PHARMACOKINETICS AND DISTRIBUTION OF KETAMINE AFTER EXTRADURAL ADMINISTRATION TO DOGS


SUMMARY
We have studied the pharmacokinetics and distribution of ketamine and its biotransformation products in dogs after extradural administration of ketamine at L4-5. The mean apparent uptake rate constants of ketamine for plasma and CSF were 4.17 (SD 1.84) and 5.15 (2.50) h⁻¹, respectively. The concentrations of ketamine in CSF were greater than those found in plasma. The elimination half-life values of the parent drug for both biological fluids were similar (4.3 (2.96) h and 4.6 (3.31) h for plasma and CSF, respectively). The apparent formation rate constant of norketamine was greater than that of dehydronorketamine. However, the concentrations of the biotransformation products in CSF were smaller than those of the parent drug. These results are similar to the distribution of ketamine and its metabolites in different cerebral structures and tissues. The concentrations decreased in concert with the increase in polarity of the metabolites. A specific distribution for all compounds was observed. Ketamine showed a greater affinity for brainstem, while norketamine and dehydronorketamine were distributed mostly in cerebellum and kidney, respectively.

KEY WORDS

In recent years the number of drugs administered by intrathecal and extradural routes has increased considerably [1]. The existence of opioid receptors in the spinal cord permits use of these routes as an alternative to parenteral administration of analgesics [2]. It has been suggested that ketamine may be administered via these routes [3]. There is evidence to suggest that ketamine binds stereospecifically to opioid receptors in the brain and spinal cord [4]. Although some pharmacodynamic studies have been carried out [3], only one has evaluated the pharmacokinetics of ketamine after extradural administration [5]; in that study only plasma concentrations were measured. Because ketamine probably has a site of action in the spinal cord and brain, and as one of its metabolites probably contributes to the pharmacological effects observed, more information may be obtained by studying the kinetics of ketamine and its biotransformation products in plasma, cerebrospinal fluid (CSF) and its redistribution in the brain.

The purpose of the present study was to examine the disposition of ketamine and its biotransformation products in plasma, CSF, different brain structures and other tissues after extradural administration.

MATERIALS AND METHODS

Animals
Four mongrel dogs of both sexes were studied (mean weight 20.7 (SD 0.9) kg). All were fasted with water ad libitum for 12 h before each study. This study fulfilled the requirements for the protection of experimental animals established by Spanish legislation and EC rules.

Induction and maintenance of anaesthesia
The animals were anaesthetized with thiopentone 20–30 mg kg⁻¹ i.v. The trachea was intubated
and mechanical ventilation initiated at a tidal volume of 300 ml and ventilatory frequency of 30 b.p.m., adjusted to maintain normal arterial blood-gas tensions.

Anaesthesia was maintained with 1% isoflurane in oxygen. Neuromuscular blocking drugs were avoided. Rectal temperature was monitored and maintained at 38 ± 1 °C with a thermal blanket.

Catheterization

After anaesthesia, a polyethylene catheter was placed in the right carotid artery for obtaining blood samples for measurement of blood-gas tensions and for monitoring arterial pressure. A femoral vein was cannulated to permit administration of fluids and a femoral artery was cannulated for obtaining blood samples. Urine samples were collected after catheterization of the bladder. CSF samples were obtained via a 60-cm polyethylene catheter (PE50, 0.6 mm i.d., 0.1 mm o.d.) placed at the C1–2 vertebral level.

Administration and sampling

Ketamine was administered at a dose of 3 mg kg⁻¹ (similar to the dose in humans) in isotonic saline 2 ml by lumbar puncture at L4–5 using a fine needle (o.d. 0.5 mm). CSF samples (0.2 ml) and blood 1 ml were collected simultaneously before and 5, 10, 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, 8 and 9 h after administration of ketamine. The blood was collected into heparinized tubes and centrifuged at 3000 £ for 15 min. After each sampling, the CSF that had been removed was replaced by an equivalent volume of artificial CSF. At the same times, the volume of urine was measured and one aliquot was collected. At 9 h after administration of the drug, the animals were killed by a large dose of thiopentone; tissues were removed (mesencephalon, cerebellum, brain, brainstem, pro- tuberance, spinal cord, heart, kidney, liver, lung, muscle and skin) to assay concentrations of ketamine and its biotransformation products. The samples of plasma, CSF, urine and tissues were stored at —20 °C until required for assay.

Analytical technique

Measurement of ketamine and its biotransformation products in plasma, CSF, urine and tissues was performed by gas chromatography with an electron capture detector as reported elsewhere [6]. The tissues were homogenized in saline solution at a proportion of 1:5 (wet weight: volume). The mean tissue recovery for the three substances was greater than 80%. The technique is based on double extraction and derivatization with heptafluorobutryric anhydride. Briefly, 1 ml of biological sample, alkalized with sodium hydroxide 1 mol litre⁻¹, was extracted with chloroform 5 ml. After 15 min of centrifugation, the chloroform layer was transferred to glass tubes containing 3 ml of hydrochloric acid 0.1 mol litre⁻¹. After 15 min of centrifugation, the hydrochloric phase was transferred to other glass tubes containing hexane 5 ml and 0.5 ml of sodium hydroxide 10 mol litre⁻¹. These tubes were centrifuged and the last organic phase utilized for derivatization of ketamine and its metabolites for assay. This procedure consisted of the addition of pyridine 50 μl and heptafluorobutryric anhydride 50 μl, and heating for 30 min in a water bath (40 °C) and the excess of heptafluorobutryric anhydride was neutralized by addition of 5 ml of sodium hydroxide 0.5 mol litre⁻¹. The tubes were shaken and centrifuged to separate the organic phase, which was transferred to other tubes containing 5 ml of hydrochloric acid 0.25 mol litre⁻¹. After shaking and centrifugation, the organic phase was evaporated to dryness under a stream of nitrogen, the residue was redissolved in hexane 100 μl and 1 μl was injected onto the chromatograph. The instruments used were a Varian mod 3700 gas chromatograph equipped with an electronic capture detector and a Varian mod CDS 111 digital integrator. The 2 m x 2 mm (i.d.) column was packed with 3% OV-17 on Gas Chrom-Q 100/120 mesh. The detector and injector temperatures were 250 °C and 210 °C, respectively. The column was heated to 195 °C, with a gas carrier (nitrogen) flow of 40 ml min⁻¹. The variation coefficients of the technique were 5.45, 5.49 and 4.15% for ketamine, norketamine and dehydrornorketamine, respectively. The sensitivity limits of the same substances were 50, 5 and 50 ng ml⁻¹. No differences between these coefficients were present for the different biological samples studied.

Pharmacokinetic analysis

Compartmental analysis. The time course of plasma and CSF concentrations of ketamine were fitted to the following triexponential equations:

\[
\text{Plasma: } C = Ae^{-\kappa t} + Be^{-\nu t} + Ce^{-\beta t} \\
\text{CSF: } C = A'e^{-\kappa t} + B'e^{-\nu t} + C'e^{-\beta t}
\]
where \( k_1, k_2 \) and \( k_3 \) = apparent rate constants of absorption, distribution and elimination of the parent drug in plasma; \( k_1', k_2' \) and \( k_3' \) = apparent rate constants of uptake of the drug into CSF and its distribution and elimination from this fluid, respectively.

The time course of the metabolites of ketamine in plasma and CSF were fitted to the following biexponential equation:

\[
C = A e^{-\alpha t} + B e^{-\beta t}
\]

where \( \alpha = \) apparent rate constant of formation or incorporation of the metabolites into CSF; \( \beta = \) apparent rate constant of elimination of the biotransformation products from CSF or plasma.

The unweighted plasma and CSF concentrations were analysed by an iterative polyexponential curve stripping program (JANA) [7] on an IBM microcomputer. Best fits were obtained using a three-compartmental open model system for plasma and CSF concentrations of ketamine and a two-compartmental open model system for plasma and CSF concentrations of metabolites. The adequacy of the kinetic models was confirmed by examining the plots of residuals and the precision of the parameters estimates according to Boxenbaum, Riegelman and Elashoff [8].

The elimination half-lives of the drug and its metabolites from plasma and CSF were calculated using the following equation:

\[
T_1 = 0.693/k
\]

where \( k = \) apparent elimination rate constant of ketamine, norketamine and dehydronorketamine from plasma and CSF.

**RESULTS**

The principal pharmacokinetic parameters of ketamine and its biotransformation products are summarized in table I.

Ketamine passed from the administration site to plasma and CSF rapidly, with mean apparent uptake rate constants of 4.17 (SD 1.84) \( h^{-1} \) and 5.15 (2.50) \( h^{-1} \), respectively (fig. 1A). Ketamine concentrations in CSF were greater than those found in plasma throughout almost the whole of the experimental period. This is reflected also in the maximum concentrations of ketamine in CSF (4.92 (1.84) \( \mu g \) ml\(^{-1} \)), which were almost twice...
FIG. 1. Mean plasma (△) and CSF (▲) concentrations of ketamine (A), norketamine (B) and dehydronorketamine (C) after extradural administration of ketamine 3 mg kg⁻¹ at the L4–5 level. (Missing data points are because of sample loss.)
FIG. 2. Mean cumulative urinary excretion curves of ketamine (○), norketamine (×) and dehydronorketamine (□), after extradural administration of ketamine 3 mg kg⁻¹ to dogs.

those in plasma (2.46 (0.78) μg ml⁻¹). Despite the differences in the maximum concentrations reached in both fluids, there were no statistically significant differences (P > 0.05) between the times at which the maximum concentration values were reached (0.31 (0.13) h vs 0.44 (0.24) h for CSF and plasma, respectively). This accounts for the greater value obtained in the AUC of ketamine concentrations for CSF compared with plasma.

The apparent formation rate constant of norketamine was greater than that of dehydronorketamine. (This metabolite represents an analytical artefact [11, 12] and it is representative of concentrations of hydroxylate metabolites.) Similar results have been reported in other species and for other routes of administration by different authors. This explains why the time taken by the demethylated derivative to reach its maximum plasma concentrations (0.94 (0.72) h) (fig. 1b) was less than that found for dehydronorketamine (1.94 (1.42) h) (fig. 1c). Nevertheless, no statistically significant differences (P > 0.05) were found between the values of the maximum plasma concentrations of the two metabolites.

Ketamine concentrations in plasma and CSF followed a biexponential decrease, unlike the time
course of the biotransformation products, which was monoeponential. The elimination half-life values of the parent drug and its biotransformation products in both biological fluids were similar.

The cumulative urinary excretion curves of ketamine and its metabolites reveal that the total percentage eliminated at 9 h after administration was 26% of the dose administered (fig. 2). Of the total amount excreted at 9 h, 1.18% comprised unaltered drug, 0.74% was the demethylated derivative and 23.86% was dehydronorketamine.

Figure 3 illustrates the tissue concentrations of ketamine, norketamine and dehydronorketamine (expressed as µg/g of wet tissue).

**DISCUSSION**

The pharmacokinetics of the extradural route of drug administration are complicated because of different processes such as dural penetration, fat deposition, and systemic absorption. Other important factors include the physicochemical characteristics of the drug, such as its pKₐ and degree of lipid solubility [13]. Ketamine is a very lipid soluble drug which is highly ionized at physiological pH. According to the physiological model proposed by Cousins and Mather [14], drugs of this type exhibit low concentrations of their non-ionized lipid soluble forms within the extradural space which are transferred rapidly to the CSF, nerve root arteries of the spine and extradural veins. Such processes account for the rapid increase in drug concentrations in CSF and plasma, as may be seen in figure 1A. Because of this, maximum concentrations of ketamine in plasma and CSF (2.46 and 4.92 µg ml⁻¹) were reached in a fairly short time (0.44 and 0.31 h, respectively). However, significant vascular absorption reduced the concentration gradient relatively quickly. Moreover, the pronounced lipid solubility of ketamine causes slow release of the drug from the lipid components of the spinal cord. These two aspects account for the change in the rate of access of ketamine with time to CSF and plasma and sustained concentrations in both fluids. These biphasic characteristics were observed also by Burm and colleagues [15] and Debruyne and colleagues [16] for some local anaesthetics after extradural and intraperitoneal administration, respectively. These authors demonstrated that the extent of biphasic change is a function of the physicochemical properties of the drug. The plasma half-life of ketamine after extradural administration was significantly greater than that obtained by Kaka and colleagues [17] after i.v. administration. This shows that the slow release of the drug from the site of administration is the process governing the time course of the concentrations of the drug on the terminal part of the CSF and plasma concentration curves. Similar results have been reported after extradural and i.v. administration to humans [5]. The slower absorption of ketamine, consistent with its physicochemical properties, suggests that systemic absorption plays a major role in the termination of the pharmacological effect and this may explain the prolonged maintenance of analgesic effects after ketamine administration via the extradural route.

As a result of the high vascular uptake and transfer of ketamine to CSF, there are no large differences between the concentrations reached in each biological fluid compared with other substances. The ratio between the two concentrations did not exceed 2, unlike other compounds such as morphine, with a low vascular re-uptake and a strong degree of migration towards CSF [18, 19]. For morphine, the ratio is approximately 100, and this explains the appearance of analgesic effects even when blood concentrations are small. In contrast, for ketamine there seems to be a correlation between the concentration of drug in plasma and the duration and intensity of pharmacological effects.

The time course of the plasma and CSF concentrations of norketamine and dehydronorketamine (figs 1b, 1c, respectively) reveal no statistically significant differences between their pharmacokinetic parameters, probably as a result of the small number of dogs studied and the considerable variability in time course of the plasma concentrations. However, it may be seen that the mean values of the constants characterizing the ascending part of the curve are greater for CSF than for plasma. Likewise, the time at which the maximum concentrations were reached in both fluids was shorter in CSF than in plasma. It may be assumed that biotransformation occurs only in the plasma compartment and that the metabolites are more water soluble than the parent drug; thus transfer to the CNS would be more limited and one would expect to observe smaller access rate constants and greater maximum time values for CSF than for plasma. The findings observed in the present study suggest that the CNS would contribute towards the increased
concentrations of metabolites in the CSF. The capacity of cytochrome P450-dependent biotransformation in brain microsomes is well documented [20]. However, Cohen and colleagues [21], in in vitro biotransformation studies, have shown that brain tissue is not able to metabolize ketamine. Thus our conclusions are based only on indirect measurements and further studies are required for confirmation.

The cumulative urinary excretion values shown in figure 2 confirm the high degree of biotransformation of this drug. The major urinary excretion product was dehydro-norketamine, which comprised 23.86 % of the total dose administered. Norketamine appeared in urine in small concentrations (0.74 %), as did the unaltered form of the drug (1.18 %). Such findings are similar to those obtained after other routes of administration.

The results of the distribution studies (fig. 3) show that there was a specific distribution of ketamine and its biotransformation products in the different tissues and brain structures studied. Whereas ketamine was located in greatest concentrations in the brainstem (mean value 4.78 μg g⁻¹), norketamine showed greater affinity for the cerebellum (mean value 2.15 μg g⁻¹). Cumulation of drug and metabolites in cerebral tissue is considered to be a function of blood flow and tissue solubility at physiological pH. A decrease in tissue concentrations occurs as the drug is biotransformed. This uneven distribution in brain has been observed also in rats for other drugs such as amitriptyline, nortriptyline, imipramine and chlorimipramine, and has been attributed to the existence of specific binding sites of the drugs in these structures [22].

REFERENCES