9% incidence obtained in other studies[107,109]. However these incidences are low compared to those obtained for other induction agents. The incidence of excitatory phenomenon for Midazolam of 5.8% obtained in this study is comparable to that of Thiopentone, which ranges from 0 to 6.7%,

Propofol 4.3% and propanidid 8%. However Methohexitone has the highest incidence of excitatory phenomenon of up to 90%. Ketamine has the most frequent occurrence of excitatory phenomenon in the form of involuntary muscle rigidity and hypertonicity[103]

The incidence for respiratory upset (cough, hiccups) was 6.67%, which is low compared to that observed when methohexital (13%) or propofol (8%) are used[93].

The incidence of transient apnoea in this study was found to be 25.84% this is comparable to the findings by other authors.[96,108,109] However this incidence is low when compared to that observed in studies done in premedicated patients. Jensen and Huttel had an incidence of almost 70%, the patients in this study were premedicated with Flunitrazepam 2mg on the eve of surgery and 0.05mg Fentanyl per 25 Kg. Body weight before induction with Midazolam[45,108]. This could explain the high incidence of apnoea observed in these two studies.

When compared to other induction agents the occurrence of apnea is less in those induced with Midazolam[99,107]. In fact apnoea in Thiopentone induction occurs as much as 5 times the occurrence in Midazolam induction, while in patients induced with Propofol the incidence is as high as 35 to 50% or even higher as observed in other studies.[105,106,107,108,] However Saarnivaara et al found that the duration

of apnoea was longest following induction with Midazolam 27seconds compared to propofol 12 seconds and methohexitone 14 seconds[96].

This incidence of apnoea and the fact that it may be prolonged rises the concern and it is imperative that, Midazolam at induction doses should be administered only by those trained in anaesthesia. Equally important facilities for artificial ventilation should be available for the support of the respiratory system during this period of apnoea.

Generally the incidence of smooth induction of anaesthesia in this study of more than 87% in unpremedicated patients reflect the suitability of Midazolam as an induction agent. This is in keeping with the fact that Midazolam facilitate the transition from consciousness to unconsciousness calmly and pleasantly with an amnesic effect, which is very valuable to patients undergoing the ordeal of anaesthesia and surgery. This smooth induction of anaesthesia is invaluable in debilitated patients or patients at an increased risk for any reason.

Induction of anaesthesia with Midazolam in this study was associated with changes in haemodynamic parameters like pulse rate, systolic and diastolic blood pressure. These changes were analyzed with respect to the haemoglobin levels, serum albumin levels and effect of intubation

The mean pulse rate of the study group changed from basal mean of 90.6±12.88 to 109.58±11.26 beats/min at 5 minutes after

of apnoea was longest following induction with Midazolam 27seconds compared to propofol 12 seconds and methohexitone 14 seconds[96].

This incidence of apnoea and the fact that it may be prolonged rises the concern and it is imperative that, Midazolam at induction doses should be administered only by those trained in anaesthesia. Equally important facilities for artificial ventilation should be available for the support of the respiratory system during this period of apnoea.

Generally the incidence of smooth induction of anaesthesia in this study of more than 87% in unpremedicated patients reflect the suitability of Midazolam as an induction agent. This is in keeping with the fact that Midazolam facilitate the transition from consciousness to unconsciousness calmly and pleasantly with an amnesic effect, which is very valuable to patients undergoing the ordeal of anaesthesia and surgery. This smooth induction of anaesthesia is invaluable in debilitated patients or patients at an increased risk for any reason.

Induction of anaesthesia with Midazolam in this study was associated with changes in haemodynamic parameters like pulse rate, systolic and diastolic blood pressure. These changes were analyzed with respect to the haemoglobin levels, serum albumin levels and effect of intubation

The mean pulse rate of the study group changed from basal mean of 90.6±12.88 to 109.58±11.26 beats/min at 5 minutes after