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Low dose intravenous infusion technique with ketamine

Amnesic, analgesic and sedative effects in human volunteers

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Summary

Low dose ketamine is a relatively new technique. The recommended doses vary considerably. It was therefore decided to establish the minimum dose of ketamine required to produce satisfactory analgesia, sedation and amnesia in 50% of a population of adult volunteers. Twenty adult volunteers aged 20 to 42 years were the subjects of the study. Twenty minutes following intravenous (iv) pre-treatment with 0·3 mg of atropine and 0·2 mg/kg of diazepam each volunteer received a bolus of ketamine 1·0 mg/kg iv followed by ketamine iv infusion at the rate of either 0·5 mg/kg/hour (10 cases) or 1·0 mg/kg/hour (10 cases). The grade of sedation was determined on a scale of 1–5 and the frequency of amnesia was assessed using visual memory cards. Analgesia was determined by pin prick.

Diazepam alone produced no analgesia and only moderate degree of sedation. Ketamine produced satisfactory analgesia to pin prick in both the groups. Ketamine bolus produced marked sedation for about 20 min followed by moderate sedation during iv infusion in both the groups. During the iv infusion of ketamine at a rate of 0·5 mg/kg/hour the amnesic effects declined to 20% in 45 minutes, while during infusion of 1·0 mg/kg/hour the frequency reached a maximum at 50–60%. The minimum dose of ketamine required to produce amnesia in 50% of this population was therefore 1·0 mg/kg/hour after a bolus injection of 1·0 mg/kg given iv.

Key words

Anaesthetics, Intravenous; ketamine.

Hypnotics; diazepam.

Low dose ketamine intravenous infusion, a relatively new technique in clinical practice, is used either to supplement light anaesthesia or as a sole anaesthetic agent. The psychomimetic side effects of ketamine, e.g. emergence delirium and postoperative dreams, are likely to be minimized by reducing the dose yet, in small doses ketamine still acts as an excellent analgesic. There are however wide variations in the recommended dose for the intravenous infusions of ketamine. Hatano *et al.*[1] described a large series in which anaesthesia was maintained with ketamine infusion at an average rate of 0·7 mg/kg/hour with N_2O:O_2 and diazepam

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Balmer & Wyte[2] used 50 μ/kg/min at a rate of 3·0 mg/kg/hour to provide awake analgesia for surgical procedures and Lilburn *et al.*[3] recommended more than 6 mg/kg/hour for the body surface and abdominal operations. Kamm & Bewes[4] following a premedication of oral haloperidol give 4–6 mg/kg/hour for spontaneously breathing patients and 2 mg/kg/hour for patients whose ventilation was controlled after muscle relaxants.

The present study was undertaken to determine the minimum dose of ketamine by intravenous infusion required to produce satisfactory analgesia, sedation and amnesia in 50% of a group of adult volunteers under controlled conditions.

Materials and methods

Twenty adult volunteers of both sexes between the ages of 20 and 42 years, who gave written informed consent, were the subjects of the study. The study was approved by the institutional committee reviewing the investigations involving human subjects. The volunteers were divided into two equal groups (A and B). Their physical characteristics are presented in Table 1. No surgery of any kind was involved and appropriate monitoring was carried out throughout the study.

Each volunteer received atropine 0·3 mg intravenously (iv) followed by diazepam 0·2 mg/kg iv as premedication. The atropine was intended to reduce the secretions and diazepam to reduce the psychomimetic side effects of ketamine. Twenty minutes after diazepam, ketamine 1·0 mg/kg was given as iv bolus followed immediately by iv infusion of ketamine at the rate of 0·5 mg/kg/hour (Group A) or 1·0 mg/kg/hour (GroupB). The infusion was continued for 45 min. The 20 min delay after diazepam was deliberate, it was intended to let the peak amnesic effect of diazepam wear off before the ketamine was injected.

Assessment

Sedation. At various time intervals during the

Table 1. Demography

Group	n	Age (yr) Mean ± SE	Weight (kg) Mean ± SE	Height (cm) Mean ± SE	Sex	Occupation	
A	10	27·5 ± 2·06	67·10 ± 4·41	165·7 ± 3·92	F 6 M 4	Anesthesiologist Secretary Nurse Other	4 2 2 2
B	10	25·9 ± 0·91	63·0 ± 3·05	167·2 ± 2·67	F 6 M 4	Anesthesiologist Secretary Nurse Other	5 3 1 1

Table 2. Investigation protocol

Drugs.	A	D		K_1 K_2				K_3
Memory card number	1	2	3	4	5	6		7
Observation points	1	2	3	4	5	6	7	8
Elapsed time (mins)	0	5	10	15	20	25	30	35	40	45	50	55	60	65

Drugs. A = atropine.
D = diazepam.
K = ketamine.
K_1 = bolus: K_2 = start infusion: K_3 = finish infusion.

study, (Table 2) the grades of sedation were noted according to the following scale: 'no sedation' = 1: 'calm but not asleep' = 2: 'sleepy, easily arousable' = 3: 'asleep, but can communicate with difficulty' = 4: 'unable to communicate' = 5.

Analgesia. The presence or absence of satisfactory analgesia was determined from response of the volunteer to pin pricks. The frontal aspect of the forearm was pricked several times manually with a sharp 25 swg needle, by the same investigator, using a standard force and pressure. The volunteer was asked to compare the sharpness of the pricks given after the drugs with the ones given before (control). Most of the time the volunteer could express verbally if the sharpness was the same or of less magnitude. On rare occasions, when the volunteer was unable to respond verbally, (sedation-grade 5), the absence of the physical responses (withdrawal or grimace) was considered to be evidence of satisfactory analgesia. Thus only the frequency of (satisfactory) analgesia was observed and not the degrees.

Memory. Each volunteer was shown seven memory cards, one at a time, at the times specified (Table 2). The memory cards consisted of black and white sketches of familiar objects and animals. The same seven cards were shown to each volunteer but they were randomised within the group. The volunteers were asked to identify each picture when shown.

Twenty-four hours following the study each volunteer was questioned by one of the authors (SKP). At the time of interview, each was asked to recollect and then recognise the memory cards from a pile of similar cards. Inability to both 'recollect' and 'recognise' a card was considered as 'amnesia' for the memory card. The volunteers were also asked about any untoward side effects during and following the study and their willingness to accept the same drugs again.

Control. Another group of ten volunteers, who received no drugs, acted as controls. They were shown the same seven memory cards and were questioned the next day in a similar manner.

Results

The two groups of volunteers were comparable in all the demographic parameters.

Sedation and analgesia

Diazepam alone produced no analgesia and moderate degree of sedation ranging from grade (mean ± SE) 2·8 ± 0·2 to 2·1 ± 0·1 in (Fig. 1).

Ketamine in both the groups produced marked sedation following bolus injection for about 20 min followed by moderate sedation during iv infusion (Fig. 1). As shown in Fig. 2 good analgesia to pin prick of more than 50% frequency was observed in both the groups during ketamine infusion.

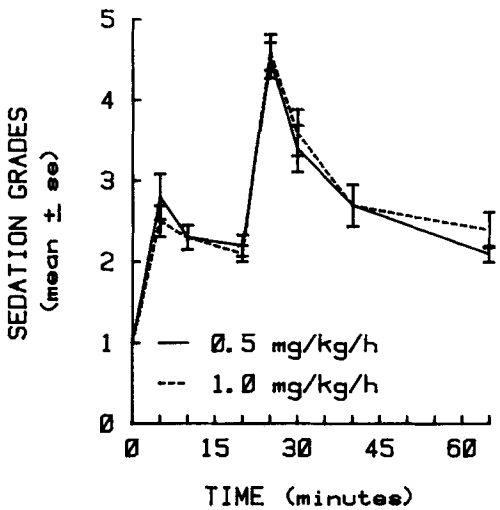

Fig. 1. Grades of sedation (mean ± SE) following diazepam (0 min) and ketamine (20 min).

Memory

The non-treated control group volunteers remembered all seven memory cards.

All volunteers who had received drugs remembered the first memory card shown to them just before diazepam administration; there was thus no retrograde amnesia to diazepam administration.

Diazepam pre-medication produced a high frequency of amnesia for short duration (Fig. 3) and the incidence declined to a low level before any ketamine was administered.

The bolus of ketamine 1·0 mg/kg followed by iv infusion produced marked sedation. Therefore there was no response to either a command or to the pin prick 5 minutes following ketamine in any volunteer and it was assumed that there was 100% amnesia at this point.

Ketamine infusion. Most of the volunteers were able to communicate and identify the

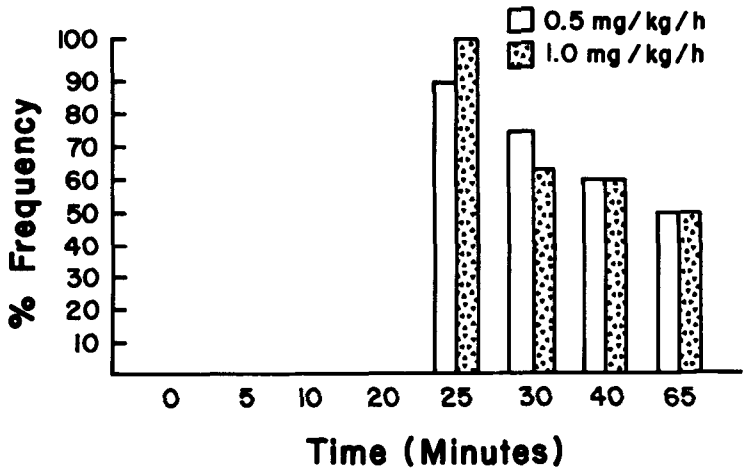

Fig. 2. Percentage frequency of 'satisfactory analgesia' following diazepam (0 min) and ketamine (20 min). *Group A* = 0·5 mg/ka/h: *Group B* = 1·0 mg/kg/h.

subsequent memory cards at the time of exposure. However, during the interview, 24 hours later, many could not recollect and/or recognise these cards.

The frequency of amnesia following 0·5 mg/kg/hour at ketamine steadily declined and was only 20%, 45 min after the start of infusion. However in the 1·0 mg/kg/hour group this frequency reached a maximum at 50–60% level (Fig. 3).

Side-effects

Cardiac. Following the bolus of 1·0 mg/kg of ketamine iv there was a transient but statistically significant rise in mean arterial blood pressure (Fig. 4) and heartrate (Fig. 5) in both the groups which lasted about 20 minutes.

Respiratory. Following the iv ketamine bolus one patient in group A and two patients in group B became apnoeic transiently and required oxygen by mask and ventilatory assistance.

Respiratory depression and shallow respiration occurred in 60% of volunteers in group A and 50% in group B (Table 3). This effect did not last for more than one minute in any case.

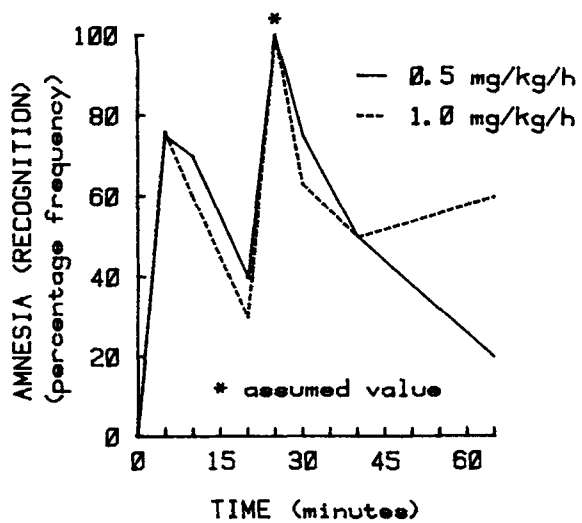

Fig. 3. Petcentage frequency of anterograde amnesia following diazepam (0 min) and ketamine (20 min).

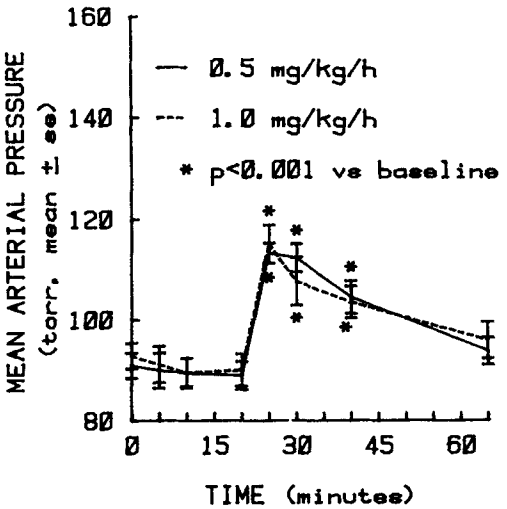

Fig. 4. Changes in the mean arterial pressure (±SE) following diazepam (0 min) and ketamine (20 min).

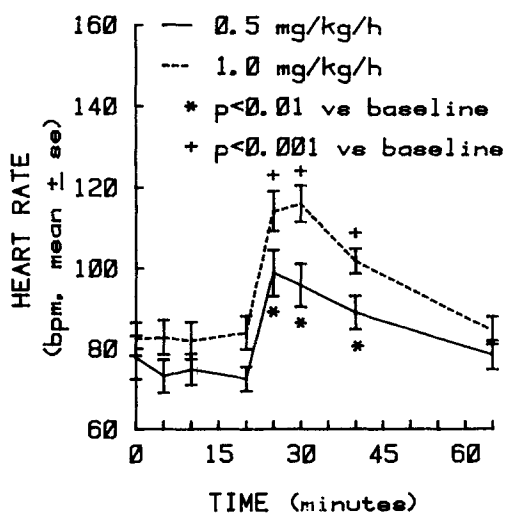

Fig. 5. Changes in the heart rate (mean±SE) following diazepam (0 min) and ketamine (20 min).

Table 3. Respiratory side-effects

	Group A	Group B
Airway problem	0	0
Secretion	0	0
Respiratory depression	6	5
Apnoea	1	2

Table 4. Psychomimetic side-effects

	Group A	Group B
Dreams:		
pleasant	1	2
unpleasant	0	1
Hallucination:		
pleasant	3	3
unpleasant	1	1
Illusion	8	8
Euphoria	4	6
Dysphoria	1	1

Psychomimetic. One volunteer in each group had unpleasant dreams and hallucinations. Visual disturbances and illusions were present in about 80% of the cases in both groups (Table 4).

Acceptance. Eighty per cent of the volunteers in group A and 90% in group B would be willing to accept the same treatment again.

Discussion

Many authors have described the introduction of ketamine as one of the most significant developments in anaesthetic practice in recent years but others would not even consider it to be a worthwhile anaesthetic. The majority of practising anaesthetists would probably like to have it on their shelves and use it only for very selective indications. The authors believe that the correct indications for, and methods of use of, this unique and controversial agent are still emerging. The use of ketamine in a relatively small dose administered in a continuous infusion is probably a step in the right direction.

One of the problems of the use of ketamine as a part of balanced anaesthesia, especially in a paralysed patient, is the difficulty in assessing the depth of anaesthesia. The main reason for this is the stimulatory effects of ketamine on the cardiovascular system. Thus, it is only by experienced guess work that one determines the dose of ketamine. This lack of objectivity is clearly indicated in the wide variability in the recommended doses.[1–4] It did not come as a surprise when Kumar *et al.*[5] reported a case of recall of the intra-operative events when they used ketamine infusion 1 mg/kg/hour without nitrous oxide or incremental diazepam for open heart surgery.

The state of anaesthesia is a complex phenomenon. It includes suppression of many bodily functions especially those of the central nervous system. The concept of MAC (minimal alveolar concentration) introduced by Eger[6] has introduced an objective way to determine the required concentration of an inhalation anaesthetic agent in clinical situations but there are limitations to this concept—lack of movement to painful stimuli does not necessarily mean lack of awareness. To extrapolate this concept for intravenous anaesthetics used to supplement balanced general anaesthesia, one would really like to know the drug requirement to produce amnesia in at least 50% of the individuals, in addition to analgesia and sedation.

In this study the frequency of amnesia to visual stimulation in non-surgical adult volunteers who were under the influence of low dose ketamine and were still able to respond to commands and identify the memory cards has been determined.

Many investigators have used visual memory cards to determine the frequency of drug-induced amnesia. This method has been found to be remarkably consistent and reproducible for this purpose under various settings.[7–11] An initial bolus injection of 1 mg/kg, followed by a continuous infusion of ketamine at a rate of 1 mg/kg/hour produces amnesia in 50% of the population. Lack of recall in 50% of the population of a visual stimulus at a given time does not necessarily mean that the same dose will suppress other central nervous system functions (such as sensations of pain) to the same extent. But fortunately the authors, as well as others[1,2,12–14] have found that ketamine is an excellent analgesic even in small doses. In this study both 0·5 mg/kg/hour and 1 mg/kg/hour of iv ketamine produced equally good analgesia.

The findings which have been reported above regarding ketamine dose requirement come very close to the dosages used by Vaughan & Stephen[15] in clinical situations (1·09 to 1·17 mg/kg/hour), with nitrous oxide and relaxants after premedication with 'Innovar' (fentanyl and droperidol). The authors agree with Lilburn *et al.*[3] who pointed out that dose requirement would probably decrease with time. Other factors such as the age of the patient, his general condition, temperature, etc. would undoubtedly modify the dose requirement of ketamine and/or supplemental agents.

Unlike the amnesic effects of diazepam[7] and lorazepam,[8] the amnesic effects of low dose ketamine were parallel to their sedative effects. It would appear that ketamine does not possess a specific depressive effect on the memory centres but rather behaves like other traditional anaesthetic agents—the depth of anaesthesia and memory suppression being dose-dependent.

In this study diazepam (0·2 mg/kg) given 20 min before ketamine did not completely abolish the psychomimetic side-effects of ketamine. This is in agreement with studies done by Bovill *et al.*[16] Diazepam (or preferably lorazepam) given towards the end of the procedure would probably work better than when given 20 min earlier.[17]

The pre-treatment with diazepam given 20 min before ketamine did not prevent the cardiostimulatory effects of the bolus administration of ketamine either. This is in agreement with Bovill *et al.*[16] but not with Kothary *et al.*[18] who found that pretreatment with diazepam (0·2 mg/kg) iv 5 min before ketamine (2 mg/kg) iv prevented its cardiostimulatory effects.

Another significant observation was the transient respiratory depression seen in a number of cases even with 1 mg/kg of iv ketamine. This is of clinical significance since it occurred in the absence of any narcotic pre-medication. In this present study these episodes were noted because the volunteers were observed very closely. Zsigmond *et al.*[19] have documented the respiratory depressant effect of ketamine (2 mg/kg) after narcotic premedication

In the authors' clinical practice ketamine infusions at the rate of 1–2 mg/kg/hour following bolus administrations of 1 mg/kg, have been used to supplement light general anaesthesia with 50–70% nitrous oxide in oxygen (sometimes with incremental diazepam injections); cases of recall of intraoperative events have not been encountered in a group of about 50 cases.

Acknowledgment

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