KETAMINE INFUSIONS: PHARMACOKINETICS AND CLINICAL EFFECTS

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SUMMARY
The clinical effects and pharmacokinetics of ketamine, administered as an i.v. infusion, were studied in 31 patients. Anaesthesia was induced with ketamine 2 mg kg\(^{-1}\) i.v. and maintained using an i.v. infusion of ketamine, supplemented by nitrous oxide. The plasma concentrations of ketamine, nor-ketamine and dehydro-nor-ketamine were analysed using gas-liquid chromatography. The average maintenance dose of ketamine was 41 ± 21 µg kg\(^{-1}\) min\(^{-1}\), but there was an obvious decrease in the dose required as anaesthesia progressed. This dose gave a stable plasma concentration of ketamine of 9.3 ± 0.8 nmol litre\(^{-1}\). Patients recovered at 2.7 ± 0.9 nmol litre\(^{-1}\). Plasma half-life of ketamine was 79 ± 8 min. Maximum concentration of nor-ketamine was 4.7 ± 2.4 nmol litre\(^{-1}\) and of dehydro-nor-ketamine 3.2 ± 1.9 µmol litre\(^{-1}\). There were transient increases (15–30% of pre-anaesthetic values) in arterial pressure, heart rate and cardiac output during operation. No post-operative respiratory depression was seen.

Ketamine has been acclaimed on account of its safety and its favourable effects upon the cardiovascular and respiratory systems (Langrehr et al., 1967; Lanning and Harmel, 1975) and, because of its sympathomimetic and antiarhythmic properties, it is useful in poor-risk and hypovolaemic patients. Over the years several anaesthetic techniques have been studied and many different supplementary drugs have been administered with ketamine. For example, a continuous infusion technique has been recommended to decrease the total dose and to obtain smoother anaesthesia. This study was undertaken to evaluate further the pharmacokinetic properties and clinical effects of a continuous infusion of ketamine supplemented with nitrous oxide.

PATIENTS AND METHODS

Patients
Fifteen male and 16 female patients undergoing major abdominal surgery were studied. The mean age was 67 yr (SD 15) (range 24–90 yr) and mean body weight 66.5 kg ± 14.3 (range 32–100 kg). The patients were classified according to the grading of physical status of the American Society of Anesthesiologists (ASA) described by Saklad (1941); two patients were grade I, five grade II, 15 grade III and nine grade IV.

All patients had normal serum creatinine concentrations. Seven were jaundiced because of extrahepatic obstruction. None of the patients in the study had a history of psychiatric disease or abuse of alcohol. Mean operation time was 159 ± 63 min.

Cardiac output was determined in six male and four female patients selected at random, mean age 68 ± 7 yr, mean ASA grade III.

To evaluate the effect of ketamine on respiration, the patients were divided into two groups with respect to premedication: group 1 (15 patients) received atropine only and group 2 (16 patients) atropine and pethidine hydrochloride or fentanyl. The mean age and ASA grade were greater in group 1.

Anaesthetic technique
Atropine 0.5 mg i.m. was given as premedication in all patients. Fourteen patients received also pethidine (Petidin, ACO) 50–75 mg and promethazine (Lergigan, Recip) 25 mg i.m. and two patients received a mixture of fentanyl 0.1 mg and droperidol 5 mg i.m. (Leptanal comp., Leo) as well as atropine.

The induction dose of ketamine (2 mg/kg body weight i.v.) was given over a period of 1 min (Ketalar 10 mg ml\(^{-1}\), Parke–Davis). The trachea was intubated under paralysis induced with suxamethonium (Celocurin-klorid, Vitrum) 75–100 mg i.v.

The lungs were ventilated artificially using a Servo-Ventilator (Elema–Schönander, Stockholm) set to deliver 65% nitrous oxide in oxygen. Adequate

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ventilation was verified by the analysis of arterial blood-gas tensions. After the induction of anaesthesia, a continuous i.v. infusion of ketamine 50 mg ml\(^{-1}\) was started via a cubital vein using a Dascon infusion pump model 300, allowing flows from 0.01 to 9.99 ml h\(^{-1}\). The initial infusion rate was 40 μg kg\(^{-1}\) min\(^{-1}\), and was adjusted to maintain sleep and produce adequate operating conditions. During the operation neuro-muscular blockade was maintained with the intermittent administration of suxamethonium or pancuronium (Pavulon, Organon). The ketamine infusion was discontinued 10-20 min before the end of the operation. All patients had 2 min of pure oxygen-breathing before removal of the tracheal tube.

Clinical observations
After the anaesthetic, recovery was considered acceptable if the patient could state his name and date of birth. In the ward after operation the patients were assessed continually with emphasis on general behaviour, alertness and the onset of pain. Two hours after anaesthesia and on the following day all patients were interviewed by a nurse anaesthetist about the anaesthetic, being questioned especially about dreaming. In this study only two nurses took part in the anaesthetic procedures and the interviews.

Monitoring of cardiovascular and respiratory function
Arterial pressure was monitored directly via a catheter which was inserted to a radial artery before anaesthesia (transducer EMT 746, Elema-Schönander, Stockholm). E.c.g. was recorded continuously. Cardiac output was determined according to Wassen (1956). All measurements were made before the induction of anaesthesia, 5-15 min after induction and during steady-state anaesthesia. Arterial blood-gas tensions and pH were measured just before anaesthesia (after premedication), during the operation, and 2 h afterwards (IL 413, Instrumentation Laboratories, Boston).

Analysis of ketamine and its metabolites
The gas–liquid chromatographic technique of Chang and Glazko (1972) was used.

Chemicals. Ketamine hydrochloride (2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride), metabolite I (2-amino-2-(o-chlorophenyl) cyclohexanone hydrochloride), metabolite II (2-amino - 2 -(o - chlorophenyl) - 3 - cyclohexen - 1 - one hydrochloride) and internal standard (2-(o-bromo-phenyl)-2-(methylamino) cyclohexanone hydrochloride) were supplied by Parke-Davis. Benzene (Merck 1785), anhydrous sodium sulphate (Merck 6649), heptafluorobutyric anhydride (Pierce 63163) and pyridine (Merck 7463) were used without further purification.

Apparatus. A Varian 3700 Gas Chromatograph equipped with a nickel-63 electron capture detector and a glass column (150 x 0.2 cm i.d.) packed with 3% OV-17 on GasChrom Q 80 /100 mesh were used for the analyses. Injection temperature was maintained at 220 °C, column temperature at 205 °C and the detector at 250 °C. Nitrogen 30 ml min\(^{-1}\) was used as the carrier gas.

Procedure. Samples of arterial blood were taken into heparinized tubes 5 and 20 min after the induction of anaesthesia, every 20 min during the steady state and 15, 30, 45, 60 and 120 min after stopping the infusion. A few samples were collected 24 h after anaesthesia. The tubes were centrifuged at 1000 g for 10 min, and the plasma was then stored at —20 °C before analysis (maximum storage time 2 months).

Statistics
The Wilcoxon test for paired observations or the Mann–Whitney test for comparison of groups were used for statistical calculations.

RESULTS
The anaesthetic technique described gave good operating conditions in all patients. Recovery was rapid; 15 patients were able to state their names and date-of-birth within 5–10 min of extubation, 13 patients showed the same degree of alertness within 30 min, and two patients within 60 min. None reported awareness or dreams during the operation, but four patients experienced dreams in the period after operation and in two of these, aged 24 and 37 yr, the dreams were unpleasant. Otherwise, no excitement, agitation, anxiety or involuntary motor activity occurred during recovery. Nausea and vomiting were noted in three patients. Directly after the operation one patient complained of pain, which was abolished by diazepam 5 mg i.v. No other patient required an analgesic or sedative during the first 2 h after operation.

Changes in systolic and diastolic arterial pressure and heart rate are shown as per cent of pre-anaesthetic value in figure 1. There was an initial increase in all values, and the peak value was reached within 10 min of the induction of anaesthesia. The maximum mean increase in systolic pressure was 31%, in diastolic pressure 27% and in heart rate 19%. About 30 min after induction arterial pressure and heart rate
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Fig. 1. Percentage change in systolic and diastolic arterial pressures and heart rate from initial values in all patients (n = 31) expressed as mean ± SD.

returned gradually to the original values where they remained throughout the remainder of the anaesthetic.

The calculated cardiac index and stroke index are shown in table I. Five to 15 min after the induction of anaesthesia cardiac index had increased significantly (P < 0.05) from 3.1 litre min⁻¹ m⁻² to 3.5 litre min⁻¹ m⁻². Later, during steady-state anaesthesia, cardiac index decreased to 2.6 litre min⁻¹ m⁻² (P < 0.01). There were no significant changes in stroke index.

| TABLE I. Changes in cardiac index and stroke index in 10 patients. Mean ± SD. P value refers to comparison with values before anaesthesia |
|---------------------------------|------------------|------------------|
| Cardiac index                   | Stroke index     |
| (litre min⁻¹ m⁻²)               | (ml beat⁻¹ m⁻²)  |
| Before anaesthesia              | 5-15 min         | During steady-   |
|                                 | after induction  | state anaesthesia|
|                                 | of anaesthesia   |                  |
| 3.1 ± 0.8                       | 3.5 ± 0.7        | 2.6 ± 0.6        |
| (P < 0.05)                      | (P < 0.05)       | (P < 0.01)       |
| 34.0 ± 9.0                      | 34.0 ± 10        | 31.0 ± 10        |
| (n.s.)                          | (n.s.)           | (n.s.)           |

Frequent ventricular arrhythmia was noted before operation in three patients, but this decreased or disappeared during ketamine anaesthesia.

Although $P_{\text{a}CO_2}$ and pH were unchanged after operation, mean $P_{\text{a}O_2}$ increased in the period after operation (P < 0.02). $P_{\text{a}O_2}$ values studied separately in the two subgroups revealed no significant change in group 1, but a significant increase in group 2 (P < 0.01) (table II).

The mean plasma concentrations of ketamine and metabolites I and II are shown in figures 2 and 3. Five minutes after the injection of the initial loading dose, a plasma concentration of ketamine of about 60 µmol litre⁻¹ was found. The plasma concentration of ketamine then decreased rapidly to about 7-10 µmol litre⁻¹ where it remained throughout the anaesthetic. Mean infusion rate for the total time of anaesthesia was 41 ± 21 µg kg⁻¹ min⁻¹. During the first 30 min of the operation the ketamine infusion rate was 58 ± 22 µg kg⁻¹ min⁻¹ and during the last 30 min it was 17 ± 17 µg kg⁻¹ min⁻¹. After the infusion was stopped, the plasma ketamine concentration decreased during the distribution phase, which lasted about 30 min. This phase was followed by an elimination phase with the ketamine concentration

| TABLE II. Arterial blood-gas tensions in all patients (n = 31) before and after ketamine anaesthesia and $P_{\text{a}O_2}$ of the patients when divided into two groups. Group 1 (n = 15) premedicated with atropine only and group 2 (n = 16) with atropine and an analgesic (pethidine or fentanyl). Mean ± SD |
|---------------------------------|------------------|
| Before operation                | After operation   | P      |
| $P_{\text{a}CO_2}$ (kPa) (n = 31)| 5.0 ± 0.4        | 5.0 ± 0.5 | n.s.  |
| $P_{\text{a}O_2}$ (kPa) (n = 31)| 10.0 ± 1.3       | 11.0 ± 1.5 | < 0.02 |
| $P_{\text{a}O_2}$ (kPa)         |                   |        |
| Group 1 (n = 15)                | 10.2 ± 1.4       | 10.4 ± 1.5 | n.s.  |
| Group 2 (n = 16)                | 10.0 ± 1.3       | 11.2 ± 1.3 | < 0.01 |

Fig. 2. Plasma concentrations of ketamine, nor-ketamine (metabolite I) and dehydro-nor-ketamine (metabolite II) during anaesthesia. Mean ± SD. All anaesthetics ≥ 150 min.
The anaesthetic plasma concentration of ketamine, calculated as the mean of the ketamine concentrations during steady-state anaesthesia, was $9.3 \pm 0.8 \text{ mmol litre}^{-1}$, while the plasma concentration during recovery was $2.7 \pm 0.9 \text{ mmol litre}^{-1}$.

Maximal concentrations of metabolite I ($4.7 \pm 2.4 \text{ mmol litre}^{-1}$) and metabolite II ($3.2 \pm 1.9 \text{ mmol litre}^{-1}$) were observed about 3 h after the induction of anaesthesia. Analysis of a few samples drawn 24 h after the operation revealed measurable plasma concentrations of metabolite II while ketamine and metabolite I were not detected.

**DISCUSSION**

Ketamine produced good surgical anaesthesia and total amnesia. In addition, however, a neuromuscular blocking drug was necessary for intra-abdominal surgery, as has been observed previously by Gjessing (1968).

Different techniques of anaesthesia have been tried in order to minimize the side-effects of ketamine, especially its psychotomimetic effects. Sedative drugs as premedication, as supplementation during anaesthesia or as postoperative sedation have been used to decrease the frequency of emergence phenomena. Diazepam (Kothary and Zsigmond, 1975), lorazepam (Dundee and Lilburn, 1978) and droperidol (Sadove et al., 1971) have been used for this purpose, but according to Lo and Cumming (1975) ketamine-induced sleep time and ketamine plasma half-life were prolonged in patients premedicated with diazepam, hydroxyzine or secobarbital. Therefore, in this study, a sedation technique was avoided as a rapid recovery was considered important.

A decrease in the dose of ketamine has been suggested as a means of reducing sequelae (Chodoff and Stella, 1966) and this can be achieved by the use of a continuous infusion for the maintenance of anaesthesia (Sabathie et al., 1976; El-Naggar et al., 1977; Hatano, Nishiwada and Matsumura, 1978; Lilburn, Dundee and Moore, 1978). The use of nitrous oxide as a supplement has been shown by Wessels, Allen and Slogoff (1973) to reduce the dose of ketamine and ketamine-dependent side-effects.

In this study, in which ketamine was given by continuous infusion with nitrous oxide as a supplement, recovery was fast and psychotomimetic side-effects were not prominent. Like Garfield and colleagues (1972), we found early verbal and tactile stimulation during the recovery period beneficial.

Using this technique of anaesthesia, a stable concentration of ketamine in the plasma was achieved. None of the patients had received drugs that might have interfered with the metabolism of ketamine or its metabolites. This is reflected in the small differences in metabolic pattern between patients. However, the relationship between the dose required and body weight was not good, a standard deviation of about 50% being obtained. Wulfsohn (1972) has reported that lean body mass is a better basis on which to calculate the dose of ketamine required for induction, and this may be true also for the maintenance dose. Moreover, it was found that the maintenance dose could be decreased gradually during the operation, the dose during the last 30 min being significantly less than that during the first 30 min. This agrees with a two-compartment model.
of pharmacokinetics with re-entry of ketamine from the peripheral to the central compartment. Lilburn, Dundee and Moore (1978) found that the amount of ketamine per unit time could be decreased for long operations. With ketamine alone, they administered about 100–200 $\mu$g kg$^{-1}$ min$^{-1}$, the dose required being smaller with controlled than with spontaneous ventilation. In this study the maintenance dose was less because of supplementary nitrous oxide and the larger loading dose, 2 mg kg$^{-1}$ instead of 1 mg kg$^{-1}$. If the initial loading dose is insufficient, anaesthetic concentrations will be attained slowly and an increased rate of infusion will be required. This will lead to greater total ketamine dosage, greater loading of tissue stores and delayed recovery after anaesthesia.

In this study metabolite I was the major metabolite noted during anaesthesia, metabolite II reaching a plasma concentration approximately equal to that of metabolite I about 2 h after the infusion was stopped. Analysis of the samples drawn 24 h after anaesthesia showed that metabolite II was the major metabolite at that time. The metabolites appeared to have no significant anaesthetic properties.

Despite liver insufficiency in seven of the patients no significant differences were seen in the metabolism of ketamine in these patients as compared with the other patients. Nor were there any differences in the dose required. This is in agreement with the results of Schaps and Hauenschild (1977).

The haemodynamic study confirmed that ketamine is a circulatory stimulant. Our results are compatible with those of Virtue and colleagues (1967) who studied healthy volunteers, and with the results of Lorhan and Lippman (1971), who studied elderly poor-risk patients. The stimulatory effect could depend on an increase in sympathetic activity, which has been demonstrated by Traber, Wilson and Priano (1968) and Zsigmond, Kelsch and Kohary (1975). Moreover, ketamine has been shown to display a vagolytic action, which can be attenuated by atropine (Traber, Wilson and Priano, 1970). Thus the stimulatory effect observed in this study was modified by atropine, given to all the patients as premedication. Lilburn, Dundee and Moore (1978) found in their study that the combination of ketamine and pancuronium produced an unacceptable degree of hypertension and tachycardia. However, such effects were not observed in this study.

Cardiac index had increased 5-15 min after the induction of anaesthesia ($P < 0.05$), a change which coincided with the maximum increases in arterial pressure and heart rate, but there was no change in stroke index—results which are in agreement with those of Tweed, Minuck and Mymin (1972).

The antiarrhythmic effect observed in this study is similar to that noted by Dowdy and Kaya (1968) who found a significant prolongation of the functional refractory period after the administration of ketamine to dogs with ventricular disrhythmia.

Analysis of arterial blood-gas tensions revealed no respiratory depression after operation when compared with the preoperative values, similar to those observed by Virtue and colleagues (1967). A significant increase in postoperative $P_{aO_2}$ was observed in the patients in group 2. The most likely explanation for this is that the pre-operative blood sample was taken when the patients were under the influence of premedication with pethidine or fentanyl and had, consequently, some depression of respiration (Eckenhoff and Helrich, 1958; Downes, Kemp and Lambertsen, 1967; Goodman and Gilman, 1970).

In this study, ketamine, given by a continuous infusion in combination with nitrous oxide, was found to produce favourable haemodynamic conditions, no respiratory depression after operation and few psychotomimetic side-effects. It may be concluded that ketamine given in this manner along with a neuromuscular blocking drug is a suitable anaesthetic technique for intra-abdominal surgery, particularly in elderly patients.


**INFUSIONS DE KETAMINE: PHARMACOKINETIQUE ET EFFETS CLINIQUES**

On a étudié les effets cliniques et la pharmacocinétique de la kéthémine sur 31 malades auxquels on avait injecté ce produit par voie intraveineuse. L'anesthésie a été produite par la kéthémine administrée par voie intraveineuse à raison de 2 mg kg⁻¹ et elle a été maintenue à l'aide d'une injection intraveineuse de kéthémine, complétée par du protoxyde d'azote. Les concentrations de kéthémine, de nor-kéthémine et de déshydro-nor-kéthémine dans le plasma ont été analysées par chromatographie en phase gazeuse–liquide. La dose moyenne de kéthémine d'entretien a été de 41 ± 21 µg kg⁻¹ min⁻¹, mais il y a eu une diminution évidente dans la dose requise, au fur et à mesure que l'anesthésie a progressé. Cette dose a donné une concentration stable de kéthémine dans le plasma de 9,3 ± 0,8 µmol litre⁻¹. Les patients ont repris conscience à 2,7 ± 0,9 µmol litre⁻¹. La demi-vie de la kéthémine dans le plasma a été de 79 ± 8 min. La concentration maximale de nor-kéthémine a été de 4,7 ± 2,4 µmol litre⁻¹ et celle de déshydro-nor-kéthémine de 3,2 ± 1,9 µmol litre⁻¹. Il y a eu des augmentations transitoires (15–30% des valeurs pré-anesthésie) de la pression artérielle, de la fréquence cardiaque et du débit cardiaque pendant l'opération. On n'a constaté aucune dépression respiratoire postopératoire.

**KETAMIN-INFUSIONEN: PHARMAKOKINETISCHE UND KLINISCHE WIRKUNGEN**

Die pharmakokinetischen und klinischen Wirkungen einer intravenöse verabreichten Kétamin-Infusion wurden bei 31 Patienten studiert. Narkose wurde durch 2 mg kg⁻¹ Ketamin intravenös eingeleitet und durch eine intravenöse Infusion von Ketamin, ergänzt durch Stickoxyd, aufrecht erhalten. Die Plasmakonzentrationen von Kétamin, Norkétamin und Dehydronorkétamin wurden bei einer Gas-Flüssigkeitschromatographie analysiert. Die mittlere Aufrechterhaltungsdosis von Kétamin betrug 41 ± 21 µg kg⁻¹ min⁻¹ doch kam es zu einem offensichtlichen Sinken der erforderlichen Dosis bei fortschreitender Narkose. Diese Dosis ergab eine stabile Plasmakonzentration von 9,3 ± 0,8 µmol Liter⁻¹ Kétamin. Patienten erholten sich bei 2,7 ± 0,9 µmol Liter⁻¹. Die Plasma-Halbwertzeit von Kétamin betrug 79 ± 8 min. Die Maximalkonzentration von Norkétamin betrug 4,7 ± 2,4 µmol Liter⁻¹, und von
Dehydronorketamin $3,2 \pm 1,9 \mu mol \text{ Litro}^{-1}$. Es gab vorübergehende Anstiege (15-30% der Vornarkosewerte) von arteriellem Druck, Herzminutenvolumen und Herzfrequenz während der Operation. Eine postoperative respiratorische Dämpfung wurde nicht beobachtet.

INFUSIONES DE QUETAMINA: EFECTOS FARMACOCINÉTICOS Y CLÍNICOS

SUMARIO
En 31 pacientes, se estudió los efectos clínicos y farmacocinéticos de la quetamina administrada como infusión i.v. Se indujo la anestesia con $2 \text{ mg kg}^{-1}$ de quetamina y fue mantenida por medio de una infusión i.v. de quetamina, complementada por óxido nitroso. Se analizaron las concentraciones en el plasma de quetamina, nor-quetamina y dehidro-nor-quetamina mediante cromatografía gas-líquido. La dosis media de mantenimiento de quetamina era de $41 \pm 21 \mu g \text{ kg}^{-1} \text{ min}^{-1}$, pero hubo una disminución evidente de la dosis necesaria a medida que progresara la anestesia. Esta dosis dio una concentración estable de quetamina en el plasma de $9,3 \pm 0,8 \mu mol \text{ litro}^{-1}$. Los pacientes se recuperaron en $2,7 \pm 0,9 \mu mol \text{ litro}^{-1}$. La media-vida de la quetamina en el plasma fue de $79 \pm 8 \text{ min}$. La concentración máxima de nor-quetamina fue de $4,7 \pm 2,4 \mu mol \text{ litro}^{-1}$ y de dehidro-nor-quetamina de $3,2 \pm 1,9 \mu mol \text{ litro}^{-1}$. Durante la operación, hubo aumentos transitorios (15-30% de los valores pre-anestésicos) en la presión arterial, el ritmo cardíaco y la función sistólica. No se registró ninguna depresión respiratoria post-operatoria.