Ketamine Hydrochloride: A Useful but Frequently Misused Drug

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ABSTRACT

Background: Ketamine hydrochloride remains the most widely misused general anaesthetic agent in our environment today. The misuse, which commonly involves non-anaesthetists, often results in disastrous consequences.
Methods: A Medline literature search was performed to identify articles concerning the pharmacology, clinical features, uses and complications of ketamine hydrochloride. Standard textbooks of anaethesia were also consulted and some local scientific publications on the subject were reviewed.
Result: Ketamine is readily available and widely used by both surgeons and general practitioners working in the tropics. The drug has been found useful for superficial minor and intermediate surgical procedures in regions where there is a dearth of anesthetists. Its unique features, simplicity of administration and relative safety, which has made it useful in the hands of non-anaesthetists, have also led to widespread abuse.
Conclusion: There is need for surgeons and other "occasional anaesthetists" to be well informed on the correct uses, limitations and dangers of ketamine anaesthesia to enhance patients' safety.

KEY WORDS: Ketamine Hydrochloride, Useful, Misuse

Introduction

The specialty of anaesthesia has long been recognised as an area with manpower problems in developing countries. [1] ffoulkes-Crabbe, [2i] reviewed the situation recently and concluded there is still great room for improvement, having estimated the physician anaesthetists manpower availability to population ratio in Nigeria to be about 1:275,000. There are generally very few physician anesthetists in the continent. The training of nurses

to administer general anaesthesia has helped, but has not quite eliminated the problems. In Nigeria, for instance, only the Teaching and some general hospitals have qualified anaesthetic personnel. In most clinics and small general hospitals, surgical procedures are done under ketamine anaesthesia administered by non-anaesthetists. Unfortunately not all personnel who administer ketamine quite appreciate the limitations and dangers of this general anaesthetic agent. As a result the drug is frequently misused and abused, often resulting in disastrous consequences. Unfortunately the prevalent low ratio of anaesthetists to the general population would imply that non-anaesthetist would continue to administer significant anaesthetic in the African sub-region. The purpose of this article is to review the common features of ketamine, its correct uses, limitations and dangers. A well-laid out practical guide is also offered at the end to serve as a quick reference guide to non-anaesthetists.

General Properties

Ketamine is a phencyclidine derivative first described in 1965, and introduced into clinical practice in 1970. [3] Since its introduction, several clinical and laboratory studies have shown this drug to have several anaesthetic and analgesic properties. Ketamine is unique as a general anaesthetic agent for a number of reasons. Of all available intravenous anaesthetic agents, it is the only one that combines hypnotic, analgesic and amnesic properties. Thus the drug provides two of the triad, (hypnosis, analgesia and muscle relaxation) of modern general anaesthesia. This makes ketamine the only true intravenous anaesthetic in that it can be used as a sole anaesthetic agent for a wide range of surgical procedures. The drug therefore remains a useful tool among single-handed surgeons working without anesthetists in most rural hospital and clinics in developing countries.

Pharmacokinetics

Mode of action

Ketamine produces its anaesthetic and analgesic effects by antagonising a subset of glutamate receptors stimulated by the agonist N-Methyl-D-asparate (NMDA). [4] These receptors are found throughout the central nervous system including the lumbar spinal cord.

Duration of action

The duration of ketamine anaesthesia depends on the total dose of drug administered. Following a single intravenous administration of a general anaesthetic dose (2mg/kg), the drug has an onset of action within 30 seconds and maximal effect occurs in about 1minute. [5] The duration of anaesthesia following this single dose is 10- 15 minutes [3] and full orientation to person, place and time occurs in 15 –30 minutes. [5] Higher doses produce more prolonged anaesthesia and sedative premedication and concurrent use of other anaesthetics will prolong the time of emergence. Also an aggregate large dose with repeated injections for maintenance will result in prolonged awakening time.

Analgesia occurs at considerable lower plasma ketamine concentrations

than loss of consciousness. This means, there will be a considerable period of postoperative analgesia following ketamine anaesthesia. Similarly, subanaesthetic doses of ketamine can be used to produce analgesia. [6]

Recovery

Recovery from ketamine anaesthesia is frequently complicated by undesirable psychological reactions of varying severity and classification. The common manifestations of these reactions include vivid dreams, hallucinations, confusion, euphoria and fear. They occur in the first hour of emergence and patient may continue to experience unpleasant dreams up to 24hrs after the drug has been given.[7] Patients at both extremes of ages (<15, >65 years) are said to be less susceptible to these reactions.[8] Several drugs have been used to reduce the incidence and severity of the reactions. Of all these benzodiazepines appear to be most effective.[9] Other drugs which have been found useful in this regard include promathezine, phenobarbitione opiods, butyrophenones and physostigmine.[7] Skillful neglect i.e. avoidance of verbal and tactile stimulation during the recovery period have also been shown to reduce the incidence of the emergence reactions.

Metabolism

Metabolism of ketamine occurs predominantly in the liver. The products are excreted in the kidney. No specific organ toxicity has been attributed to ketamine[7]

Routes of administration

Ketamine can be administered orally and rectally for premedication[10] and intravenously or intramuscularly to provide surgical anaesthesia or analgesia.[4] Successful epidural and subarchnoid administrations for analgesia and anaesthesia have also been documented.[4]

Pharmacological Actions

Effects on the cardiovascular system

Ketamine stimulates the cardiovascular system, resulting in increases in heart rate, blood pressure and cardiac output.[11] The cardiovascular stimulation is mediated principally through the sympathetic nervous system.[11, 12] The drug has been shown not only to support the circulation, but also to preserve organ blood flow in hypovolaemia. This makes it a useful anesthetic in trauma patients with extensive blood loss and other shocked states. Furthermore, ketamine has been shown to reduce the need for inotropic support in septic patients.[13] However, the cardiovascular responsiveness associated with ketamine has marked individual variability. Alarming increase in blood pressure has been reported following induction of anaesthesia with ketamine in otherwise normal patients. Fortunately, there is no evidence of damage occurring from these short episodes of hypertension.

Effects on the respiratory system

The drug has been shown to have minimal effects on the central respiratory drive[14] Following a slow intravenous induction, there may be a transient decrease in minute ventilation, but thereafter breathing is well maintained and may even increase slightly. Recent research, using a

pulse oximeter, showed that an intravenous induction dose of ketamine (2mg/kg) caused a fall in oxygen saturation. However, there were no associated untoward effects.[12] Rapid administration of a normal dose, administration of unusually large dose and concurrent use of sedative or other anaesthetic drugs may be associated with respiratory depression or even apnoea.[12, 15] Ketamine causes bronchodilation making it a useful anaesthetic for patients with asthma.[11, 12] Ketamine also increases salivation, especially in children, and it is best to premedicate all patients with atropine. The recommended premedication dose of atropine is 10-20mcg/kg (to a maximum dose of 600mcg) intramuscularly, 30minutes before anaesthesia. Alternatively the same dose can be given intravenously at the time of induction of anaesthesia.

Effects on the central nervous system

Ketmine produces a dose-related state of unconsciousness and profound analgesia.[4] The anaesthetic state is frequently described as "dissociative anaesthesia", a state in which patients are detached from their surroundings. The patients appear to be awake (cataleptic state) in that movements may occur, the eyes remain open and many of the protective reflexes such as the cornea, swallow, cough and gag reflexes are intact. The amnesic effect of ketamine, which often persists for up to one hour after recovery of consciousness, ensures that there is no recall of surgery or anaesthesia.

Effects on the uterus

Ketamine crosses the placenta readily and plasma concentrations of the drug in the fetus are said to approximate those in the mother. Few reports show that neonates from mothers induced with ketamine may fare less well and exhibit depressed neurobehavioral responses.[16] However, there is no documented report that ketamine is contraindicated in obstetric anaesthesia when the mother is not hypertensive. In fact the drug may actually increase uterine artery blood flow, [17] and may be useful especially in the very ill or hypovolaemic patient.

Effects on the muscles

Muscle tone is often increased following ketamine administration. This makes ketamine anaesthesia unsuitable for surgical procedures like intrabdominal and intrathoracic operations, where significant muscle relaxation is required. The drug, may however, be used in conjunction with muscle relaxants and intermittent positive pressure ventilation to produce good condition for these types of procedures.

Clinical Uses

Ketamine has an important and seemingly unrivaled place in surgical practice in developing countries. The drug has been found useful as the sole anaesthetic agent for wide variety of superficial minor and intermediate surgical procedures. The poor risk patients, (ASA $\geq$ IV), represent the candidates for ketamine anaeshtesia because of the sympathomimetic effects of the drug.

Ketamine enjoys wider application in paediatric anaesthesia because paediatric patients have less adverse reaction than do adults.[5] Also

ketamine can be given intramuscularly in the absence of an intravenous access – a situation that is common in children. The drug is particularly suitable for sedation of paediatric patients undergoing procedures away from the theatre e.g. radiotherapy.

Ketamine is an invaluable agent for treatment of the trapped casualty or even the mass casualty situation.Ketamine has a useful role in repeated anesthetics for procedures like burns dressing. Ketamine bronchodilation and profound analgesia make the drug an excellent choice for the induction of patients with reactive airway disease.

Recent studies have also demonstrated the effectiveness of small doses of ketamine in preemptive analgesia[4, 18] and the addition of ketamine to bupivacaine has been shown to improve the duration and quality of analgesia provided by caudal block in children.[19]

Dosage

This depends on the desired therapeutic effects and route of administration. The vast majority of clinical uses involve intravenous and intramuscular administration, where the drug rapidly achieves therapeutic level.

Intravenous administration

Induction: 1 -2mg/kg as bolus dose.
Maintenance: 0.5mg/kg when the depth of anaesthesia lightens.
Or
As an infusion of 1mg/m1 ketamine in 5% dextrose or normal saline at a rate of 1-2mg/kg per minute.

Intramuscular administration

Induction: 5-10mg/kg as bolus.
Maintenance: 3-5mg/kg as required.

Oral and rectal administration

For premedication: 3-10mg/kg

Contraindications

From the discussion so far it is clear that the use of ketamine hydrochloride will obviously be contraindicated in certain conditions. These are:

1. Cardiovascular diseases e.g. hypertension and Ischaemic heart disease.
2. Previous cerebro-vascular accident.
3. Psychiatric disorders.
4. Raised intraocular pressure and intraocular surgery.
5. Raised intracranial pressure.
6. Hypersensitivity to the drugs.

Practical Guide to Safe Use

The apparent simplicity and relative safety of ketamine in the hands of non-anaesthetists should not be taken for granted. It must always be remembered that the drug is a general anaesthetic and its use demands all precautions necessary for safe use of all general anaesthetics. Although the airway is usually well maintained in children and young adults, older patients may need some form of airway correction or manipulation. The administrator of ketamine, ("the anaesthetist"), must be experienced enough to carry out resuscitative measures in case of prolonged apnoea or respiratory obstruction which can lead to hypoxic cardiac arrest.

The following may serve as a useful guide for the 'not too experienced

administrator'.

1. Thorough preoperative assessment to identify any contraindication or specific factors of caution in the administration of the drug.
2. Premedicate the patient with an antisialogogue e.g. atropine 10 – 20mcgkg $^{-1}$, (to a maximum dose of 600mcg), administered intramuscularly 30 minutes-1 hour before anaesthesia or same dose given intravenously just before induction of anaesthesia.
3. Make available in the operating room, simple life saving equipment like suction pump (e.g. manually operated suction pump) and suction catheters, and resuscitation drugs like adrenaline, hydrocortisone, promethazine and atropine. Availability of a self-inflating bag with appropriate size facemask, and a source of oxygen supply (e.g. bull-nose cylinder), delivery mask, catheter or cannula, is also desirable.
4. Calculate the dose of ketamine required. This depends on the patient's weight, age, state of nutrition, circulatory status, premedication and concurrent medication.
5. Withdraw all drugs into syringes and label appropriately.
6. Establish a reliable intravenous access.
7. Measure and record the baseline vital signs e.g. pulse rate and blood pressure.
8. Apply a precordial stethoscope.
9. Pre-oxygenate and continue O_2 after induction.
10. Administer a precalculated dose of ketamine I.V slowly. or intramuscularly as the case may be. This may be preceded by the intravenous administration of the calculated dose of a benzodiazepine e.g. diazepam 0.2mg kg $^{-1}$.
11. Observe the colour of the patient's skin and pattern of ventilation. Palpate the peripheral pulse, and continuously monitor the heart and breath sounds with the precordial stethoscope. Measure the arterial blood pressure immediately after induction of anaesthesia. This level of monitoring should be continued throughout the entire duration of anaesthesia.
12. Maintenance of anaesthesia by continuous intravenous infusion technique is preferred and often recommended. The drug should be infused at a rate of 1-2mg per minute. This is an average adult dose, but some patients may need as much as 4mg/minute. Hence the infusion should actually be titrated to effect, care being taken to avoid an overdose. A separate infusion line will be required for fluid and blood replacement. If adequate anaesthesia has been ensured during the operation, the infusion may be turned off about 10 minutes to the end of the operation or when the surgeon is closing the skin.
13. Recovery should take place in a quite room devoid of tactile or auditory stimulation. The anaesthetist should supervise the recovery, and adequate care should be taken to ensure an unobstructed airway and adequate ventilation. Monitor pulse, blood pressure and respiration and oxygen saturation.

Ketamine anaesthesia is not suitable for a patient in prone position

because maintenance of a patent airway cannot be guaranteed. Also, the use of ketamine anaesthesia for procedures in patients with full stomach is to be discouraged. Similarly this method of anaesthesia is not suitable for oral surgery and most otorhinolaryngologic procedures. A method incorporating tracheal intubation is advised, instead, in these situations to isolate and protect the airway from soilage.

Although ketamine may not be the perfect anaesthetic, it possesses most of the properties of the ideal anaesthetic agent. The drug has been found useful for superficial minor to intermediate surgical procedures in regions where there is a dearth of anaesthetists. It produces safe and satisfactory state of unconsciousness with proper supervision of the administrator. Experience with the use of the drug has shown that careful selection of dose and patients will result in fewer complications. The administrator must be experienced enough to carry out immediate resuscitative measures.

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