PHARMACOKINETICS AND ANALGESIC EFFECT OF KETAMINE IN MAN

J. A. CLEMENTS AND W. S. NIMMO

SUMMARY
The pharmacokinetics and analgesic effect of i.v. ketamine in doses of 125 \( \mu g \) kg\(^{-1}\) and 250 \( \mu g \) kg\(^{-1}\) were determined in five healthy volunteers. Analgesia was measured with the submaximal effort tourniquet test. Both doses of ketamine prolonged the period of pain-free ischaemic exercise while the plasma ketamine concentration was greater than 100 ng ml\(^{-1}\). Ketamine was distributed rapidly (\( T_{1/2} = 17 \) min). The elimination half-life was 186 min.

Ketamine (2-o-chlorophenyl-2-methylamino-cyclohexanone) rapidly produces sleep following i.v. injection of 1-2 mg kg\(^{-1}\) (Ghoneim and Korttila, 1977). It has analgesic properties (Caro, 1974; Wilson, Herrin and Richey, 1978) and has been used as repeated i.v. injections of 0.5 mg kg\(^{-1}\) or as an infusion of 1-2 mg min\(^{-1}\) to provide analgesia after operation (Ito and Ichiyanagi, 1974; Clausen, Sinclair and Hasselt, 1975; Austin, 1976).

We have investigated the pharmacokinetics and analgesic activity of i.v. ketamine at two dose concentrations.

METHODS
Five fasting healthy adult males (age 33.8 ± 1.4 yr, (SEM) height 1.83 ± 0.02 m, weight 74.8 ± 2.1 kg) were studied on three occasions at least 1 week apart: once after ketamine 250 \( \mu g \) kg\(^{-1}\), once after ketamine 125 \( \mu g \) kg\(^{-1}\) and once after a placebo injection of saline. The order was randomized and the test injection was given i.v. to the antecubital vein over a period of 15 s. Neither the subject nor the person recording the pain score was aware of the nature of the injection. Blood samples were taken from a venous cannula distal to the injection site in the dominant arm at intervals for 7 h. Plasma was separated and analysed for ketamine and its two metabolites by gas-liquid chromatography.

Analgesia
The method used was similar to that of Harrison and Bigelow (1943). With the subject supine, a sphygmomanometer cuff on the non-dominant arm was inflated to 250 mm Hg and the subject was required to squeeze a rubber ball once per second. At 15-s intervals he was asked to describe pain in the forearm as none, mild, moderate or severe. When the pain became intolerable, the sphygmomanometer cuff was immediately deflated and the "tourniquet time" noted. Subjects were tested at 5-min intervals for a 30-min control period. Ketamine (Ketalar, Parke Davis) or saline was then injected and the subject tested at 5-min intervals for 20 min and then at 10-min intervals for a further 40 min. Tests of statistical significance were carried out by paired \( t \) test.

Ketamine analysis
Plasma samples were analysed for ketamine, norketamine (metabolite I) and dehydro-norketamine (metabolite II) as their heptafluorobutyryl derivatives using a gas–liquid chromatograph with electron-capture detection (Walle and Ehrsson, 1970; Chang and Glazko, 1972). The extraction and derivatization procedure was that of Chang and Glazko (1972) with the following modifications. Toluene was used as the solvent; derivatization was carried out using pyridine 20 \( \mu l \)itre and heptafluorobutyric anhydride 20 \( \mu l \)itre and by heating for 10 min at 40 °C. Oven temperature was maintained at 195 °C. The electron capture detector (nickel-63 source) was set at a pulse frequency of 6 kHz and operated at 250 °C. The internal standard was 2-o-bromophenyl-2-methylaminocyclohexanone hydrochloride. Peak height ratio (analyte : internal standard) was proportional to the concentration in plasma for ketamine in the range 20–200 ng ml\(^{-1}\) and for metabolites I and II in the range 10–100 ng ml\(^{-1}\). The
coefficients of variation for replicate analyses \((n = 5)\) on standard solutions were 5.3\% (concentration 50 ng ml\(^{-1}\)) for ketamine and 7.4\% (concentration 500 ng ml\(^{-1}\)) for metabolite I.

After mixing the internal standard solution (1.0 ml) and the plasma sample (1.0 ml), the solution was carried through the assay procedure. The concentrations were calculated from peak height ratios with reference to standard solutions run on the same day. All plasma samples were analysed in duplicate.

**RESULTS**

**Pain measurements**

Ketamine prolonged the period of pain-free ischaemic exercise as shown by the pain scores at 15-s intervals (fig. 1) and by the "tourniquet times" (table I). In the 30-min period before injection the "tourniquet times" did not differ significantly from one another and the pain scores were the same in all three groups; moderate to severe pain was experienced within 60 s of inflation of the cuff. Immediately after the administration of

![Fig. 1.](image)

**TABLE I.** Times to reach intolerable pain during ischaemic exercise of the arm ("tourniquet times"). Mean times ± SEM (s). n.s. = Not significantly different from control times before injection. * Significantly greater than times before injection \((P < 0.05)\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Before injection</th>
<th>0</th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>81.4 ± 6.0</td>
<td>89.2 ± 5.6</td>
<td>84.6 ± 5.4</td>
<td>86.8 ± 8.5</td>
<td>87.0 ± 8.3</td>
</tr>
<tr>
<td>Ketamine 250 µg kg(^{-1})</td>
<td>75.8 ± 7.9</td>
<td>106 ± 13*</td>
<td>105 ± 23*</td>
<td>75.2 ± 4.0</td>
<td>74.4 ± 5.4</td>
</tr>
<tr>
<td>Ketamine 125 µg kg(^{-1})</td>
<td>74.4 ± 5.1</td>
<td>94.2 ± 4.3*</td>
<td>76.6 ± 6.6</td>
<td>73.6 ± 4.3</td>
<td>69.8 ± 3.6</td>
</tr>
</tbody>
</table>
either dose of ketamine and also at 5 min after the larger dose, the pain was graded as none to mild at 75 s. Similarly, immediately after both doses of ketamine and also 5 min after the larger dose, the "tourniquet time" was significantly prolonged. At other times and following placebo injection, pain scores and "tourniquet times" were similar to those recorded in the period before injection. Thus the analgesia produced by ketamine 250 µg kg⁻¹ i.v. lasted more than 5 min while that produced by 125 µg kg⁻¹ lasted less than 5 min.

Pharmacokinetics

Plasma ketamine concentration–time data were fitted satisfactorily by a two-compartment open model by non-linear regression analysis (Clements and Prescott, 1976). Typical results in one subject are given in figure 2. There were no significant differences in any of the pharmacokinetic parameters following either dose (table II). The mean terminal plasma half-life was about 3 h and the total body clearance was 17 ml min⁻¹ kg⁻¹. Plasma concentrations of norketamine increased rapidly and reached a mean peak concentration of 40 ± 14 ng ml⁻¹ (+ SEM) at 75 min and 21 ± 3 ng ml⁻¹ at 45 min after the larger and smaller dose respectively. No dehydro-norketamine was detected in plasma samples in the study; if present, the concentration was less than the limit of detection of 50 ng ml⁻¹.

DISCUSSION

Previous studies of ketamine in patients have been performed with infusions (Ito and Ichiyanagi, 1974; Clausen, Sinclair and Hasselt, 1975) and there is little information on the duration of action of a single analgesic dose of the drug. In our study a single injection of 250 µg kg⁻¹ increased the pain threshold for more than 5 min at a time when the plasma ketamine concentration was greater than 100 ng ml⁻¹.

The early rapid disposition of ketamine with a mean half-life of 17 min is consistent with a high oil: water partition coefficient (Cohen and Trevor, 1974) and extensive distribution within the body (White et al., 1976). The pharmacokinetic values following the smaller and larger doses did not differ significantly, suggesting that disposition of ketamine is not dose-dependent in this range. The pharmacokinetics of ketamine in analgesic doses have not been reported previously.

In patients receiving an anaesthetic dose of ketamine, plasma half-lives of 17 min and more than 4 h have been reported for the fast (α phase) and slow (β phase) disposition phases respectively (Chang et al., 1970; Chang and Glazko, 1972). A plasma half-life of 79 min has recently been reported in patients who had received an i.v. infusion (Idvall et al., 1979). In a study of five anaesthetized patients receiving ketamine 2.5 mg kg⁻¹, the plasma concentration–time data fitted a two-compartment open model; the mean disposition half-lives of 11 min and 151 min (Wieber et al., 1975) are in good agreement with the values in our study (17 min and 186 min respectively). In addition, the values of the apparent volume of distribution (214 litre) and total body clearance (1.23 litre min⁻¹) were similar to the values obtained in our study (347 litre and 1.32 litre min⁻¹ respectively). This suggests that the pharmacokinetics of ketamine are not markedly altered by the dose over a 20-fold range.
In patients receiving ketamine 2.2 mg kg$^{-1}$, consciousness returned 9–20 min after the i.v. injection when plasma concentrations were in the range 700–1120 ng ml$^{-1}$ (Little et al., 1972). After i.v. infusion, consciousness returned when plasma concentration was less than 640 ng ml$^{-1}$ (Idvall et al., 1979). It appears that the analgesic effect of ketamine occurs at much lower concentrations than the anaesthetic effects.

ACKNOWLEDGEMENTS

We are grateful to Mrs E. Cripps for technical assistance and to The Scottish Hospital Endowments Research Trust for financial support.

REFERENCES


PHARMACOCINETIQUE ET EFFET ANALGESIQUE DE LA KETAMINE CHEZ L'HOMME

RESUME

La pharmacocinétique et les effets analgésiques de l'administration de ketamine par voie intraveineuse en doses de 125 µg kg$^{-1}$ et de 250 µg kg$^{-1}$ ont été déterminés sur cinq volontaires en bonne santé. L'analgesie a été mesurée à l'aide de l'essai du tourniquet à effort submaximal. Les deux doses de ketamine ont prolongé la période d'exercice ischémique sans douleur alors que la concentration de ketamine dans le plasma était supérieure à 100 ng ml$^{-1}$. La ketamine s'est répartie rapidement ($T_{1/2} = 17$ min). La demi-vie d'élimination a été de 186 min.

PHARMACOKINETISCHE UND ANALGETISCHE WIRKUNG VON KETAMIN BEIM MENSCHEN

ZUSAMMENFASSUNG

Besagte Ketamin-Wirkung von intravenösen Dosen zu 125 µg kg$^{-1}$ und 250 µg kg$^{-1}$ wurde bei fünf gesunden Freiwilligen untersucht. Die schmerzlindernde Wirkung wurde mit dem untermaximalen Knebelwirkungstest gemessen. Beide Ketamin-Dosen verlängerten die Periode der schmerzfreien ischämischen Übung, während die Ketamin-Plasmaskonzentration über 100 ng ml$^{-1}$ lag. Ketamin wurde rapide verteilt ($T_{1/2} = 17$ min). Die Ausscheidungs-Halbwertszeit betrug 186 Minuten.

EFFECTOS FARMACOCINETICOS Y ANALGESICOS DE LA KETAMINA EN EL HOMBRE

SUMARIO

Se determinaron en cinco voluntarios sanos los efectos farmacocinéticos y analgésicos de la ketamina intravenosa, en dosis de 125 µg kg$^{-1}$ y 250 µg kg$^{-1}$. La analgesia se midió con la de tourniquete de esfuerzo supramáximo. Ambas dosis de ketamina prolongaron el periodo isquémico sin dolor, mientras que la concentración de ketamina en el plasma fue superior a 100 ng ml$^{-1}$. La ketamina se distribuyó rápidamente ($T_{1/2} = 17$ min). El período de vida media para la eliminación fue de 186 min.