Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration

B. V. S. Murthy¹, K. S. Pandya¹, P. D. Booker*, A. Murray, W. Lintz² and R. Terlinden²

Royal Liverpool Children’s NHS Trust, Eaton Road, Liverpool L12 2AP, UK
*Corresponding author

We have studied the pharmacokinetics of a single bolus dose of tramadol 2 mg kg⁻¹ injected either i.v. or into the caudal epidural space in 14 healthy children, aged 1–12 yr, undergoing elective limb, urogenital or thoracic surgery. Serum concentrations of tramadol and its metabolite O-demethyl tramadol (M1) were measured in venous blood samples at various intervals up to 20 h by non-stereoselective gas chromatography with nitrogen-selective detection. All pharmacokinetic variables were evaluated using a non-compartmental model.

After a single i.v. injection (n=9), the mean elimination half-life of tramadol was 6.4 (SD 2.7) h, with a volume of distribution of 3.1 (1.1) litre kg⁻¹ and total plasma clearance of 6.1 (2.5) ml kg⁻¹ min⁻¹. All of these pharmacokinetic variables were similar to those reported previously in adults. After caudal epidural administration (n=5), mean elimination half-life was 3.7 (0.9) h, volume of distribution was 2.0 (0.4) litre kg⁻¹ and total clearance was 6.6 (1.9) ml kg⁻¹ min⁻¹. The caudal/i.v. quotient of the AUC was 0.83, which confirms that there is extensive systemic absorption of tramadol after caudal administration. Serum concentrations of M1 after caudal administration were lower than those after i.v. injection.

Keywords: analgesics opioid, tramadol; pharmacokinetics, tramadol; analgesia, paediatric; children; analgesic techniques, i.v.; analgesic techniques, epidural

Accepted for publication: September 6, 1999

Tramadol is a centrally acting analgesic which has been licensed for use in children older than 12 yr in the UK since 1994, although it has been licensed in children older than 1 yr of age in many other European countries since 1977. It acts at opioid receptors and also appears to modify transmission of pain impulses by inhibition of monoamine reuptake.¹ Tramadol is a racemic mixture of two enantiomers. The (+)-enantiomer has a moderate affinity for the opioid µ receptor, greater than that of the (–)-enantiomer. In addition, the (+)-enantiomer inhibits serotonin reuptake and the (–)-enantiomer is a norepinephrine reuptake inhibitor. These complementary properties result in a synergistic antinociceptive interaction between the two enantiomers.¹ The result is an opioid with a striking lack of respiratory depressant effect despite an analgesic potency approximately equal to that of pethidine.²–⁴ Furthermore, animal work has suggested that tramadol may have a selective spinal action.⁵ Tramadol has been shown to provide effective, long-lasting analgesia after epidural administration in both adults⁶,⁷ and children.⁸,⁹ In addition, biotransformation of tramadol in the liver results in many phase I and II metabolites. Of all the metabolites, O-demethyl tramadol (M1) is the only active metabolite¹⁰ with a greater affinity for the µ receptor than the parent compound.¹¹

Although the pharmacokinetics of tramadol in adults after i.v. and enteral administration have been studied,¹²,¹³ there are no comparative data in children. Therefore, we have investigated the pharmacokinetics of a single bolus dose of tramadol 2 mg kg⁻¹ injected either i.v. or into the caudal epidural space in children.

Patients and methods
After obtaining approval from the Local Ethics committee and written, informed parental consent, we studied 14 healthy children, ASA I and II, aged 1–12 yr, undergoing elective surgery. Nine children requiring limb and thoracic surgery were given a single i.v. injection of tramadol and five children requiring urogenital surgery were given a single injection of tramadol into the caudal epidural space. Children were excluded if they were undergoing day-case surgery or were receiving concurrent medications.
No premedication was given. EMLA cream (Astra UK Ltd) was applied over two visible veins 1–1.5 h before surgery. On arrival in the anaesthetic room, i.v. cannulation was performed and anaesthesia was induced with thiopental 5 mg kg\(^{-1}\). In four patients, neuromuscular block was achieved with atracurium 0.5 mg kg\(^{-1}\) for facilitation of tracheal intubation, while in other children (n=10) a laryngeal mask airway was inserted. Anaesthesia was maintained with an end-tidal isoflurane concentration of 0.5–1% and 66% nitrous oxide in oxygen. A second large i.v. cannula (20-gauge) was inserted into a long saphenous vein at the ankle to facilitate subsequent blood sampling. Before surgery, i.v. injection of tramadol (Zydol, Searle UK Ltd) 2 mg kg\(^{-1}\) diluted in 0.9% saline 10 ml was given over 30 s via the cannula in the hand to those children undergoing limb or thoracic surgery (n=9). For those children undergoing hypoplasias repair (n=5), an injection of tramadol 2 mg kg\(^{-1}\), diluted with 0.9% saline to a total volume of 0.75 ml kg\(^{-1}\), was given into the caudal epidural space. During and after operation, rescue analgesia was provided using i.v. morphine, rectal diclofenac or oral paracetamol, as indicated clinically.

For subsequent evaluation of serum concentrations of tramadol and its metabolite M1, 2-ml blood samples were obtained from the indwelling venous cannula at regular time intervals after injection of drug. In the i.v. group, blood samples were obtained at 10, 20, 30, 45 and 60 min and at 2, 3, 4, 6, 8, 10, 12, 16 and 20 h after injection. In the caudal group, blood samples were obtained at 15, 30, 45 and 60 min and at 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 20 h after injection of tramadol. The samples were centrifuged, the serum separated and stored at −20°C until assay. Serum concentrations of tramadol and its metabolite M1 were measured simultaneously by non-stereoselective gas chromatography with nitrogen-selective detection. Diazomethane was used as the derivatization agent for M1. The calibration curves with sample concentrations of 2.5–500 ng ml\(^{-1}\) for tramadol and 2–200 ng ml\(^{-1}\) for M1 were linear, with a coefficient of correlation greater than 0.997. The precision and accuracy of the assay were high with a coefficient of variation of 4.2–8.4% for tramadol and 2.9–

8.4% for M1. Checks were made to ensure that lidocaine, thiopental, morphine, diclofenac and paracetamol did not interfere with the non-stereoselective assay method.

The pharmacokinetic evaluation was performed using the model-independent method, with the software program MODINDEP developed by the Department of Pharmacokinetics of Grunenthal GmbH and validated with the non-compartmental part of TOPFIT 2.0. Peak serum concentrations (\(C_{\text{p, max}}\), time to peak concentrations (\(t_{\text{C, p, max}}\)) and area under the serum concentration curve (AUC) were derived from individual concentration–time courses. The elimination half-life (\(t_{1/2}^\beta\)), total clearance (\(Cl_{\text{tot}}\)), volume of distribution (\(Vd^\beta\)) and mean residence time (MRT) were calculated using standard formulae. All values are expressed as mean (SD). Patient characteristics in both groups were compared using an unpaired t test (SPSS, UK Ltd). A probability of <0.05 was considered statistically significant.

**Results**

Patient characteristics and pharmacokinetic variables for those who received i.v. and caudal tramadol are shown in Table 1. The median age of children in the i.v. group was 2.42 (range 1.17–6.58) yr, which was significantly different from that in the caudal group (median age 6.0 (5.5–12) yr).

**Tramadol**

After i.v. injection, the serum concentration decay curve followed a biexponential pattern with a highest mean concentration of 1079 (SD 442) ng ml\(^{-1}\) at 0.19 (0.06) h (Fig. 1). After caudal administration, the serum mean concentration of 709 (259) ng ml\(^{-1}\) at 0.5 (0.11) h (Fig. 1). At 4 h after i.v. injection, mean serum concentration was 369 (133) ng ml\(^{-1}\), whereas a mean concentration of 411 (106) ng ml\(^{-1}\) was obtained after caudal administration.

**O-demethyl tramadol (M1)**

After i.v. injection, the metabolite M1 had a mean peak serum concentration of 63.9 (30.7) ng ml\(^{-1}\) at 4.9 (1.9) h

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics and pharmacokinetic variables (mean (SD or range)) of tramadol and its metabolite M1 after a bolus dose of tramadol 2 mg kg(^{-1}) injected either i.v. (n=9) or caudally (n=5). *P&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tramadol</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>(C_{\text{p, max}}) (ng ml(^{-1}))</td>
</tr>
<tr>
<td>(t_{\text{C, p, max}}) (h)</td>
</tr>
<tr>
<td>AUC (h ng ml(^{-1}))</td>
</tr>
<tr>
<td>(T_{\text{1/2}}^\beta) (h)</td>
</tr>
<tr>
<td>(Cl_{\text{tot}}) (ml kg(^{-1})min(^{-1}))</td>
</tr>
<tr>
<td>(Vd^\beta) (litre kg(^{-1}))</td>
</tr>
<tr>
<td>MRT (h)</td>
</tr>
</tbody>
</table>
Murthy et al.

After caudal administration, the peak value (40.3 (4.3) ng ml$^{-1}$) of M1 was observed at 6.4 (1.5) h (Fig. 2).

**Discussion**

We found that mean serum concentrations of tramadol and its metabolite M1 after a single i.v. injection of tramadol were only slightly higher than those in adults.$^{12}$ Similarly, none of the pharmacokinetic variables calculated was significantly different from those reported previously in healthy adults.$^{12}$ In our study, tramadol had a mean Vd of 3.1 (1.1) litre kg$^{-1}$, which agrees with a value of 2.74 (0.54) litre kg$^{-1}$ in adults.$^{12}$ Mean elimination half-life was 6.4 (2.7) h and mean total plasma clearance 6.1 (2.5) ml min$^{-1}$ kg$^{-1}$, which are comparable with values of 5.1 (0.8) h and 6.31 (1.68) ml min$^{-1}$ kg$^{-1}$, respectively, in healthy adult volunteers.$^{12,13}$ Thus our results give no indication of any clinically significant difference in the pharmacokinetics of tramadol between children (1–12 yr) and adults after i.v. injection. It would appear, therefore, that on the basis of the pharmacokinetic data available at present, children require the same body weight related doses as adults. We cannot compare our results from children given a caudal epidural injection of tramadol with those in adults, as no pertinent data are available.

Although tramadol is a racemic mixture of two enantiomers,$^7$ stereoselective analytical methods in adults have demonstrated that the pharmacokinetic differences between the enantiomers of tramadol and its metabolite are of minor significance.$^{17}$ In addition, the inter-individual variability of (+)-tramadol/total tramadol and (+)-M1/total M1 ratios are low (cv <5%) (data on file at Grunenthal GmbH). Moreover, pilot experiments using stereoselective analytical methods have shown that the same is true for the pharmacokinetics of tramadol and M1 in children (data on file at Grunenthal GmbH). Hence application of a non-selective analytical method in the present study was justified.

In view of the differences in age and weight, it may be that they were different populations. In addition, the two different anaesthetic techniques would have affected blood flow to the various compartments and some of the pharmacokinetic data. Hence comparison of the two groups is not possible. In our study, peak serum concentrations of tramadol were observed at 0.55 (0.11) h after caudal administration whereas maximum serum concentrations after i.m. injection in healthy adults occurred at 0.75 (0.38) h.$^{18}$ These data would suggest that there is more rapid transfer of tramadol to the systemic circulation after caudal administration than after i.m. administration. Moreover, in our study, the mean AUC after caudal administration was only 17% lower than that after i.v. injection, confirming that there is extensive systemic absorption of tramadol after caudal administration. An exact value for the extent of systemic bioavailability after epidural administration cannot be determined because the data for the two modes of administration were obtained from two different subject groups. Hence analgesia that is produced after epidural injection may be attributable to systemic availability alone. The significant delay in onset time for analgesic effect after caudal administration, demonstrated in clinical studies,$^8$ is in accordance with the fact that peak serum concentrations are reached significantly later after caudal epidural than after i.v. injection. We hypothesize that tramadol, injected into the epidural space, has a prolonged duration of action because of sustained release of drug from epidural fat and other relatively poorly perfused tissues.

Recently published results suggest that the metabolite M1 has a $T_{1/2A}$ of 6–7 h in healthy adult volunteers$^{13}$ and contributes to the analgesic effect of the parent drug.$^{19}$ As O-demethylation of tramadol is carried out by cytochrome P-450 systems$^{20}$ and P-450 activity has usually reached adult levels by 1 yr of age,$^{21,22}$ it is not surprising that the M1/tramadol serum concentration ratio after i.v. injection we found in children was similar to that reported previously in adults.$^{13}$

In summary, we believe that there is no logical reason to inject tramadol into the epidural space. Injection of tramadol into the epidural space appears to act only as a depot for immediate and delayed systemic absorption. Administration by other enteral and parenteral routes is equally efficacious and long lasting, particularly if repeated doses are given. We believe that further pharmacokinetic studies of tramadol in children examining blood concentrations after repeat i.v. or oral administration would be justified.
References

16. Wagner JG. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. J Pharmacokin Biopharm 1976; 4: 443–67