DEPARTMENT OF ANAESTHESIOLOGY

Head: DR. H. LWENO

KETAMINE ANAESTHESIA

(A Review and Personal Experience in some clinical cases of Ketamine-Diazepam anaesthesia)

A Dissertation submitted in partial Satisfication of the Requirements for the Degree of Master of Medicine, Anaesthesiology, University of Dar es Salaam.

By:

ANDREW M. HELLAR M.B.Ch.B. (Makerere University Kampala)

Supervisor:

Prof. Dr. J.F. CRUL, (Director)

Department of Anaesthesiology

University of Nijmegen

Nijmegen

Holland.

CERTIFICATE

This is to certify that this dissertation is the result of my sole effort. Help was obtained from one anaesthetic assistant in the preparation of drugs and equipment as well as preparation of the patient to undergo anaesthesia. All this was under my direction.

External examiner

DECLARATION

I declare that the whole of this work has not been submitted for a degree in any other University.

External examiner

CONTENTS Page:

ACKNOWLEDGEMENT 3

SUMMARY 5

PART I: A REVIEW OF THE LITERATURE

Introduction

History 8

Properties of Ketamine 14

Cardiovascular changes 16

Respiratory System 17

EEG Changes 18

Metabolism 18

PART II: CLINICAL ASPECTS OF KETAMINE 20

Ketamine in developing Countries 26

PART III: A PERSONAL EXPERIENCE IN SOME CLINICAL CASES OF KETAMINE-DIAZEPAM ANAESTHESIA.

Ketamine-Diazepam Anaesthesia..... 29

Patient and Method 29

Table I 30

Anaesthetic Technique 31

Measured Parameters 33

Table II (a) 35

Table II (b) 36

Contd.

Page:

Comment 37

Table III 38

Table IV 39

Comment 40

Table V 42

Criteria for acceptability 43

Comment 44

PART IV: DISCUSSION AND CONCLUSION

Discussion 46

Conclusion 50

References 51

ACKNOWLEDGEMENT

The department of Anaesthesiology, University of Dar es Salaam which has newly been started encourages both clinical and research work for both members of staff and residents.

At present for the degree of Master of Medicine Anaesthesiology, the course is stagged in two phases. The first phase consisting of pre-clinical postgraduate training, is done at the University of Dar es Salaam whereas the second phase which consists of clinical attachment is done at a recognised University Institute outside Dar es Salaam University.

For the clinical aspect which enabled me to write this dissertation, I am particulary grateful to the staff members of St. Radboudziekenhuis, University of Nijmegen, Holland for their constant assistance; and more especially to Prof. Dr. J.F. Crul, Director of the institute of Anaesthesiology who constantly advised, encouraged and supervised this study.

I am also grateful to the surgical colleagues who allowed me to carry out my investigations on their patients and to the nursing staff both in the operating theatre and recovery room to whom this study would never have been possible without them.

I am also particularly greatful to Dr. H. Lweno, Head of the department of anaesthesiology Dar es Salaam University, and to Dr. E.A. Swai, who together assisted me in correcting and making few recommendations for the dissertation. Lastly and not least to Mrs. H. Msisi for her secretarial work.

To all I owe my most sincere gratitude.

Dar es Salaam.

August 1980.

SUMMARY

A literature Survey of ketamine anaesthesia has been reviewed including personal clinical experience in some cases.

Ketamine hydrochloride (Ketalar) has been found to be a good anaesthetic agent with strong analgesic and hypnotic properties. The only draw back is its cardiovascular stimulating effects which are not diserable in certain situations. There is an increase in both systolic and diastolic blood pressure as well as pulse rate. This is associated with an increase in cardiac output, and coronary blood flow. Cerebral blood flow is also increased. Despite the increase in coronary blood flow, there is a reduction in the total oxygen contents in the coronary sinus because of an increased myocardial oxygen consumption. The increase in blood pressure, however, makes Ketamine a drug of choice for induction of anaesthesia in shocked patients.

Because of the above-mentioned cardiovascular stimulating properties ketamine has to be used with caution in heart surgery, pre-existing hypertention, and coronary insufficiency. In obstetrics it has also to be used with caution because it can cross the placenta easily due to its high lipid solubility.

The other problem with ketamine anaesthesia is its psychotomimetic effects which affect mostly adults. These make the drug rather unpopular. However, premedication with drugs such as diazepam or lorazepam reduces the psychic effects and increases patients' acceptability to ketamine anaesthesia.

Other drugs have been tried for the reduction of its cardiovascular stimulating effects. Lobetalol which has both α and β blocking properties has proved to be a promissing drug and is worth of further investigations. In developing countries such as Tanzania ketamine proves to be a very useful drug. It is very popular and has been administered by less qualified people. Complications might have happened without much notice due to lack of proper documentation, as it is with the other fields of Medicine. It is therefore advisable to teach all people who will administer Ketamine anaesthesia to be aware of the techniques, indications, contrindications and complications of the drug. Lastly ketamine anaesthesia is a rather expensive method of administering anaesthesia and should not therefore, whenever possible, replace other conventional methods such as regional block techniques.

PART I

A REVIEW OF THE LITERATURE

1:1 Introduction

HISTORY

Intravenous anaesthesia was first introduced into clinical practice with sodium thiopentone forty years ago. Thiobarbiturates, with thiopentone as the prototype are widely used as induction agents because of their rapid onset and short duration of action. The less desirable aspects of their use include:

a. increased sensitivity to somatic pain. (Dundee 1960)

b. limitation of the route of administration, i.e. only intravenously.

c. Large doses are required to obtund reflex response to surgery when this agent is used as the main or sole anaesthetic. Hence frequent injections are necessary. This leads to overdose at the end. The potential for drug interaction and cumulative dose effect is obviously increased because of this long (non neural) tissue half life.

d. Thiobarbiturates can cause profound circulatory and respiratory depression such that they are relatively contraindicated as the sole

anaesthetic agents in the aged as well as in the presence of hypovolaemia.

e. Termination of thiopentol's anaesthetic action appears as a result of redistribution primarily, as it is only slowly metabolised by the liver and excreted via the kidney; a substantial proportion of a given dose remains in the body (i.e. fat), following recovery from its anaesthetic effect.

There was therefore a need for a safe, potent and short acting parenterally administered anaesthetic, which combines analgesia and sleep producing effect, without significant cardiovascular or respiratory depression. This led to the clinical evaluation of the Phencyclidine compounds. Preliminary clinical study by Meifentein et al (1955) on the clinical usefulness of phencyclidine as an anaesthetic agent, showed that although it produces an adequate anaesthetic state in most patients, its undesirable and occasionally long lasting non-reversible psychotomimetic side effects during the post anaesthetic period, precluded its wide spread clinical acceptance.

As a result of research to find an analogue of phencyclidine that would provide adequate surgical anaesthesia and rapid recovery without its prominent psychotomimetic properties, ketamine

(2 - O - Chlorophenyl) - 2 - (methylamino) - cyclohexone hydrochloride, initially refered to C1 - 581, was synthesized in 1961. Ketamine was introduced as an agent capable of producing a unique anaesthetic state, unlike the common inhalation and injectable anaesthetics. It was characterized by a state of katalepsy where the eye remain open with a slow nystagmic gaze. The corneal and light reflexes, and occational seemingly purposeful movememnts correlated to painful stimuli were noted in the presence of surgical anaesthesia (Domino 1965).

The so called "dissociative" anaesthetic state produced by ketamine was described as a functional dissociation between the thalamocortical and limbic system where profound analgesia was coupled with a somnolent state in which the subject did not appear to be anaesthetised but rather "disconnected" from the surrounding environment (Corsen et al 1968).

Preliminary observations indicated that ketamine has a shorter, more controlable duration of action, and less propensity of inducing seizures and severe emergence phenomenon as the chemically related phenylcyclochexalamine compounds (McCathy et al 1965). Domino et al (1965) in his studies in human volunteers confirmed that ketamine would be more suitable than its parent drug for clinical anaesthesia. The early clinical experience with ketamine indicated that it produces transient but minimal depression of respiratory function, elevation of both systolic and diastolic blood pressure

and occasionally emergency reaction: in adults consisting of a transient phase of vivid dreaming, with or without psychomotor activity, manifested by confusion; change in mood and affect, irrational behaviour and halluciantions (Domino et al 1965; Corsen & Domino 1966). These later psychotomimetic effects appear to be controllable by avoiding early verbal and tactile stimulation and/or by the administration of a small dose of short acting sedative hypnotic drug (Corsen et al 1965, Lofty et al 1970).

According to data compiled by the manufactures of this drug from over 1,500 cases, Corsen & Domino 1966 the most common complications were:-

1. transient abnormal change in blood pressure, and heart rate 13%
2. inadequate pulmonary gas exchange secondary to mechanical causes such as increased secretions and/or obstruction of the upper airway - 5%.
3. Emergence phenomenon including hallucination, euphoria, disturbance of body image, and numbness - 7%.
4. Finally seemingly purposeful movement of the extremeties, vomitting and other post anaesthetic complications - 3%.

The major undesirable characteristics of this drug include the production of hypertension, tachycardia and psychic changes. Ketamine was initially advitised as a potent, rapid and short acting parenterally

administered anaesthetic with profound analgesia outlasting the duration of unconsciousness. It was considered to be useful in brief diagnostic and surgical procedures especially in children where psychic abberations were uncommon (Roberts 1967, Corsen et al 1969, Wilson et al 1969). A further advantage of ketamine in paediatrics is that induction can be achieved with only a single intramuscular injection and transient to general anaesthesia was smooth and accompanied by stable vital signs.

Ketamine proved to be useful in radiotherapy in order to overcome the difficulty in providing adequate sedation to the patient without the anaesthetist being inside the irradiation area (Corsen 1972, Baltmore 1973, Amberg & Crordon 1976). Ketamine was also employed with good results in patients undergoing anaesthesia for debridment, and grafting of acute burns. It was also used in reconstructive plastic surgery for removal of burn contracture scars, without tolerance development (Wilson et al 1969b, Seingold & MacMahou 1975, R. Sachez et al 1978).

After extensive clinical investigations including nearly 2000 anaesthetic administration, ketamine hydrochloride (ketalar) was approved in 1970. The clinical use for which ketamine was initially recommended include:

1. Brief minor surgical and diagnostic procedures that didn't require skeletal muscle relaxation

(e.g. Incission &Drainage Abses, G.I.T. endoscopy, cardiac catheterization, otorhino-laryngology, opthalmologic and neuroradiologic procedures).

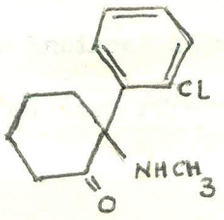
2. Induction of inhalational anaesthesia where the intramuscular route of administration was preferred or when an ultra short acting barbiturate induction was contraindicated on avoidance of cardiovascular depression.
3. To supplement low potence nitrous oxide/oxygen anaesthesia.

However, in spite of all these advantages, the use of ketamine in adults in many places remain controversial because of the reportedly high incidence of undesirable side effects associated with induction and emergence (King & Stephen 1977, Sunder et al 1970 & 1971, Morgan et al 1971, Winters 1972b). Many investigators have reported its use with minimal complications (Corsen et al 1968, Oduntan & Cool 1970, Lorhan & Limpman 1971, Sauchez et al 1971, Mag bag beokla 1971, litte et al 1972, Walker 1972, Klose & Peter 1973 Langrehr & Heutman 1973, Bidwar et al 1978, Elnaggar et al 1973.)

1:2 PROPERTIES OF KETAMINE

1. Physical properties:

Ketamine hydrocloride (Ketalar) is 2- (o-chlorophenyl) -2 (methylamine) cyclohexanone hydrochloride respresented by the structural formular:



It is a white crystaline solid, soluble in water to a 20% clear solution, which is stable at room temperature. The base component is 86,7% of the salt. The solution has a ph between 3.5 and 5.5. Benzethonium hydrochloride is added as a preservative.

Ketamine hydrochloride is also highly lipid soluble.

2. Pharmacological actions:

Ketamine has unusual anaesthetic properties in that it produces unconsciousness plus profound analgesia.

Pharmacological studies indicate that whereas conventional

anaesthetic agents result in cardiovascular depression, ketamine's transient haemodynamic effects appear to be a resultant of both inhibitory and excitatory actions. According to Traber et al(1968 & 1970) ketamine has both direct depression effects on the cardiovascular system as well as indirect stimulatory effects. The indirect stimulatory effects predominate at lower doses.

Cardiovascular changes

At higher doses and in the absence of both sympathetic and vagal control, the elevation on heart rate, blood pressure and cardiac output were diminished through a direct depression effect on the myocardium (Faber 1965, Treese et al 1973, Schwartz & Howitz 1975). The elevation of heart rate and blood pressure were abolished by a ganglion blocker. It was further postulated that residue pressor response produced by ketamine after muscarinic blockade were mediated via the sympathetic nervous system. Furthermore the absence of a significant effect by adrenergic blockade on the cardiovascular response to ketamine implied that neither sympathetic innervation to the heart, nor circulating endogenous catecholamines were responsible for the cardiostimulatory effects (Kumor et al 1975).

It was concluded that ketamine increased adrenergic discharge and reduces vagal discharge to the heart such that in the absence of sympathetic and vagal influence, the drug exerts a negative ionotropic effect on the myocardial contractility. Cardiovascular studies in humans by Kreuscher and Crauch (1967) and Virtual et al (1967) indicate that the pressor response observed during induction of anaesthesia with ketamine was due primarily to an increased cardiac output. Ketamine has also been found to produce a significant decrease in coronary sinus oxygen content despite an increase in

myocardial oxygen consumption. It has also been shown to increase cerebrolspinal fluid (C.S.F.) pressure and presumably intracranial pressure secondary to increase cerebral blood flow (Dawson et al 1972, Tatceshita et al 1972, Crardner et al 1971, Evans et al 1971 and Shapiro et al 1972.)

RESPIRATORY SYSTEM

On the respiratory system, ketamine does not alter markedly respiration although depression on minute ventilation often occur immediately after parenteral administration of a large dose of the drug (McCathy et al 1965, Corsen and Domino 1966, Pander 1971, Coppel and Dundee 1972).

The mild respiratory depression produced is rapidly followed by a return to baseline ventilatory volumes without loss of carbon dioxide responsiveness (Virtue et al 1967). However, Folts et al (1965) reported significant decrease in minute ventilation when ketamine was administered with a sedative hypnotic/narcotic mixture.

Various investigators have noted preservation of pharyngeal and laryngeal reflexes with maintenance of an adequate airway without intubation (Wilson et al 1967, Virtual et al 1967, Doubrava Sharson 1971, Larnning and Harmel 1975). Nevertheless tracheal soiling and aspiration have been noted after ketamine induction (Penrose 1972). Ketamine also stimulates salivary gland secretion which must be

blocked by an antisialogogue (Lanning & Harmel 1975) agent. Respiratory airway resistance is not altered by ketamine although it does decrease the overal chest compliance (Watermath & Vergman 1974).

EEG Changes

The electro encephalographic (E.E.G.) changes observed during ketamine anaesthesia have been interpreted to imply that sensory impulses might indeed reach the cortex but they are not percieved because of depression of the association areas of the brain (Corsen & Domino 1966, Corsen et al 1968). Both the E.E.G. changes and the psychotomimetic side effects observed during ketamine anaesthesia have all been reported as temporary changes.

Metabolism

A brief mention of the metabolism of ketamine is necessary. Ketamine undergoes n-demethylation and hydroxylation of the cyclohexanone ring with the formation of conjugates which are excreted in the urine. The unconjugated n-demethylated metabolite has 1/6 the potency of ketamine and the unconjugated cyclohexanone derivatives have only one tenth the potency of ketamine. The duration of analgesia is much more prolonged due to these metabolites (I & II) while in actual fact their hypnotic effects are much shorter due to the fact that the metabolites are not as effective in producing hypnosis.

PART II

CLINICAL ASPECTS OF KETAMINE

2:1 III CLINICAL ASPECTS OF KETAMINE

The introduction of the drug ketamine to clinical anaesthesia by Corse and Domino in 1966 brought in a promising and new dimension to the practice of anaesthesia. The drug definitely produces both good analgesia and hypnosis with a relatively stable cardiovascular system and an adequate maintenance of the airway.

However as already mentioned both circulatory, respiratory as well as pharyngeal and laryngeal reflexes can be affected. The main disadvantage of ketamine are the hypertension and tachycardia, which are not desired in certain circumstances such as pre-existing hypertension, coronary insufficiency and in cardiac surgery.

There is also undersirable psychotomimetic effects observed during the post operative period.

Various investigators have tried to find ways to minimise some of these effects.

2:2 In 1976, Hatano et al, investigated whether small doses of ketamine when administered with a micro infusion technique with a result of a more even blood level will provide sufficient analgesia throughout the operation and a more stable haemodynamic status without undersirable respiratory depression. Hatano et al also used diazepam premedication and an intra various bollus dose of diazepam 0.3 mg/kg and 1 mg/kg ketamine hydrocholoride during induction.

The use of diazepam was intended to minimise the post anaesthetic psychtomimetic side effects.

Their patients were undergoing open heart surgery for various corrective procedures.

The results for the 200 cases were excellent.

Induction and maintenance was simple and smooth.

The effects on the cardiovascular and respiratory systems were minimal. There was a wide margin of safety and 100% oxygen can be given whenever required.

Hallucinations, dreams and excitement were almost totally absent.

The same authors (Hatano et al 1978) extended their use of ketamine microdrip infusion in combination with an intravenous dose of diazepam during induction.

The patients were premicated with either diazepam, droperidol or hydroxyzine, in combination with scopolamine or atropine.

Their results indicated that patients premedicated with droperidol and scopolamine were the most sedated at the time of induction and had the slowest emergence especially in the geriatric age group. Excitement was seen in four out of the 250 patients and this was easily controlled with droperidol 2.5 to 5mg. Four patients reported dreams but no patient developed hallucinations. No patient recalled surgery and all had antero-grade amnesia.

2:3 This followed evaluation of several premedications to attenuate the psychotomimetic effects of ketamine. Lilburn et al (1978) evaluated the effect of diazepam, Lorazepam, flunitrazepam, neurolept combination, hydralazine and promethazine in reducing emergence exitement or delirium and unpleasant post anaesthetic

dreams. This study was carried out in patients undergoing minor gynaecological procedures.

The drugs were given 10 minutes before induction of anaesthesia, induction was done with 2 mg/kg of ketamine intravenously and maintained with an intermittent dose of ketamine 0.25 mg/kg. body weight as needed. The best results in attenuating the psychotomimetic effects were obtained with lorazepam seconded by flunitrazepam. Dundee and Lilburn (1978) investigated the effect of lorazepam 4 mg given either i.v. 30 - 40 minutes preoperatively, 60 minutes i.m. preoperatively, or orally 90 minutes preoperatively to 205 patients undergoing minor gynaecological operations. The induction doses of ketamine was either 05, 1, 1.5 mg/kg and 2 mg/kg body weight, intravenously. The result shows that lorazepam premedication did not have any obvious effects on the occurrence of excitatory effects (Tremor, involuntary muscle movement of hypertonous) of ketamine. The result show that with the small dose of ketamine 0.5 mg/kg the incidence of rise in BP of more than 20 mm Hg, systolic was significantly less after i.m. lorazepam. The protection offered by oral lorazepam was less marked but significant. In contrast with the higher dose of 2.0 mg/kg, lorazepam premedication did not reduce the incidence of hypertension. However the preoperative administration of lorazepam by any of the three routes virtually abolished the occurrence of severe

emergence delirium following ketamine. Mild delirium occurred frequently, but was not a problem. It was mostly associated with oral lorazepam and 2 mg/kg ketamine. More observation on the technique, dosage, and cardiovascular effects were done by Lilburn, Dundee and Moore (1978). The initial study which included 20 patients was done to determine the adequate average dose which will provide sufficient anaesthesia in spontneously breathing patients. This is because on giving a paralysing dose of a muscle relaxant the obvious signs of adequate anaesthesia are abolished, and there is a danger of a return to consciousness when supplementary inhalational drugs are not given.

After this study patients were induced with ketamine and maintained on an infusion of ketamine 0.1% and muscle relaxants. Various non depolarising muscle relaxants were tried. The combination of ketamine and gallamine was abandoned because of the chronotropical effects of both drugs. Cardiostimulatory effect was greater in patients relaxed with pancuronium because of the vagolytic action of pancuronium than in those relaxed with d-tubocurarine.

There was greater patient acceptability of the anaesthesia, less emergence sequelae and dreams. The preoperative use of lorazepam is supposed to have contributed to this effect.

At the same time proctalol failed to block the tachycardia resulting from the phentolamine-ketamine combination. Promethazine had a moderate vasodilatory effect, but 25 mg. i.v. failed to block the cardiostimulatory effect of ketamine. Hexamethonium which is a ganglion blocker was effective in blocking ketamine hypertention in 3 out of 4 cases, but caused an unacceptable degree of tachycardia and was followed by prolonged post operative hypotention, and visual disturbances. Procainamide: This is a local anaesthetic with a direct myocardial depressant effect. It proved to have no effect on the cardiostimulatory action of ketamine,

Verampamil: This drug is a derivate of papaveretum, which blocks the uptake of the myocardial cell membrane of ionised calcium which is necessary for the breakdown of ATP by ATP ase. This action reduces myocardial contractility and is referred to as negative ionotropic action. It gave a good control of blood pressure, but was not effective in reducing the tachycardia.

Labetalol: A drug with both α and β adrenergic blocking properties, gave a fair to good control of blood pressure, and controlled the heart rate in most patients. Hence labetalol in

doses of 0.5 mg/kg to 1.0 mg/kg. proved to be the most promising drug and is worthy further study.

2:4 KETAMINE IN DEVELOPING COUNTRIES

Kamm and Bewes (1975) tried to investigate on a simple way of giving ketamine anaesthesia by continuous infusion using an ordinary drip set. They determined the dose and cost relationship in one of the developing countries (Tanzania). Ketamine is a very common drug in anaesthetic practice in Tanzania. It is usually used as an induction agent i.m. in children and mostly i.v. in adults and repeated i.v. injections can be used in short procedures such as dilatation and curretage of the uterus. In their study they found that in spontaneously ventilating patients an intravenous dose of 4 to 6 mg /kg body weight/hour is sufficent to maintain anaesthesia. When patients are ventilated, the dose required is 2 mg/kg. From the dose cost relationship, it is clear that the running cost of a draw over vapourizer such as an E.M.O. ether/air technique is cheaper than that of a ketamine infusion drip. They made no recommendation that ketamine should replace convensional anaesthetic technique such as E.M.O. ether/air or the use of regional blocks where applicable.

Hence the extent of the use of ketamine in anaesthetic practice still remains rather limited.

In some places such as Nijmegen University, it is not commonly used, and this applies to the majority of the developed countries such as the western European countries, whereas in developing countries such as Tanzania, it is so common that sometimes it is administered by less qualified personnel. This is due to the discovery in developed countries of better anaesthetic techniques, though expensive, such as neuroleptanaesthesia whereby more expensive drugs such as fentanyl and droperidol are used. In developing countries this would be considered a rather expensive technique and in fact such drugs are therefore not readily available except under special circumstances.

We therefore had to look on the safe method of administering ketamine anaesthesia which when modified could be used without much problem. The method can then be taught to those who will have to administer ketamine anaesthesia in places where there is even less supervision by a qualified anaesthesiologist. In places like Tanzania where sometimes nitrous oxide is not readily available the use of ketamine eliminates this problem. The patient can be ventilated with a simple technique of using an Ambu bag and a

mixture of air and oxygen, if the oxygen is available, or just air alone; and anaesthesia maintained with an infusion of ketamine and muscle relaxant.

PART III

A PERSONAL EXPERIENCE IN SOME CLINICAL CASES OF KETAMINE - DIAZEPAM ANAESTHESIA

3. IV KETAMINE - DIAZEPAM ANAESTHESIA

A study of ketamine anaesthesia in combination with diazepam was done at the University of Nijmegen, Holland. This was done with a view to minimising both the cardiovascular manifestations by the use of continuous ketamine infusion; and the psychotomimetic effects minimised by the use of diazepam.

3:1 PATIENT AND METHOD

Patients in this study included those with no history of psychosomatic disorders, non-alcoholics and those with no history of cardiovascular disorders. The age limit was between 15 and 60 years. The type of operations included those requiring muscle relaxation in general surgery such as intra-abdominal operations and those requring no muscle relaxation, in patients undergoing body surface operations. Table I below gives the patients number, age and type of operation done.

TABLE I

No.	AGE	SEX	TYPE OF OPERATION
1	16	m	Open reduction fracture tibia and repair tendon
2	24	m	Arthroscopy
3	23	m	Removal pins and plate right tibia
4	21	m	Corrective osteotomy tibia
5	33	m	Removal pins and plate tibia
6	48	f	Varices (L)
7	18	m	Appendicectomy
8	34	f	Breast tumour (L) excission biopay
9	25	m	Varices (L)
10	23	f	Excission biopsy neck tumour (L)

3:2 Anaesthetic technique

Patients were given 10 mg diazepem orally for night sedation, the night before the operation.

In the morning before the operation the patient received a dose of 0.25 mg of atropine intramuscularly and 10 mg diazepam orally one hour before the operation.

Induction: Patients were brought to the induction room where normal procedures such as placing an i.v. infusion, blood pressure cuff and ECG skin electrodes were done. Blood pressure and pulse were monitored before the induction.

The patient was then given an intravenous bollus dose of 0.2 to 3 mg/kg body weight of diazepam followed within one minute by an induction dose of ketamine 1 to 2 mg/kg body weight.

Most patients have a vacant appearance and usually the corneal and eyelid reflexes are not abolished. At this time a face mask was placed and the patient allowed to breath 100% oxygen. If intubation was necessary, the patient was given succinylcholine 1 mg/kg weight to facilitate intubation of the trachea, and continued to be ventilated with the 100% oxygen during the apnoea caused by succinylocholine.

Immediately after induction a drip infusion of 0.1% ketamine (1 ml = 1 mg of ketamine) in 500 ml glucose 5% was started using an Ivac drip apparatus which delivers 20 drops/ml. The ketamine infusion was connected to the normal dextrose/saline infusion through a T connector via the Abbocath intravenous cannula.

The initial rate was set at 40 to 50 drops/minute, and this was later varied according to the depth of anaesthesia. The aim was to provide a minimum dose of 1 mg of ketamine/kg/hour. The patient was transfered to the operating room, where monitoring of the blood pressure, pulse rate and depth of anaesthesia were continued at 10 minutes intervals from the time of induction.

If at any time anaesthesia was considered to be inadequate the drip speed was increased or an additional bollus dose of ketamine was given at the dose of 0.25 mg/kg. In case muscle relaxation was required, pancuronium bromide was given at the dose of 0.06 mg/kg body weight, The patient was then ventilated using a mixture of 30% oxygen in air with an ambu bag or a machine such as Engstrom or Drager which can deliver a mixture of air and oxygen. Small doses of valium, or pentothal (50 - 100 mg) were used at any time when rapid deepening of anaesthesia was required during surgery, The patient was closely observed for signs of sweating or any movements. At the end of operation the ketamine infusion was stopped 5 to 15 minutes before the end of anaesthesia and non-depolarizing neuromuscular drugs were reversed with mestinon (pyridostigmine), an anticholineterase drug, and atropine if the patient was still curarised. If the patient showed any signs of psychomotor disturbance 5 to 10 mg

of dominal Forte(prothipendyl hydrochloride)which is a tranquilizer and sedative, with an anti emetic effect, was given intravenously.

3.3. Measured parameters: In this study blood pressure and pulse were monitored immediately before induction and at an interval of an hour after the operation.
Capnograph, plethsmograph and ECG were monitored during the operation. After stopping the ketamine infusion the time for the patient to be fully conscious and well orientated was noted. The amount of ketamine used through the ketamine infusion drip and the duration of time from starting to stopping the infusion noted, and any additional doses. Any adverse signs and symptoms during anaesthesia were recorded during operation.
Postoperative complications such as hypertension, arrythmias and other cardiovascular manifestations as well as delayed emergence, excitation and delirium were noted.

At the end of the operation the surgeon was asked how he felt about this type of anaesthesia and also noting if the patient has been moving during surgery which gives a negative point from the side of the surgeon.

The nurses at the recovery room were also interviewed on the way they liked the recovery period of the patient and whether they had to give extra attention to the patient or give more analgesic drugs postoperatively. They were also asked whether the patient vomitted during the immediate postoperative period.

The patient was also visited the evening after the operation and the next postoperative day. The patient was specifically asked whether he/she was aware during the operation; if he had dreams and whether they were pleasant or upleasant. He was asked whether he felt pain at all, postoperatively and the time the patient received any analgesic was noted from the anaesthetic chart.

The patient was also asked whether he felt nauseated or vomitted after the operation.

Finally he was asked whether he was willing to undergo the same type of anaesthesia if he had to be operated again. This gives the acceptability of this type of anaesthesia to both anaesthetist, surgeon, nursing staff and most important the patient.

3:4 RESULTS

Changes in blood pressure and pulse are recorded in Table II (a) below:-

TABLE II (a)

CASE NO.	BP & PULSE BEFORE INDUCTION	BP & PULSE 10 Min. AFTER INDUCTION	CHANGES IN			BP & PULSE INTRA-OPERATIVELY	BP & PULSE POST-OPERATIVELY
			SYSTOLIC BP mm Hg	DIASTOLIC BP mm Hg	PULSE Rate/ min.		
1	140/80 70	150/90 80	+10	+10	+10	stable	stable
2	140/80 60	130/70 55	-10	-10	- 5	stable	stable
3	130/80 50	140/70 100	+10	-10	+50	stable	stable
4	140/80 64	160/80 110	+20	0	+50	stable after 30 min.	stable
5	160/90 108	165/100 110	- 5	+10	+ 2	stable after 45 min.	stable
6	120/80 72	130/85 90	+10	+10	+18	stable after 45 min.	stable
7	120/60 72	130/70 90	+10	+10	+18	stable	stable
8	130/70 80	130/80 110	0	+10	+20	stable	stable
9	130/80 80	140/90 105	+10	+10	+25	stable	stable
10	120/80 110	130/80 140	+10	0	+30	stable	stable

TABLE II (b)

CASE NO.	BEFORE			AFTER			Δ % MAP	Δ%HR
	BP	MAP	HR	BP	MAP	HR		
1	140/80	100	70	150/90	110	80	10	14.2
2	140/80	100	60	130/70	90	55	10	8.3
3	130/80	97	50	140/70	93	100	4.1	100
4	140/80	100	64	160/80	107	110	7.0	71.8
5	160/90	113	108	165/100	122	110	7.9	1.2
6	120/80	93	72	130/85	100	90	7.5	25
7	120/60	80	72	130/70	90	90	1.2	25
8	130/70	90	80	130/80	97	110	7.7	25
9	130/80	97	80	140/90	117	105	2.6	31.2
10	120/80	93	110	130/80	97	140	4.3	27.2
Mean SEM		96 96+9	77 77+20		101 101+9	99 99+20	6.2	33

COMMENT

Table II (b) above shows the mean arterial pressure before and 10 minutes after induction, calculated by the formular:

Mean arterial pressure = Diastolic pressure + $\frac{1}{3}$ (Systolic-Diastolic pressure)

It also shows the % change of the mean arterial pressure and the heart rate. The mean and standard errors of the means for both arterial blood pressure and heart rate are shown. By the Analysis of Variance, there is a statistically significant increase in blood pressure and heart rate.

Table II (a) shows an increase in systolic blood pressure of 20 mm Hg in one patient (case no. 4) which was also accompanied by an increase in pulse frequency not associated with a rise in blood pressure. This is not surprising since the main effect of ketamine is chronotropic and hence a significant effect on increase pulse rate for patient no. 3 and 4, while there is a significant rise in blood pressure and pulse, most patients remained stable within half an hour after induction and all patients had stable blood pressures and pulse rates during the post-operative period. No arrythmias were recorded post-operatively. Refer also table II (b) with explanations.

Table III below shows the dosage of ketamine required to maintain adequate anaesthesia during the operation and the effect of the dosage on the recovery time:

TABLE III

CASE NO.	DOSAGE OF KETAMINE IN mg/kg/hour	TYPE OF VENTILATION AND ANAESTHETIC GASES USED	DURATION OF THE OPERATION (min)	RECOVERY TIME (min)
1	4.5	N_{20}/O_2 - spont. magills syst	120	115
2	6.0	N_{20}/O_2 - spont. magills syst	50	48
3	7.0	Air/O_2 - Engstrom IPPV	40	150
4	5.6	Air/O_2 - Engstrom IPPV	70	33
5	2.0	Air/O_2 - Engstrom IPPV	20	8
6	6.0	Air/O_2 - Drager IPPV	60	28
7	5.2	Air/O_2 - Ambu Bag IPPV	35	60
8	4.6	Air/O_2 - Drager IPPV	100	120
9	4.0	Air/O_2 - Drager IPPV	120	80
10	5.7	Air/O_2 - Engstrom IPPV	45	70

Table IV below shows the induction doses of ketamine and valium and the additional doses of valium, and pentothal used during the operation.

TABLE IV

CASE NO.	AGE (YRS)	WEIGHT (KG.)	INDUCTION DOSE VALIUM (mg)	INDUCTION DOSE KETAMINE (Mg)	ADDITIONAL VALIUM (mg)	ADDITIONAL PENTOTHAL (mg)
1	16	40	10	50	15	100
2	24	74	20	100	-	-
3	23	80.3	25	150	5	150
4	21	74.5	25	150	5	200
5	33	87.5	25	175	5	100
6	48	67.9	25	150	10	50
7	18	65	20	130	5	50
8	34	67.5	20	135	5	250
9	25	74	22.5	150	-	-
10	23	70.5	20	140	-	-

COMMENT:

From table III and table IV above, the dose required to maintain anaesthesia is between 2 to 7 mg/kg body weight with an average of 5.0 mg/kg body weight. This dose includes the additional dose of ketamine used during surgery. The low dosage in case No. 5 can be explained due to the short duration of operation and at the same time the addition of 100 mg pentothal in total. No additional dose of ketamine was used for this patient, and he had also the shortest recovery time. The recovery time ranged between 8 minutes to 150 minutes and the longest recovery time was associated with the largest maintanance dose of ketamine in patient no. 3. We had to use nitrous oxide and O_2 in the first two patients because of technical difficulties in the operating room. We had no anaesthetic machine which could deliver Air/O_2 at that material time in the operating room and there was no ambu bag with an adequate valve to permit spontaneous breathing with out rebreathing.

The rest of the patients were ventilated with either an Engstrom or Drager anaesthetic machine, and one was ventilated using an ambu bag. Blood gas analyses were normal for this patient during the whole operation. The patients were also monitored with a capnograph and the end tidal PCO_2 maintained between 4 and 5.

TABLE V: ACCEPTABILITY OF ANAESTHESIA

CASE NO.	ANAESTHETIST	SURGEON	NURSING STAFF	PATIENT	EXCITEMENT, DREAMS DELIRIUM
1	reasonable	reasonable	reasonable	good	nil
2	good	good	good	good	nil
3	reasonable	reasonable	reasonable	good	nil
4	good	good	reasonable	good	nil
5	good	good	reasonable	bad	nil
6	good	reasonable	reasonable	good	nil
7	good	reasonable	rea good	good	nil
8	good	good	good	good	nil
9	good	good	good	good	nil
10	good	good	good	good	nil

Criteria for acceptability

Anaesthesia was considered reasonable by the anaesthetist if the patient showed slight movement which was easily controlled by administration of a small dose of pentothal or valium or additional ketamine and when the anaesthesia was not deep enough. The same applies to the surgeon. It was considered bad if the patient showed excessive movement, sweating and signs of light anaesthesia.

Anaesthesia was considered good by the nursing staff if there has been no postoperative vomiting delayed recovery or the necessity of extra care to the patient such as to ensure maintenance of an adequate airway at the recovery room.

The patient considered the anaesthesia good if he experienced no awareness during the operation. No postoperative nausea and vomiting, no dreams and if the patient was willing to undergo the same type of anaesthesia if he has to be operated again.

COMMENTS

The results are summerized on Table V above. Only one patient considered the anaesthesia bad because he had vomitted three times postoperatively. There was no patient who experienced bad dreams, excitement or delirium. The type of anaesthetic was considered good and reasonable for most of the surgeons.

No patient reported awareness inspite of some of the patients who had slight movement of the limbs. Sometimes the patient opened his or her eyes. This was not accompanied by any change in blood pressure, pulse rate and there was no sweating. This was abolished by a small dose of pentothal (50mg) or diazepam (2.5-5mg) or increasing the ketamine infusion drip speed.

One of the patients was operated in one operating theatre with facilities of an EEG monitor which was connected to the patient (case no. 3).

The EEG showed more cerebral activity as evidenced by increased spikes when additional ketamine was given. This is in keeping with the study done by Corsen and Domino (1966) and Corsen et al (1968) as reported before. The increased spikes were abolished when the additional ketamine was followed by a dose of 50 mg of pentothal.

PART IV

DISCUSSION AND CONCLUSION

DISCUSSION

From this study and other studies reviewed, it is obvious that ketamine has strong analgesic properties associated with good amnesia. The cardiovascular effects mostly seen include a tachycardia associated with hypertension. There is increased cardiac output and increased coronary artery blood flow. Due to increased myocardial work, there is a definate decrease in coronary sinus oxygen content as a result of increased myocardial oxygen consumption. This could be a disadvantage in patients with severe myocardial disease. However the increased cardiac output is sometimes beneficial in certain hypovolaemic states such as shock. Various research have been done to attenuate the cardiostimulatory effects of ketamine with little success. It is reported that labetalol which has both α and β adrenergic blocking properties should be further investigated.

When ketamine is used and muscle relaxation is necessary, it is better to avoid gallamine. Pancuronium bromide can be used although (in combination with ketamine) it may also produce an increase in heart rate. Some investigators found no evidence for this as already reported.

d-tubocurarine can be used safely if there is no contra-indications such as allergic reactions. It produces no tachycardia. Hence ketamine is to be avoided in patients with hypertension or other severe cardiovascular diseases where an increase in blood pressure and pulse could be detrimental to the patient. In women with pre-eclampsia (toxaemia of pregnancy) or pre-existing hypertension it is commonly accepted that a rise in blood pressure may induce eclampsia and ketamine is contra-indicated in these women. The uterine contractile effect of ketamine used in obstetrics causes reduction of blood loss after delivery (Roopnarine Singh 1974).

However this effect can be a serious disadvantage in cases of placental insufficiency and intra-uterine hypoxia, as it may cause reduction of uterine circulation prior to delivery. At the same time it has been shown that ketamine very rapidly passes the placenta, because of its high lipid solubility and relatively low molecular weight.

Anna Elington et al (1977) investigated 10 healthy mothers who underwent forceps delivery indicated by a delayed second stage of labour. Two of the newborns showed a low apgar score and one was probably attributed to the ketamine anaesthesia. Hence it is wise to use ketamine with care in obstetrics.

The other drawback of ketamine anaesthesia is its psychotomimetic effects. These have been shown to be reduced by the use of various premedicant drugs such as Diazepam, lorazepam and flunitrazepam. In our small number of cases no patient showed any psychotomimetic effects. By the evidence produced by other investigators these effects can effectively be reduced or abolished completely. There have been no serious post operative complications in our series.

One problem was the excessive secretions sucked out at the end of the operation. These can be blocked by atropine. The dose of atropine used in the first cases was 0.25 mg one hour preoperatively. This was thought to be inadequate and in the later cases a dose of 0.5 mg was used. There was some reduction in secretions. At certain places a dose of 1.2 mg of atropine is sometimes used pre-operatively. It is feared that this may produce an unacceptable tachycardia especially in combination with ketamine.

These reviews on ketamine and the personal experience reported here, show that ketamine can prove to be a useful anaesthetic drug in certain circumstances. Contra-indications are clear and easy to be understood by the practising anaesthesiologist, who can teach other doctors and medical staff on the use of this useful drug.

Ketamine has been used in many developing countries, and Tanzania is no exception. It has been widely used by trained anaesthetists, doctors and other junior staff. Problems encountered are not as serious as thought to be, though there hasn't been any proper documentation on the serious effects of ketamine. Since this drug is commonly used in Tanzania, I feel doctors, assistant medical officers, medical assistants and nurses should be taught on the use of ketamine, so that they are aware of the indications, contra-indications and the safety use of this drug. It can be administered for induction, maintainance in short cases by repeated injections or a ketamine drip infusion technique. If ventilation is required an Ambu bag can be used safely with or without the addition of oxygen. Nitrous oxide which is rare in some instances, is not necessary in this type of technique.

CONCLUSION

Ketamine can be used with much safety provided that the person who administers it is aware of its contra-indications, just as in many drugs used in anaesthetic practice. When patient safety is paramount to the point that vivid dreams are un-important, and when rapid analgesia with maintanance of circulation and respiration are needed and when relaxation is unnecessary, ketamine can be nothing short of magic!! For the majority of surgical procedures, methods of eliminating side effects have not been standardized Further research can certainly be continued to make this drug more acceptable and useful in anaesthetic practice. In this study valium has been used to attenuate the psychotomimetic effects of ketamine. It is easily available and not so expensive. Other drugs however have been used with good effect. To avoid pain and thrombophlebitis, diazepam should be injected slowly in a big vein, where the infusion speed can be made fast to dilute it.

REFERENCES

Albin, M.S., and Dresher, A.J. (1969)
Emergence reactions associated with the administration of ketamine hydrochloride (ketalar- Park-Davis)
Read before the anaesthesia symposium on anaesthesie vigile et subvigile ostend Belgium. April 17-20 1969.

Amberg, H.L., (1976)
Low dose intramuscular ketamine for paediatric Radiotherapy: A case report.
Anaesth. Analg. (Cleve) 54 (6): 800 - 5
Nov - December'75.

Barclay, B.A., Houlton, P.C., Downing, J.W., (1980)
Total intravenous anaesthesia a technique using flunitrazepam, ketamine, muscle relaxants and controlled ventilation of the lung.
Anaesthesia, 35, 281 - 290

Beekhuis, H.J., Klegon, R.B., Kann, D.L.,(October 1978)
Anaesthesia for facial cosmetic surgery: Low doses ketamine diazepam anaesthesia.
Laryngoscope 88, 1709 - 1712.

Bovil J.G., Dundee J.W.: (1972)
Alteration in Response to somatic pain associated with anaesthesia: Ketamine.
Br. J. Anaesth. 43: 496 - 500.

Bovil, J.G. Clarke R.S.J., Davis E.A., Dundee J.W., (1971)
Some cardiovascular effects of ketamine in man
Br. J. Pharmacology 41: 748.

Bovil J.G. Dundee J.W.: (1972)
Attempts to control the cardiostimulatory effects of ketamine in man.
Anaesth. 27:709

Chany T. Glazko A.Y. (1974)
Biotransformation and disposition of ketamine
Int. Anaesthesiology Cl.12; 159 - 177

Chodoff, P., Stella J.G., (1966)
use of Cl.581 - A phencyclidine derivative for obstetric anaesthesia.
Anaesthesia. Analg. 45:527.

Coppel D.L., and Dundee J.W., (1972)
Ketamine anaesthesia for cardiac catheterisation
Anaesthesia 27:25

Corsen et al: (1969)
Electro encephalographic effects of ketamine anaesthesia in children.
Anaesth. Analg. Curr. Res. 48:141

Corsen G., (1972)

Ketamine for high risk cardiac patients

Anaesthesiology 36:413. (April 1972).

Corsen, G., Gutierrez, J., Reves J.G. (1972)

Ketamine in anaesthetic management of asthmatic patients

Anaesth. Analg. (Cleve) 51:588 - 96 July - August'72.

Corsen, G., Allade, R., Brosch, F., Arbenz G., (1970)

Ketamine as a sole anaesthetic in open heart surgery.

Apreliminary Report

Anaesth. Analg. 49:1025

Corsen, G., Domino, E.F., (1966)

Dissociative anaesthesia. Further pharmacologic studies and first clinical experience with the phencyclidine derivative Cl-581.

Anaesth. Analg. (Cleve) 45: 29 - 39.

Corsen G., Miyasaka M. Domino, E.F. (1968)

Changing Concepts in pain control during surgery-dissociative anaesthesia with Cl.581.

Anaesth. Analg. (Cleve)47:746 - 759

Corsen, G., Groves E.H. Gomez, S., and Allen R.J.,
Ketamine: Its place in anaesthesia for neurosurgical diagnostic proceedures.
Anaesth. Analg. Curr. Res. 48:181.

Corsen G., Hayward, J.R., Gunter J.W., Groove R.H. (1969)
A new parenteral anaesthesia for oral surgery J. of oral surg.27:627

Dhadphale, P.R., Jackson, A.P.F., Alsen, S., (1970)
Comparison of Anaesthesia with diazepam and ketamine versus morphine in patients undergoing heart vulve replacement.
Anaesthesiology 51., 200 - 203.

Domino, E.F., Chodoff, Corsen, G., (1965)
PHarmacologic effects of GL 581, a new dissociative anaesthetic in man. Clinical Pharmacol. Ther. 6:279 - 291

Dowdy, E.C., Kaya, K., (1968)
Studies on the circulatory effects of Cl.581
Anaesthesiology 29:931 - 943.

Dundee J., Bovill, S.C., Clarke, R., et al (1971)
Problems with ketamine in adults.
Anaesthesia 26:56.

Dundee J.W., Lilburn, J.K., (1978)

Attenuation of psychic sequelae of ketamine by lorazepam.

Anaesthesiology 33: 312 - 314

Dundee J.W., Moore J.,

Alteration in response to somatic pain associated with anaesthesia I.

A method of Analgesimetry Br. J. Anaesth. 32:396.

Dundee J.W. (1960)

Alteration in responce to somatic pain associated with anaesthesia II

The effect of Thiopentone and phenobabitone

Br. J. Anaesth. 32:407 - 14. Sept.'60.

Ellington, A., Haram, K., Sagen, N., (1977)

Ketamine and Diazepam as anaesthesia for forceps delivery.

A comparative study.

Acta Anaesthesia Sca. 21: 37 - 40

Ellington, A., Haram, K., Sagen N., Solheim, E., (1977)

Transplacental passage of ketamine after intravenous administration.

Acta Anaesth. Scand. 21: 41 - 44

El-nagar et al (1975) ketamine as an induction agent and as an

adjunct to nitrous oxide-oxygen curare anaesthesia sequence.

Mid. East J. Anaesthesiology 4 (4) 14-22 Feb'75.

El-nagar M. et al. 1975.
Effect of ketamine on the blood pressure and pulse rate
(a comparison of thiopental and Fentanyl)
Mid. East J. Anaesthesiology 4(4) 29-42 Feb'75

Feingold et al (1975)
Patients preference for ketamine. A case report of multiple
Anaesthesia
Anaesth. Analg. (Cleve) 54 (1) 35-7 Jan-Feb'75.

Gassner S. Cohen, M., Aygan M., et al (1974)
The effect of ketamine on pulmonary artery pressure.
An experimental and clinical study
Anaesthesia 29: 141 - 146

Hatano, S., Keane, D.M. Boggs, R.E., Maggar, N.A., Sadove M.S., (1976)
Ketamine anaesthesia for open Heart Surgery.
A microdrip administration technique.
Canadian anaesthetist society Journal 23 No.6

Hatano S., Sadove, M.S., Boggs, R.E. (1976)
Diazepam ketamine anaesthesia for open Heart Surgery
"micro mini" drip administration technique.
Anaesthetist, 25; 457 - 463.

Hatano S, kean D.M. Watle M.A., Sadove M.S., (1974)
Diazepam Pentazocine Anaesthesia for cardiovascular surgery
Canadian Anaesth. Soc . J. 21:586.

Houlton, P.J.C., Dowing, J.W., Brockutine, J.A., (August 1978)
Intravenous ketamine anaesthesia for major abdominal Surgery.
An assessment of technique and the influence and ataractic drugs
on the psychotomimetic effects of ketamine.
Anaesth., Intens, Care 6:22-225

Ito, Y. Ichiyanagi K. (1974)
Post operative pain relief with ketamine infusion
Anaesthesia 29:222.

Jackson A.P.F. Dhadphale P.R. Callghan, M.L.,
Haemodynamic studies during induction of anaesthesia for open Heart Surgery using Diazepam and ketamine.
Br. J. Anaesth. 50: 375 - 378.

Kamm, G.D., Bewes, P.C., (April 1978)
Ketamine anaesthesia by continuous intravenous drip.
Tropical Doctor 68 - 72.

King; C.H., and Stephen: (1967)
A new Intravenous or Intramuscular anaesthetic
Anaesthesiology 28:258.

Kingston, H.A., Bretherton, K.W., Holloway, A.M.
Sowning, I.W., (February 1978)
A compafison between ketamine and diazepam as induction agents for pericardiotomy.
Anaesth. Intens. Care 6:66 - 70

Knoche, E., Traub E., Dick, W., (October 1978)
Effects of Diazepam and Flunitrazepam on the undesired post operative side effects of ketamine anaesthesia.
Anaesthetist 27, 302 - 308.

Kolhany S.P. Zsigmond E.K. (1972)
A double blind study of effective antihallucinatory dose of diazepam prior to ketamine anaesthesia Clin. Pharmacol. Therap. 21:108 - 109.

Korttila, K., Levanen, J., (1978)
Untoward effects of ketamine combined with diazepam for supplementing conduction anaesthesia in young and middle aged adults.
Acta Anaesthe. Scand. 22; 640 - 648.

Kumar, S. M. Kothery, S.P., Zsigmond, E.K.,
Plasma free norepinephrine and epinephrine concentration following diazepam - ketamine Induction in patients undergoing cardiac Surgery.

Liang, H.S., Liang, H.G., (1975)
Minimizing emergence phenomenon: subdissociative dose of ketamine in balanced surgical anaesthesia
Anaesth. Analg. (Cleve) 54:312 - 316.

Lilburn, J.K., Dundee, J.W., Nair S.G., Tee, J.P.H.,
Johnston, M.L. April 1978
Ketamine Anaesthesia, Evaluation of the ability of various premedicants to attenuate its psychic effects.
Anaesthesia 33: 307 - 311.

Lilburn, J.K., Moore, J., Dundee, J.W., (1978)
Attempts to attenuate the cardiostimulatory effects of ketamine
Anaesthesia 32: 499 - 505

Lilburn J.K., Dundee, J.W., Moore, J. (1978)
ketamine infusions
Observations on technique dosage and cardiovascular effects.
Anaesthesiology 33:

McCarthy, D.A. and Chen, G.M. (1965)
General anaesthetic action of 2 - (Opchlorophenyl) - 2-methylamino cyclohexamone H. C. (Cl. 581) in the Rhesus Monek Monkey
Fed. Proc. 24: 268.

McCarthy, D.A., Chen. G., Kaump, D.H., Ensor, C., (1965)
General anaesthesia and other pharmacological properties of 2-(o-chlorophenyl) - 2-methylamino cyclohexanone H. Cl. (Cl.581)
Journal of New drugs.

Moore, J., McNabb, T.G., Dundee, J.W., 1971
Preliminary report on ketamine in obstetrics
Br. J. Anaesth. 43:779 - 782.

Oduntana, S.A., Cool, R.Y. (1970)
Clinical trail of ketamine (Cl. 581) A preliminary Report.
Can. Anaesth. Soc. J. 17:411 - 416.

Peuler M. et al 75
ketamine and intraocular pressure
Anaesthesiology 43 (5) 575 - 8. Nov. 75.

Radney, P.A., Arai T., Nagashima, H., (1974)
ketamine gallamine anaesthesia for a great vessel operation in Infants
Anaesth. Analg. 53:365,

Riemasch-Beckers, C., Muller, H., (August 1977)
Dual anaesthesia for surgical and diagnostic procedures in Paediatric Opthalmology
Anaesthetist 26; 391 - 394.

Sadove, M.S. Hatano, S., Radlin, T., et al (1971)
Clinical study of droperidol in prevention of the side effects of ketamine anaesthesia.
Anaesthesia analgesia 50:526 - 532

Sadove, M.S., Shulman, M., Hatano S.,
Fevold M, (1971)
Analgesic effects of ketamine administed in subdissociative doses.
Anaesth. Analg. 50: 452.

Samuels S.I., Lim. F., Maze, A. (Sept. 1978)
Failure to produce satisfactory operating condition following larger doses of ketamine hydrochloride.
Anaesthetist rev. 5: 23 - 24

Slogoff, S., Allen, G.W. Wessel, J.V., et al. (1974)
Clinical experience with subanaesthetic ketamine
Anaesthesia. Analg. (Cleve) 53. 354 - 358

Souches R., Elissonde, M.B., Choollet, J.F., Neretti, J., Masse, C., (May 1978)
our experience with ketamine in burn patients associated with blood gas measurement.
Anaesth. Rean. 36: 470 - 510

Shapiro H.M. Wyte, S.R., Hernis, A., (1972)
Ketamine Anaesthesia in patients with intracranial pathology.
Brit. J. Anaesth. 44 ;1200 - 1204

Takashita, H., Okuda, Y., Sari, A.,
The effects of ketamine anaesthesia on cerebral circulation and metabolism in man
Anaesthesiology 36; 69 - 75

Takki, S., Nikki, P., Luatella et al (1972)
ketamine and plasma catecholamines
Brit. J. Anaesth. 44:1318 - 1321; (1972)

Takahashi K., Shima, T., Koga, Y. et al (19710)
The effect of ketamine hydrochloride on pulmonary haemodynamics in dogs.
Jpn. J. Anaesthesiology 20:842 - 846

Traber et al (1968)
Differentiation of the cardiovascular effect of Cl. 581.
Anaesthesiology 29:931.

Traber D.L., and Wilson R.D., (1969)
Involvement of the sympathetic Nervous system in the pressor response to ketamine
Anaesth. Analg. Curr. res. 48:248

Tweed W.A. Minuck, M., Myamim of (1972)
circulatory Response to ketamine Anaesthesia
Anaesthesiology 37: 613.

Virtue, R.W., Alanis J.M., Mori M., (1967)
An anaesthetic agent: 2 orthochlorophenyl methylamino
cyclohexanone H. Cl. (Cl.581)
Anaesthesiology 28: 833

Wilson, R.D., Richey, J.D., Forestner, E., Hendrickson, M.H.,
Herrin, T.J., Norman, P.F., (September 1979).
Cardiovascular effects of drip ketamine.
Anaesthesiology 3: Sep. 1979

Wilson, R.D., Traber, D.L. and McCoy N.R. (1968)
Cardiopulmonary effect of Cl.581. The New dissociative anaesthetic
Stch. Med. J. (Bgham Ala) 61: 692.
Wong D.H.W. Jenkins L.C. (1974)
An experimental study of the mechanism of action of ketamine
on the central Nervous system.
Can. An. Soc. J. 21: 57 - 67.

Zsigmond et al (1975)
Arterial hypoxaemia caused by intravenous ketamine
Anaesth. Analg. (Cleve) 54 (6) 800 - 5

Zsigmond et al
Rise in plasma free norepinephrine during anaesthesia
induced with ketamine.
Behaviour Neuropsychiatry 6 (1 - 12): 81 - 4 April 74 - March 75.

MED.REF.
~~RD.REF~~
RD86
.H44
1981