Pharmacokinetics of Oral Tramadol Drops for Postoperative Pain Relief in Children Aged 4 to 7 Years—A Pilot Study

K. A. Payne, MBChB, FFARACS, FANZCA, MD,* J. A. Roelofse, MBChB, MMED, PhD,† and E. A. Shipton, MBChB, FCA, MD‡

*2 Military Hospital, Wynberg, South Africa, and University of Stellenbosch, Tygerberg, South Africa, †Faculty of Health Sciences, University of Stellenbosch, Tygerberg, South Africa, and ‡Department of Anesthesia, Christchurch Medical School, University of Otago, Otago, New Zealand

Tramadol hydrochloride is an analgesic with μ receptor activity suitable for administration to children as oral drops. As the serum concentration profile and pharmacokinetic parameters in young children are not known via this route, we studied 24 healthy ASA 1 children to determine those parameters. The children's mean age was 5.3 ± 1.1 years and their mean weight was 17.8 ± 3.1 kg. They underwent general anesthesia with sevoflurane for dental surgery. The mean duration of anesthesia was 27.9 ± 10.1 minutes. Tramadol 1.5 mg/kg (this dose was chosen because we have previously shown it to be effective in providing analgesia following pediatric dental surgery) was administered as oral drops 30 minutes before anesthesia. Venous blood samples were taken following the tramadol at 30-minute intervals for 4 hours, every 2 hours for 6 hours, and every 4 hours for 12 hours. The samples were centrifuged and the serum stored at −20°C, and nonstereoselective gas chromatography was used to determine the concentration of (+) and (−) tramadol enantiomers plus their *o*-demethyltramadol (M1) metabolite concentrations. The tramadol absorption was rapid, the maximum measured serum concentration present occurring before the first sample at 30 minutes. That first sample had a concentration of 352 ± 83.4 ng/mL. The concentration remained above the 100 ng/mL analgesic level until 6.8 ± 0.9 hours. The elimination half-life was 3.6 ± 1.1 hours, the serum clearance 5.6 ± 2.7 mL/kg/min, and the volume of distribution 4.1 ± 1.2 L/kg. The (+) enantiomer concentration was 14.2 ± 4.9% greater than that of the (−) enantiomer. The M1 metabolites had a (−) enantiomer concentration 92.3 ± 75.1% greater than the (+) enantiomer. From the peak concentration at 4.5 ± 1.5 hours, the concentration of the metabolite was approximately one third that of the parent drug. The M1 elimination half-life was 5.8 ± 1.7 hours. Apart from the rapid rise in the serum concentration, these kinetic parameters are similar to those seen in healthy young adults. The concentration profile supports an effective clinical duration in the region of 7 hours.

Key Words: Phamacokinetics; Tramadol drops; Analgesic; Pediatric.

Tramadol hydrochloride (Tramal[R], Grünenthal, Germany) is a racemic mixture of 2 enantiomers. It is a centrally acting analgesic with spinal and supraspinal sites of action.[1,2] The (+) enantiomer has a greater μ receptor affinity than the (−) enantiomer. Their further actions are synergistic in that the (+) enantiomer inhibits serotonin reuptake and the (−) enantiomer inhibits noradrenaline reuptake.[2] Of the metabolites, only the *o*-demethyltramadol (M1) is active, with a greater affinity

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Address correspondence to Prof J. A. Roelofse, University of Stellenbosch, Private Bag X1, 7505 Tygerberg, South Africa; jar@gerga.sun.ac.za.

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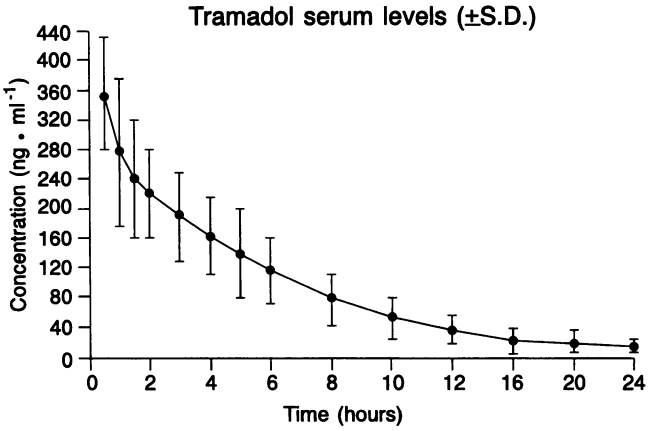

Figure 1. The tramadol serum concentration (in mg/mL) is shown against time (in hours); values given as mean ± standard deviation.

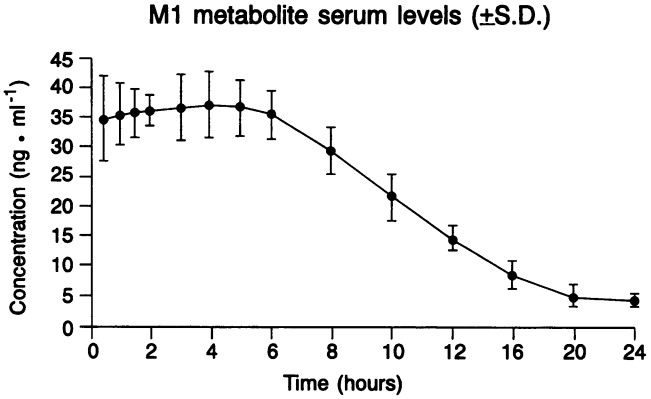

Figure 2. The M1 metabolite serum concentration (in ng/mL) is shown against time (in hours); values given as mean ± standard deviation.

for the μ receptor than the parent compound. However, as the plasma concentration of M1 is reported to be less than 25% of the parent compound,[3] the primary analgesic action rests with the parent compound.

Tramadol has been licensed for use in children over 1 year of age in many European countries, although others have limited its use to children over 12 years of age.[2] Pharmacokinetic data is available in young children following intravenous and caudal routes of administration,[4] but no kinetic studies have been published using oral drop administration in children. Children prefer the oral route of administration for all medicines.[5] We have shown oral tramadol to be efficacious for dental surgery pain, with minimal effects on the cardiovascular and respiratory systems at a dose of 1.5 mg/kg.[6]

We therefore wished to study the serum concentration profile resulting from the oral administration of tramadol drops, 1.5 mg/kg, in healthy young children.

METHODS

The study was approved by the University Ethics Committee, and the parents signed written consent forms. Twenty-four healthy ASA 1 children took part. They underwent dental extraction under general anesthesia with sevoflurane in nitrous oxide and oxygen. The anesthetic duration was 10 to 55 minutes (27.9 ± 10.1). The children's ages ranged from 4 to 7 years (5.3 ± 1.1 years) and their weights from 13 to 25 kg (17.8 ± 3.1 kg). Tramadol hydrochloride was administered as oral drops, 1.5 mg/kg, 30 minutes prior to anesthesia.

Following the induction of anesthesia, a suitable gauge intravenous cannula was inserted into a forearm vein. Two milliliters of venous blood was drawn at 30-minute intervals for 2 hours, hourly for 4 hours, every 2 hours for 6 hours, and every 4 hours for 12 hours. The blood samples were centrifuged and the serum was stored at −20°C prior to assay. Serum concentrations of the 2 tramadol enantiomers and their M1 metabolites were determined by nonstereoselective gas chromatography using nitrogen-selective detection. Diazoethane was the derivatization agent used for M1. The calibration curves with sample concentrations of 2.5 to 250 ng/mL for tramadol and 1 to 200 ng/mL for M1 were linear, with a coefficient of assay variation of under 10%. The pharmacokinetic parameters were calculated using standard formulas for compartmental models according to Gibaldi[7] and Schwilden et al.[8]

RESULTS

The absorption of the orally administered tramadol drops was rapid. The highest measured serum concentration was 352 ± 83.4 ng/mL in the first sample, taken at 30 minutes. Figure 1 shows the serum concentration of the combined tramadol enantiomers. While the serum concentration of the 2 enantiomers paralleled each other closely, the (+) enantiomer was 14.2 ± 4.9% greater than the (−) enantiomer throughout the time course.

Figure 2 gives the serum concentration of the combined M1 enantiomers. In the case of the M1 metabolite, the C_{max} of 37.5 ± 5.2 ng/mL was seen at 4.5 ± 1.5 hours. However, with the metabolites, the (−) enantiomer had a serum concentration greater than the (+) enantiomer. This was a mean of 92.3 ± 75.1% higher. The Table gives the pharmacokinetic data. Results are given as mean values and standard deviations.

Pharmacokinetic Parameters (Mean ± SD) of Tramadol and Its M1 Metabolite

	Tramadol	**M1**
C_{max}(ng/mL)	352 ± 83.4	37.5 ± 5.2
T_{max}(hours)	—	4.5 ± 1.5
$t^{1/2}$(beta-halflife)	3.6 ± 1.1	5.8 ± 1.7
Serum clearance (mL/kg/min)	5.6 ± 2.7	—
Volume of distribution (L/kg)	4.1 ± 1.2	—
AUC (h/ng/mL)	4268 ± 2098	765 ± 259

DISCUSSION

After oral administration in adults, tramadol capsules demonstrate a bioavailability of 68%[9] due to an 18 to 30% first-pass metabolism following absorption from the upper small intestine.[10] The peak plasma level in adults is reached within 2 hours, with analgesia commencing at between 20 and 40 minutes.[9,11] Previously, the absolute bioavailability of oral tramadol drops (100 mg in adult patients) has been shown to be 66.3%, based on AUC data.[12] Also, the T_{max} of tramadol drops was determined to be 1.20 ± 0.39 hours, the absorption half-life $t½_{kh}$ to be 0.34 ± 0.18 hours, with a lag time of 0.23 ± 0.01 hours.[12] This shows that, after the drop administration, the active ingredient tramadol is rapidly absorbed with a similar absolute bioavailability as with oral tramadol capsules.

In this pediatric oral drops study, absorption was unexpectedly rapid. The highest measured serum concentration was the first one at 30 minutes, suggesting that the peak level may have already taken place. This assumption is supported by the T_{max} of the M1 metabolite being at 4.5 ± 1.5 hours, which is very similar to the 4.9 ± 1.9 hours found by Murphy et al[4] following intravenous tramadol in children. If the pattern of the serum concentration of tramadol following oral administration closely follows that after intravenous administration, it would be expected that the M1 metabolite's peak serum concentration would also be similar.

In the study of Murphy et al,[4] tramadol via caudal epidural injection provided an M1 metabolite serum peak at 6.4 ± 1.5 hours. This was some 6 hours after the serum peak of the parent drug at 0.5 ± 0.25 hours. In children, the peak serum concentration of the M1 metabolite therefore occurs some 4 to 6 hours following the peak serum tramadol level. In that oral tramadol drops provided a high serum level at 30 minutes, absorption may have taken place at a higher level than the normal upper intestinal tract area, possibly as high up as the buccal mucosa.

The elimination kinetics can be described as a 2-compartment model, with an elimination half-life of 5.1 hours for tramadol and 9 hours for the M1 derivative after a single oral capsular dose of 100 mg.[9] In adults, the use of tramadol drops (100 mg) has been found to result in a biological half-life in the terminal phase ($t½_{beta}$) of 5.5 ± 0.9 hours.[12] But in young children, the elimination half-life ($t½_{beta}$) of 3.6 ± 1.1 hours appears much shorter. This may be due to simply too few plasma levels analyzed per child. Nevertheless, it still compares favorable to that of 3.7 ± 0.9 hours seen following caudal administration in children.[4]

As the analgesic serum level for tramadol has been put at 100 ng/mL,[2] the onset of analgesia following oral drops in children is likely to be rapid. The 6.8 ± 0.9 hours that the serum concentration remained above 100 ng/mL supports a dosing schedule of 6 to 8 hours. In view of the reported minimal cardiovascular and respiratory effects,[13] this dosing schedule should prove safe and effective.

The serum clearance of 5.6 ± 2.7 mL/kg/min is similar to that reported in children,[4] 6.6 ± 1.9 mL/kg/min, and in adults,[14] 6.3 ± 1.68 mL/kg/min. These similar pharmacokinetic parameters indicate that there should be few pharmacodynamic differences between children and adults.

The serum concentrations of the 2 enantiomers of the parent drug parallel each other closely, keeping at 14.2 ± 1.9% of each other throughout their time course. This supports their synergistic action[2] being maintained throughout the clinically effective time frame.

In adults, the M1 metabolite concentrations are reported as no more than 25% of those of tramadol,[1,2] and in Murphy's pediatric study,[4] concentrations were in the region of 15%. However, from the T_{max} of the M1 at 4.5 ± 1.5 hours, we found our M1 serum concentrations to be approximately 33% that of the parent compound for the next 18 hours.

Tramadol is metabolized via the hepatic cytochrome P450 enzyme system by O-demethylation.[15] In adults, this leads to an M1 concentration of no more than 25% that of the tramadol concentration. However, children have a more active metabolism than adults,[16] and their more rapid conversion to the metabolite could explain why our M1 concentrations were approximately 33% of those of tramadol from 6 to 24 hours. The slower M1 elimination half-life may also contribute to this.

As the metabolite has a higher mu opioid receptor

affinity than the parent drug,[17] this may well extend the clinical action by a further 2 to 3 hours (beyond the 6 to 8 hours if only due to the parent compound on its own). The longer elimination half-life of the M1 metabolite (5.8 ± 1.7 hours) as compared with the parent drug (3.6 ± 1.1 hours) would also tend to prolong the analgesic effect.

As with the parent drug, the (+) M1 has stronger mu opioid receptor activity than the (−) MI,[2] hence the 92% higher plasma concentrations of (−) M1 indicate a lesser clinical analgesia than if the reverse had been the case.

Absorption from oral drop administration is rapid, peak serum concentrations being achieved within 30 minutes. The resultant serum concentrations of tramadol and its M1 metabolite suggest a duration of action of 6 to 9 hours following a of dose 1.5 mg/kg.

In conclusion, the use of tramadol drops in young children undergoing dental extractions results in rapid absorption to the extent that the absolute bioavailability is similar to the oral administration of tramadol capsules. However, the pharmocokinetics of tramadol drops and its M1 metabolite in young children (aged 4 to 7 years) may differ from that found in young adults regarding their terminal elimination half-lives and their (+) and (−) enantiomers. A larger study is being planned to closely examine these discrepancies. Also, the use of capillary isotachophoresis may help determine the exact tramadol dosage in droplet form.[18]

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