Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children†

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Summary

It has been suggested that nasal administration of ketamine may be used to induce anaesthesia in paediatric patients. We have examined the pharmacokinetics of ketamine and norketamine after nasal administration compared with rectal and i.v. administration in young children. During halothane anaesthesia, 32 children, aged 2–9 yr, weight 10–30 kg, were allocated randomly to receive ketamine 3 mg kg\(^{-1}\) nasally (group IN3) or ketamine 9 mg kg\(^{-1}\) nasally (group IN9); ketamine 9 mg kg\(^{-1}\) rectally (group IR9); or ketamine 3 mg kg\(^{-1}\) i.v. (group IV3). Venous blood samples were obtained before and up to 360 min after administration of ketamine. Plasma concentrations of ketamine and norketamine were measured by gas liquid chromatography. Statistical comparisons were performed using ANOVA and the Kruskall–Wallis test, with P < 0.05 as significant. Mean plasma concentrations of ketamine peaked at 496 ng ml\(^{-1}\) in group IN3 within 20 min, 2104 ng ml\(^{-1}\) in group IN9 within 21 min, and 632 ng ml\(^{-1}\) in group IR9 within 42 min. Plasma concentrations of norketamine peaked at approximately 120 min after nasal ketamine, but appeared more rapidly after rectal administration of ketamine and were always higher than ketamine concentrations in the same situation. Calculated bioavailability was 0.50 in groups IN3 and IN9 and 0.25 in group IR9. We conclude that nasal administration of low doses of ketamine produced plasma concentrations associated with analgesia, but using high doses via the nasal route produced high plasma concentrations of ketamine similar to those that induce anaesthesia. However, the large volume of ketamine required was partly swallowed and led to an unacceptable variability of effect that precludes this route for induction of anaesthesia. (Br. J. Anaesth. 1996; 77: 203–207)

Key words


Although psychic emergence phenomena from ketamine anaesthesia restrict its use in paediatric patients [1], it may be used with premedication (i.e. midazolam) which prevents these phenomena [2] when administered first. The original agent remains popular for induction of anaesthesia in young children as it can be given as the sole anaesthetic agent and by alternative non-invasive routes such as rectally [3, 4].

Previous studies have reported its use by the oral and nasal routes. After oral ketamine 6 mg kg\(^{-1}\), approximately 25 % of a paediatric population appeared asleep or barely arousable within 10 min [5]. The nasal route has been investigated for midazolam [6] or opioid [7] premedication and it has been tested with ketamine as an adjunct for induction of anaesthesia [8]. Loss of responsiveness occurred within 3–10 min in 35 % of children after one to three 3-mg kg\(^{-1}\) nasal ketamine doses [8]. This suggests that nasal administration of ketamine might be used for induction of anaesthesia.

Ketamine pharmacokinetics have been described after i.v. [9], i.m. [10], oral [10] and rectal [4] administration, but not after nasal administration. In this study we have determined and compared the pharmacokinetics of ketamine and its main metabolite, norketamine, when administered by nasal, rectal and i.v. routes in healthy anaesthetized children.

Patients and methods

After obtaining institutional approval and written informed consent from parents, we studied 32 ASA I boys, 2–9 yr of age, weighing 10–30 kg, undergoing minor urological surgery. Exclusion criterion included: rhinopharyngitis, digestive disorders, going minor urological surgery. Exclusion criterion included: rhinopharyngitis, digestive disorders, an anaesthetic procedure involving barbiturate administration.

Anaesthesia was induced with halothane (2 MAC) and 50 % nitrous oxide in oxygen via a face mask. Anaesthesia was maintained with halothane for induction of anaesthesia (1 MAC and during ketamine administration) without tracheal intu-
bation. After cannulation of a vein on the forearm using a short 20-gauge catheter and i.v. injection of atropine 15 μg kg⁻¹, children were allocated randomly to one of four groups to receive 5% ketamine (Parke Davis Lab.) as follows: group IN3 (n = 8) received ketamine 3 mg kg⁻¹ nasally; group IN9 (n = 8) ketamine 9 mg kg⁻¹ nasally; group IV3 (n = 8) ketamine 3 mg kg⁻¹ i.v.; and group IR9 (n = 8) ketamine 9 mg kg⁻¹ rectally. In groups IN, half of the indicated dose was administered in each nostril within 15 s. All children received an enema 1 h before anaesthesia and rectal administration was performed via a short air-washed cannula. After i.v. administration, the venous catheter was flushed with physiological saline 10 ml. In all groups, heart rate and pulse oximetry were monitored continuously, and non-invasive arterial pressure and ventilatory frequency recorded at regular intervals during anaesthesia. Administration of halothane was stopped 15 min after administration of ketamine in all children. Time elapsed between ketamine administration and complete recovery from anaesthesia (when the child was able to open his eyes and answer correctly to verbal command) was recorded. Doses and time of analgesic requests during the post-operative period were noted.

Thirteen 5-ml venous blood samples were obtained before and 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300 and 360 min after administration of ketamine. Plasma was separated by centrifugation and stored at −20°C until analysis. Plasma concentrations of ketamine and its major metabolite, norketamine, were measured by gas-liquid chromatography (supplied by Parke-Davis-France). The internal standard was diphenhydramine 5 μg ml⁻¹.

The calibration curves for ketamine and norketamine were linear within the range 0–2000 ng ml⁻¹. Greater concentrations required dilution of plasma samples before extraction. The standard variations for ketamine and norketamine were, respectively, 4.4% and 6.9% for 20 ng ml⁻¹, and 1.7% and 3.4% for 2000 ng ml⁻¹.

Pharmacokinetic variables were calculated by conventional means from plasma concentration–vs–time data. Ketamine and norketamine concentration–vs–time curves obtained for individual patients were fitted to the sum of exponential functions derived from Colburn [11] and interpreted as one- or two-compartment models. Pharmacokinetic data were fitted using the Siphar program [12], with a weighing function of 1/y². The quality of fit of the two-compartment model was assessed by the presence of a random scatter of data around a calculated value [13], and by visual assessment of the residuals of the observed values from the fitted curve. After modelling, the rate constant for elimination (kₑ) was obtained, and the elimination half-life (T₁/₂ₑ) was calculated as (0.693 kₑ). The area under the plasma concentration curve from 5 to 360 min (AUC₅–₃₆₀) was calculated by the trapezoidal rule and was extrapolated from the origin to infinity (AUC₀–∝) from the kₐ and kₑ slopes. Clearance was calculated using the formula: Cl = dose/AUC. Analysis from the extrapolated area allowed estimation of steady state volume of distribution (Vᵦₑ). Availability (F) for the different routes was calculated after children were paired between each non-i.v. group and group IV according to weight. In each non-i.v. group, peak ketamine concentration and its time were estimated from the fitted model. Statistical comparisons were carried out using ANOVA and the Kruskall–Wallis test where appropriate; P < 0.05 was considered significant. Data are presented as mean (SD).

Results

Mean age and weight of the children were, respectively, 4.8 (range 2–8) yr and 18.6 (SD 2.9) kg in group IV3; 4.8 (3–9) yr and 18.4 (4.7) kg in group IN3; 3.3 (2–7) yr and 17.1 (14.9) kg in group IN9; and 4.0 (3–9) yr and 17.8 (5.7) kg in group IR9 (ns). Surgical procedures included herniorrhaphy, repair of undescended testis, circumcision or hypospadias.
repair. No children experienced coughing or defaecation, nasal disturbances or rectal postoperative lesions after intranasal or rectal administration of ketamine.

Mean arterial pressure and heart rate did not vary significantly from baseline values in any group during halothane anaesthesia or ketamine administration. \(\text{SpO}_2\) did not decrease except in two children who received i.v. ketamine and demonstrated a transient decrease at 88 % and 89 % from baseline values of 98 %; these children had plasma ketamine concentrations greater than 2000 ng ml\(^{-1}\) at 5 and 10 min after administration of ketamine. Assisted ventilation via a face mask was used temporarily (less than 5 min) in these patients. Ventilatory frequency did not vary in groups IN3 and IR9, but increased significantly at 5 min in group IV3 and at 10 min in group IN9 (+34 (12) % and 46 (21) %, respectively). No additional analgesia was required in any group during surgery or during the 6 h after operation. Complete recovery from anaesthesia was delayed in group IN9 (107 (23) min) compared with the other groups: group IN3, 72 (15) min; group IR9, 57 (11) min; and group IV3, 63 (16) min (\(P < 0.01\)).

Because of blood sampling difficulties, two children were excluded from pharmacokinetic analysis (one in group IN9 and another in group IR9). Mean ketamine and norketamine plasma concentration–vs–time curves for each group are shown in figure 1. Logarithmic conversion of mean plasma concentration–vs–time curves for ketamine in each group are presented in figure 2. Individual \(C_{\text{max}}\) and \(t_{C_{\text{max}}}\) values for ketamine in the different groups are shown in table 1. Pharmacokinetic variables are summarized in table 2. After pairing children according to weight and age, estimated bioavailabilities were, respectively, 0.50 (0.19) after nasal ketamine 3 mg kg\(^{-1}\) and 0.50 (0.27) after 9 mg kg\(^{-1}\), and 0.25 (0.19) after ketamine 9 mg kg\(^{-1}\) rectally.

**Discussion**

We have found that the same dose of ketamine (9 mg kg\(^{-1}\)) induced more rapid and greater plasma concentrations after nasal than after rectal administration, but that the rectal route was associated with earlier appearance of norketamine because of first-pass metabolism.

The does used in our study were those that induced general anaesthesia by the i.v. and rectal...
Table 3 Comparative data published previously on the pharmacokinetic variables of ketamine in adults and children. F = Bioavailability after non-i.v. administration of ketamine. A = Adults; C = children; *unpremedicated patients; i.r. = rectal administration; i.v. = i.v. injection; i.m. = i.m. administration; NR = not reported

<table>
<thead>
<tr>
<th>Author</th>
<th>Route</th>
<th>Dose of ketamine (mg kg(^{-1}))</th>
<th>(T_{1/2}^b) (min)</th>
<th>(V_m) (litre kg(^{-1}))</th>
<th>CL (ml kg(^{-1}) min(^{-1}))</th>
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<td>Wieber [21]</td>
<td>A i.v.</td>
<td>2.5</td>
<td>151</td>
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<tr>
<td>Domino [20]</td>
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<tr>
<td>Domino [23]</td>
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<tr>
<td>Grant [9]</td>
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<td>2.0</td>
<td>158 3.2 28</td>
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<tr>
<td>Grant [10]</td>
<td>A i.m.</td>
<td>0.5</td>
<td>153 2.3 13</td>
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<td>Idvall [4]</td>
<td>A oral</td>
<td>0.5</td>
<td>93</td>
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<td>Present study</td>
<td>C i.r.</td>
<td>3.0–9.0</td>
<td>125</td>
<td>2.8</td>
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<td></td>
<td>C i.v.</td>
<td>3.0</td>
<td>NR</td>
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<td></td>
<td>C i.m.</td>
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<td></td>
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<td>C i.v.</td>
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routes, and for the nasal route were those reported as effective in a previous study [8]. However, a relationship with clinical effects may not be established as sampling occurred during general anaesthesia. Moreover, it may be noted that the volumes administered nasally in group IN9 were large and probably unacceptable in a conscious, unpremedicated child.

There are several problems in the pharmacokinetic interpretation of the data obtained after different models of administration of ketamine as children were not their own controls. However, such comparisons between non-i.v. and i.v. administrations of anaesthetic agents are frequently made in children who are not their own controls [14–16]. Therefore, in order to obtain a meaningful analysis, children were paired accordingly to age and weight between non-i.v. and i.v. groups for estimation of ketamine bioavailability. Furthermore, to facilitate venous access and blood sampling, ketamine was administered during general anaesthesia to ensure maintenance of anaesthesia and postoperative analgesia as a result of generation of norketamine which is a potent analgesic drug [10]. Such a study design is seldom used but ketamine associated with propofol has been proposed for ambulatory surgery [17]. Our study did not allow pharmacokinetic analysis of norketamine because the sampling period could not be extended further than 6 h in those children treated on a day-case hospital stay basis.

Ketamine metabolism is dependent on hepatic blood flow and could therefore be influenced by co-administered drugs, for example halothane. Halothane induces a marked decrease in hepatic blood flow, reduces intrinsic drug metabolism capacity [18] and diminishes ketamine clearance [19]. Its use could therefore enhance ketamine plasma concentrations and delay norketamine generation. However, all children exhibited a similar haemodynamic state when they received the same dose of halothane, and therefore the influence of halothane on hepatic blood flow was probably the same in all children.

The pharmacokinetic variables after i.v. ketamine were similar to those reported previously in adult patients or children [9, 20–24] and are summarized in table 3. The volume of distribution of approximately 3 litre kg\(^{-1}\) reflects the high liposolubility of ketamine and a high clearance (22 ml kg\(^{-1}\) min\(^{-1}\)) accounts for the relatively short elimination half-life. As described previously the appearance of norketamine was delayed which suggests that norketamine plays a role in the clinical duration of action of ketamine. In all children, plasma concentrations of norketamine 6 h after administration of i.v. ketamine were greater than 150 ng ml\(^{-1}\), the threshold for analgesia reported previously [10].

The amount of ketamine which reached the systemic circulation was reduced with the non-i.v. routes. The bioavailability of ketamine in the absence of a first-pass hepatic effect, as observed via the nasal route, was approximately twice that observed via the rectal route. Certainly, ketamine administration during general anaesthesia leads to maximal mucosal absorption of the drug, proportional to the dose administered, with an early plasma peak in both nasal groups. Plasma ketamine concentrations in group IN9 were consistent most of the time with those associated with induction of anaesthesia. However, general anaesthesia and the supine position avoided expulsion of part of the dose from sneezing or coughing, or swallowing; however, two children receiving a large volume in group IN9 exhibited plasma concentration decay curves consistent with digestive absorption of the drug. Nevertheless, the amount of drug required with the current formulation of ketamine implies that intranasal administration of a large volume of solution which would probably be swallowed by a conscious child would be even more than that observed in this study. This leads to an unacceptable variability of effect which precludes the use of this route for induction of anaesthesia.

After rectal administration, ketamine absorption was delayed and interindividual variations were large. Despite the fact that every child in this group received a rectal enema before induction of anaesthesia, rectal evacuation was never certain, and the differences in rectal pH values of children [24]
might modify drug absorption. As described previously [4], norketamine generation was rapid in this group, because of first-pass metabolism. These early high plasma norketamine concentrations may participate in the anaesthetic action of ketamine in this situation, and partly compensate for low bioavailability. This low bioavailability is similar to that previously [4], norketamine generation was rapid in this group, because of first-pass metabolism. These early high plasma norketamine concentrations may participate in the anaesthetic action of ketamine in this situation, and partly compensate for low bioavailability. This low bioavailability is similar to that described after oral administration of ketamine [9].

References