PHARMACOKINETICS OF RECTAL KETAMINE IN CHILDREN

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Ketamine is an anaesthetic and potent analgesic drug derived from phencyclidine. Several authors have proposed that the rectum may be an appropriate route of administration of the drug for anaesthetic and analgesic purposes in minor surgery and modern investigative techniques in paediatric populations [1,2]. There is little information on the pharmacokinetics of ketamine in infants and children when it is administered by the i.v., i.m., oral and rectal routes.

The aim of the present study was to examine the pharmacokinetics of ketamine after rectal administration to children.

MATERIALS AND METHODS

Drug administration and sampling

The study was undertaken in five children aged 6–9 yr (mean 7.8 (SD 1.2) yr) and weight 18–34 kg (28.80 (6.55) kg). Prior consent was obtained from each child’s parents. All patients were undergoing surgery on the eye muscles for correction of strabismus.

Ketamine (Parke-Davis) was administered by the rectal route in an approximate dose of 10 mg kg⁻¹. The formulations used were suppositories of 2 g containing 150, 200 and 400 mg of active ingredient in a fatty excipient (stearine-C), according to the weights of the children.

Twenty minutes after administration of ketamine, anaesthesia was induced with thiopen-pentone 5 mg kg⁻¹ i.v. with atropine 0.02 mg kg⁻¹ followed by suxamethonium 2 mg kg⁻¹, with the patient breathing oxygen. After tracheal intubation, anaesthesia was maintained with 0.5% isoflurane in oxygen. Anaesthesia lasted 50–103 min. During this period the patients received physiological saline 3 ml kg⁻¹ h⁻¹ i.v. Throughout anaesthesia, the ECG and cardiac rate were monitored continuously.

Venous blood samples (2 ml) were obtained in heparinized tubes at 15, 30, 45 min and 1.0, 2.0 and 3.0 h after administration of ketamine. After centrifugation at 2500 g for 15 min, plasma was removed and stored immediately at −20 °C until assay.

SUMMARY

We have studied the pharmacokinetics of ketamine administered rectally in a dose of 10 mg kg⁻¹ to five children aged 6–9 yr and mean weight 28.80 (SD 6.55) kg. An acceptable level of anaesthesia was not obtained in any patient. Despite this, the degree of analgesia obtained was good and no child required further administration of analgesics during the postoperative period. Tolerance to the suppositories was excellent. The absorption of ketamine was found to be relatively fast, with a median peak concentration of 160 ng ml⁻¹ (range 96–250 ng ml⁻¹) at 0.75 h (range 0.50–1.00 h) after administration. The plasma concentrations of norketamine were greater than those of the parent drug, with a maximum of 510 ng ml⁻¹ (range 450–810 ng ml⁻¹) at 0.81 h (range 0.50–1.00 h) after administration. The medians of the half-lives of ketamine and norketamine were 3.15 h and 2.56 h, respectively (range 1.57–4.95 h and 1.47–5.30 h, respectively).

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Sample analysis

Plasma concentrations of ketamine and its demethylated metabolite, norketamine, were measured by gas chromatography using an electron capture detector [3]. The method is based on double extraction and derivatization with heptfluorobutyric anhydride. The instruments used were a Varian Mod 3700 gas chromatograph and a Varian Mod CDS 111 digital integrator. The coefficients of variation were 5.45% and 5.49% for ketamine and norketamine, respectively. The limits of sensitivity were 10 and 15 ng ml\(^{-1}\), respectively.

Pharmacokinetic analysis

The plasma concentration-time curves of ketamine and its metabolite were fitted to the following biexponential equations using the JANA program [4]:

Ketamine: \(C_k = A \cdot e^{-K_a(t-t_0)} + B \cdot e^{-K_c(t-t_0)}\)

Norketamine: \(C_{nk} = A' \cdot e^{-K_f(t-t_0)} + B' \cdot e^{-K_n(t-t_0)}\)

where \(K_a\) and \(K_c\) represent the apparent rate constants of absorption and elimination of the parent drug, \(K_f\) is the apparent formation rate constant of norketamine, \(K_n\) its first order elimination rate constant and \(t_0\) is the lag time.

The elimination half-lives of the drug and its metabolite were calculated with the following equation:

\(T_{1/2} = 0.693/K\)

where \(K\) is the apparent elimination rate constant of ketamine and its biotransformation product.

The maximum plasma concentration (Cmax) and the time taken to reach this concentration (Tmax) were determined from the curves of ketamine and norketamine, respectively. The area under the curve of the plasma concentrations (AUC) from time zero to infinity was calculated from the area under the curve from time zero up to 4 h (obtained by the linear trapezoid method) plus \(C_4/K\), where \(C_4\) is the plasma concentration value of ketamine at 4 h after administration.

RESULTS

No significant changes were observed in the ECG or cardiac rate during anaesthesia. At the end of surgery the children awoke with good analgesia and did not require further administration of analgesics. During and after operation, tolerance to the suppositories was good and there were no signs of irritation in the rectum or anus.

The absorption of ketamine after rectal administration was relatively fast, with a median peak concentration of 160 ng ml\(^{-1}\) (96-250 ng ml\(^{-1}\)) occurring at 0.75 h (0.50-1.00 h) (table I, fig. 1). The estimated time between administration and appearance of ketamine in plasma (lag time) was approximately 0.15 h (0.00-0.39 h); the median values of the absorption rate constant and elimination half-life were 2.68 h\(^{-1}\) (1.35-8.80 h) and 3.15 h (1.57-4.95 h), respectively.

Norketamine appeared in measurable amounts in plasma after 0.19 h (0.00-0.32 h). The apparent rate constant of formation of the metabolite was 4.30 h\(^{-1}\) (2.70-8.20 h\(^{-1}\)); the plasma concentrations of norketamine were greater than those of ketamine and the maximum concentration values for the metabolite (510 ng ml\(^{-1}\) (450-810 ng ml\(^{-1}\)) were reached at 0.81 h (0.50-1.00 h). Thereafter, its log-concentration followed a linear course with a half-life of 2.56 h (1.47-5.30 h).

DISCUSSION

Weiber and colleagues [5] have related the anaesthetic effect of ketamine with i.v. plasma concentrations greater than 500 ng ml\(^{-1}\), whereas Grant, Nimmo and Clement [6] found that analgesic effects were associated with plasma concentrations greater than 40 and 150 ng ml\(^{-1}\) following oral and i.m. administration, respectively. As may be seen in figure 1, the plasma concentrations observed in this study were inadequate for induction of anaesthesia, and all our patients required a full induction dose of thiopentone. These results contrast with those of Saint-Maurice and colleagues [7], who were able to induce anaesthesia in 140 of 150 children 5-6 min after rectal administration of 8-10 mg kg\(^{-1}\) of a 1% or 5% solution of ketamine. These
differences may be attributed to the different formulations used.

The median value for the elimination half-life of ketamine obtained in our study (3.15 h) is considerably longer than that reported after i.v. and i.m. administration of the drug (0.8–1 h) to paediatric patients [8]. However, studies on experimental animals [9, 10] have shown that the elimination half-life of ketamine is similar when the drug is administered i.v., i.m. and as a solution rectally. Release of ketamine from the lipophilic stearine suppositories used in our study is slow compared with administration in solution and this probably accounts for the differences between our results and those of Saint-Maurice and colleagues [7].

Throughout the study, the plasma concentrations of norketamine were greater than those of the parent compound (fig. 1). However, the relationship between the area under the plasma concentration–time curve of the metabolite and the drug was not as close as that reported by Grant and colleagues [6] following oral administration. This suggests decreased first pass effect metabolism when the drug is administered rectally, compared with oral administration. Similar findings have been reported in animal studies [9, 10].

Grant and colleagues [6] observed that low concentrations of ketamine associated with high concentrations of metabolite following oral administration provided good analgesia, as a result of pharmacological activity of norketamine. As the plasma concentrations of ketamine and norketamine in the present study were considerably higher than those obtained by Grant and colleagues [6], one would expect a marked and prolonged effect. This was confirmed by the excellent state of the children after surgery and the fact that additional analgesia was not required.

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