KETAMINE

A Revolutionary Anaesthetic Agent for the Battle Casualty

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SUMMARY: The use of ketamine hydrochloride (Ketalar), C 1-581, Parke-Davis & Co. in 75 cases is described. This drug, an injectable anaesthetic agent of the dissociative type may be given by intravenous (I.V.), intramuscular (I.M.) or combined (I.V. + I.M.) injection. It was used for both induction and maintenance of anaesthesia and the results are described together with their possible relevance to a military or mass casualty situation.

Introduction

Whilst broadly agreeing with the views of Sir Robert Macintosh (Macintosh 1970) that the pressing need in anaesthesia is not for new drugs and discoveries but for the application of facts already well known, we believe that in the field of military surgery and mass casualties anaesthesia there is still room for new techniques. Conventional techniques depending on supplies of compressed gases or volatile anaesthetic agents may not be applicable for logistic reasons.

In 1950, Rees and Gray divided anaesthesia into three basic components, namely narcosis, analgesia and relaxation, but since the term analgesia is meaningless in the unconscious patient, Gray (1960) changed this term to "reflex suppression". With this triad in mind, it is possible to vary one component without affecting the others and it is not necessary to subject the patients to deep levels of central depression. Prior to this concept, anaesthesia had largely depended on depression at all levels of the central nervous system to produce an acceptable state for surgery.

Following these ideas, a few years later came the introduction of the potent butyrophenone tranquilizers, haloperidol and droperidol (Janssen et al 1963), and the safer and more potent narcotics, phenoperidine and fentanyl (Janssen, Niemegeers and Dony 1963), which give us the highly effective anaesthetic state known as neuroleptanalgesia but, unfortunately, the use of these drugs does not give sufficient reflex suppression for surgery unless respiratory depression is also produced.

Exploration of other means for the selective inhibition of pain mechanisms lead to a group of compounds which produce the state known as "dissociative anaesthesia". The prototype of this group was phencyclidine (Sernyl). This agent was investigated as an intravenous anaesthetic agent but was found to be unsuitable for clinical use in humans because of its powerful psychotomimetic action (Griefenstein et al 1958). Ketamine, (Ketalar, C 1-581), the drug investigated in this study, is chemically related to phencyclidine and cyclohexamine (C 1-400).

The term "dissociative anaesthesia" denotes profound analgesia coupled with a trance-like state in which the patient does not appear to be asleep or anaesthetised

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but rather disconnected from his surroundings (Corssen 1968). Ketamine has a quite dissimilar structure to other intravenous anaesthetic agents such as the barbiturates or eugenols. It is 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride (Fig. 1). It is slightly acid in solution (pH 3.5—5.5) and is available as a clear

FIG.1

KETAMINE HCl

aqueous solution containing 10 mg or 50 mg ketamine base per ml. Its pharmacology was reported by Chen (1965) and by McCarthy et al (1965). They described its cataleptic, analgesic and anaesthetic properties, but drew attention to the fact that it is not a true hypnotic. Domino, Chodoff and Corssen (1965) carried out clinical pharmacological studies which introduced the substance as an anaesthetic agent, and since then well in excess of 12,000 administrations have been reported, many in children. One of the latest reports in the literature (Knox, Bovill, Clarke and Dundee 1970) describe the use of ketamine as an induction agent. Our object was to investigate this interesting drug when used as the sole anaesthetic agent.

Method

Initially only fit adults of either sex undergoing non-emergency surgery were included, though later a few children and others undergoing emergency procedures had ketamine. One patient had two procedures with ketamine and 73 had one procedure. Forty-six were males, twenty-nine females. Sixty-four patients were in the age group 17 to 32 years, five were less than 8 years old, none were older than 65 years.

Table I
Premedications used

Premedication	Number
Pethedine 100 mg + atropine 0.6 mg	37
Papaveretum 20 mg + hyoscine 0.4 mg	11
Pethedine 50 mg + atropine 0.6 mg	2
Pethedine 100 mg + promethazine 25 mg + atropine 0.6 mg	4
Atropine 0.6 mg	21
Total	75

Premedication

The patients were visited the evening before surgery and premedication ordered for approximately 60 minutes before surgery, to be given by deep I.M. injection as in Table I. The largest group of patients (32) had orthopaedic procedures performed, whilst 17 had general surgical operations. Eleven dilatations and curettages made up the third largest group, whilst the remainder were relatively minor procedures such as dental extractions, cystoscopy, plastic surgery and others. No body cavity surgery was attempted in this study.

Anaesthesia

After recording the pulse, respiration and blood pressure, a plastic in-dwelling needle was inserted into a vein on the dorsum of the hand. This stayed in place until the patient left the recovery area. The patient was given the initial dosage of ketamine using the solution containing 10 mg per ml at a calculated dosage of 2 mg per kg body weight. We gave further dosage of 10 to 50 mg as necessitated by patient movement. We always injected ketamine slowly intravenously, taking at least a minute over the induction dose. After gaining some experience in using ketamine intravenously we decided to combine this method with an intramuscular dose. Nineteen patients were anaesthetised with this combined technique. The more concentrated (50 mg per ml) solution of ketamine was used. A total planned dosage of 7 mg/kg as recommended by Phillips (1970) for his purely intramuscular technique was drawn into a syringe, 2 mg/kg were given intravenously and the remainder given by deep intramuscular injection into two sites in the vastus lateralis muscle. Two sites were used in the hope of providing a quicker absorption of the drug from the muscle depots. If the patients made movements of a degree likely to interfere with surgery further increments were given intravenously rather than intramuscularly in order not to delay recovery. Three children who were under five years old received an intramuscular injection alone. All three weighed between 12 and 24 kg and all received one dose of ketamine using the 50 mg/ml solution into the vastus lateralis: the dosage range was 8.3–11.9 mg/kg body weight. Phillips (1970) used a dosage of 12 mg/kg for children weighing from 12–24 kg as our children all did; our dosage was therefore on the low side by his standards. All patients were induced in the supine position with the exception of eight who were induced in the prone position into which they had rolled themselves. In two of the patients, both of whom were fit adults who had received papaveretum 20 mg plus hyoscine 0.4 mg intramuscularly one hour previously, induction was accomplished using ketamine 2 mg/kg intravenously. Their anaesthetic was continued with d-tubocurarine 0.7 mg/kg, nitrous oxide, oxygen and intermittent positive pressure ventilation (I.P.P.V.) Reversal was accomplished at the end of these two cases with a full dosage of atropine and neostigmine. The patients were supervised by two anaesthetists, one to supervise the general condition of the patient and to give further ketamine as necessary and the other to make recordings.

Recovery

At the end of surgery, the patients were taken to the recovery area, where they were disturbed as little as possible except when necessary to take blood pressure. The time of awakening was recorded as the time they first showed appropriate response to simple questions.

Assessment

Immediately the operation ended the anaesthetist recorded his impression of the anaesthetic in one of four grades: "excellent", "good", "fair", or "poor". The surgeon gave an independent assessment as did the patient when fully orientated. The patients were also invited to give a further opinion the following day, and at the same time a fairly elaborate psychological questionnaire along the lines suggested by Wilson (1969) was completed (The Ketamine Acceptance Test).

Results

Induction

Induction was rapid and of the order of thirty seconds with the I.V. dose described. Painful procedures such as the application of exsanguinating tourniquets could be proceeded with in a minute or two. A blotchy rosy-red rash developed in 15 per cent of patients often localised to the face and upper chest. The site of appearance did not appear to be related to the site of the injection of the drug. Urticaria was never seen. This rash disappeared after ten minutes to be replaced after about twenty minutes by skin pallor seen in nearly all patients: sweating was rare.

Maintenance

Further intravenous doses of ketamine were given as dictated by movement interfering with surgery. We rapidly gained the ability to judge when an incremental dose was necessary by such signs as rapid opening and shutting of the eyes, head movements and swallowing. All these tended to occur as a prelude to "large" limb movement.

Duration

The duration of the procedures and the recovery times were as set out in Table II.

Table II
Duration of procedures and recovery times

Technique	Number of cases	Length of operation in minutes, $\pm$ standard deviation	Recovery time as defined in text in minutes $\pm$ standard deviation
I.V.	53	31.5 ± 19	29.3 ± 20
IV. + I.M.	19	40 ± 12.7	55 ± 17.8
I.M.	Case 1	35	85
I.M.	Case 2	15	15
I.M.	Case 3	25	29

Dosage

The total dosage of ketamine used is shown in the histogram (Fig. 2). We found that in the patients having the combined technique (I.V. + I.M.) it was possible to complete the planned surgery on the initial doses as described above in 21 per cent of cases. All the others needed further intravenous increments. One, a highly resistant male discussed more fully later, required 20 increments. None of the patients showed any tissue reaction to the drug given either I.V. or I.M. either immediately or at follow up.

Blood pressure and pulse

The mean initial values and the changes induced by ketamine are set out in Table III. The changes induced tended to revert to their original levels in 15-20 minutes.

Table III
Changes in blood pressure and pulse rate

Mean Values ± standard deviation	Systolic B.P. mm/Hg	Diastolic B.P. mm/Hg	Pulse Rate
Before induction	123 ± 8.1	74 ± 8.1	78 ± 17
After induction	157 ± 23	96 ± 15	112 ± 25

Respiration

No constant pattern of respiration emerges. Increasing rate was seen on surgical stimulus inadequately covered by ketamine and along with patient movement was an indication for further dosage. Apnoea following a dose of ketamine was only seen in one case, was quite transient, and responded to a few seconds I.P.P.V. with mask and inflating bag, using air.

Airway

We did not find that the airway remained clear in all positions and at all times (Phillips 1970) though this was mainly true. All the eight patients induced in the prone position needed no assistance with their airways. Of the supine patients a few snored; this could always be abolished by holding the chin forward for a few breaths. Vocalisation did occur with this drug in a few patients, and varied from grunts through howls to seemingly rational speech. One patient, prone and towelled, having a naevus removed from his back suddenly exclaimed in the middle of the procedure, "Where am I? Sleep, sleep—deep sleep". He remembered nothing of the incident afterwards. Another, a very fit paratrooper insisted on yelling the battle-cry of his colleagues, "Geronimo!" over and over again during the recovery period.

Case histories

In the first 73 cases, surgery was completed on ketamine alone, except in two cases. One was an examination under anaesthetic in which the abdominal muscles were too tight. She was given suxamethonium, intubated and ventilated with air. The depolarisation disappeared in the normal time, the tube was removed and a dilation of the cervix and curettage of the uterus completed uneventfully under ketamine alone. A second patient could not be kept still despite large doses of ketamine: her anaesthetic was concluded with halothane, and this case, together with a male patient who also proved resistant to ketamine is discussed later. In the first of the patients induced with ketamine (2 mg/kg) and paralysed with d-tubocurarine, reversal at 100 minutes brought as rapid a reorientation of the patient as would a barbiturate induction. The second patient so treated but reversed earlier, at 45 minutes, was still partially disorientated and dissociated. Only two of our cases required an anaesthetist to be called to the recovery area. They were quite well but exhibited an increasing bradycardia, which responded to I.V. atropine. Both had had the I.V. + I.M. technique with a paparevetum/hyoscine premedication.

Evaluation

The evaluation of the anaesthetic is given in Table IV.

Table IV
Percentage evaluation of the anaesthetic

Evaluation by	Excellent	Good	Fair	Poor
Anaesthetist	81	15	1	3
Surgeon	66	23	6	5
Patient on recovery	52	42	6	—
Patient after twenty-four hours	45	40	10	5

Side effects

Side effects were neither common or serious. Pressor effects, tachycardia and tachypnoea were not regarded as side effects as they are practically invariable after ketamine. Bradycardia occurred twice, but never in patients who had received atropine. Diplopia was experienced by 41 per cent of our patients during the recovery phase.

Psychomimetic effects and patient acceptance

As regards patient acceptance of this anaesthetic, 54.5 per cent had dreams during it and 29.0 per cent found these dreams unpleasant. Some 12 per cent expressed dissatisfaction with their anaesthetic. One of the most distressed described the sensation of feeling that his mind had been taken away. No one ever complained of having felt any pain during ketamine dissociation.

Resistance

Two patients, one of each sex, proved resistant to ketamine in that despite high dosage, movement continued to interfere with surgery. The male was given a total of 22.7 mg/kg for a 60 minute patellectomy and this was completed with ketamine as the sole agent under difficulty. The female did not stop moving in response to increasing dosage of ketamine and after a total of 11.5 mg/kg for a 30 minute varicose vein strip had been passed, it was necessary to resort to halothane.

Discussion

A new era of pain relief, without central depression, has arrived. As yet the drug has imperfections and newer dissociative drugs are under trial. CL 1848c which has a similar pharmacology to ketamine but a dissimilar formula has been given to normal human volunteers (Wilson et al 1970), Figure 3.

FIG.3

It seemed to us at first this otherwise excellent drug might be judged to have two important disadvantages. There are a small group of patients (2.6 per cent in our series) who are highly resistant to it in that movement makes surgery difficult despite high dosage. A larger group (29 per cent in our series) complained of unpleasant symptoms during the emergence phase. The existence of these two groups of patients does not, in our view, lessen the importance of the future role of ketamine in emergency situations such as the battle field. If the patient proves resistant to ketamine this only means changing to a more conventional agent and as yet no one has demonstrated any incom-

patibility between ketamine and other agents. In the patients who suffer unpleasant emergence phenomena, this would seem a small price to pay for rapid, safe relief of pain in an emergency situation. One of our patients, a four year old male, with recent bilateral fractures of the tibia was safely anaesthetised with I.V. ketamine in an inconvenient, temporary casualty department, so that he could be undressed and X-rayed. Shock was simultaneously treated with I.V. 'Macrodex'. He was painlessly moved 70 metres across a rough yard, with no airway problems, his fractures manipulated and put in plaster. No postoperative analgesics were necessary. Ketamine can render the injured easy and pain-free to move; this may become an important use for it in battle casualties. We saw no special advantages in giving this drug I.M., except that being able to use it in this way is useful in small children, or those with difficult veins. The recovery period to reorientation is doubled in most patients who receive the combined technique (I.V. + I.M.) as compared with I.V. alone (Table II).

Conclusions

The final place of ketamine and other dissociative agents in anaesthesia have yet to be defined. That it, together with other and better drugs which may succeed it will have a place, cannot be doubted. It, or better successors, will have special applications, in addition to their normal anaesthetic role, on the battlefield, for instance to enable the rapid extraction of the trapped and wounded from burning tanks, and for moving the injured generally. It would not be difficult to develop a "syrrette" type pack of the drug to use under battle conditions, especially since ketamine is now available experimentally in a strength of 100 mg/ml solution.

In our opinion, all military anaesthetists should be familiar with the drug and supplies should be made available to them in peace and war. However, the idea should not get abroad that ketamine is a completely safe agent, that can be used by anyone to allow pain-free surgery anywhere. As with all anaesthetic agents, the necessary skill and equipment must be immediately at hand for resuscitation though in most cases this does not imply more than a doctor could easily carry on his person.

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