Pharmacokinetics of rectal tramadol in postoperative paediatric patients

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Background. Postoperative analgesia in children may be improved by using tramadol. The pharmacokinetics of rectal tramadol in young children were therefore investigated.

Methods. The pharmacokinetics of rectal tramadol and its active metabolite were studied in 12 young children (age: 1–6 yr) postoperatively. On the basis of these data, a population model was constructed. Using this model, the pharmacokinetics of different doses of tramadol were calculated.

Results. The pharmacokinetics of rectal tramadol could be adequately described by a one-compartment model. The pharmacokinetic parameters derived from the model indicate that a low variability was present. Elimination half-life was 4.3 (0.2) h (SEM) and the apparent clearance was 16.4 (1.5) litre h⁻¹ (SEM).

Conclusions. The study showed that after rectal administration, tramadol is absorbed at a reasonable rate and with a low inter-individual variability in small children. The data also suggested that a rectal dose of tramadol 1.5–2.0 mg kg⁻¹ is therapeutic.


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Tramadol is a centrally acting opioid analgesic and is classified as a phase II analgesic according to the WHO pain score. The product is marketed as a racemic mixture (±)-tramadol, of which the (+)-enantiomer is a weak \( \mu \)-opioid receptor agonist, which also inhibits serotonin re-uptake. The (−)-enantiomer inhibits norepinephrine re-uptake thereby amplifying the analgesic effect mediated by the \( \mu \)-opioid receptor agonist. The \( O \)-demethylated metabolite (M1) contributes to the analgesic effect by stimulation of \( \mu \)-opioid receptors.1 Tramadol is increasingly used for the treatment of acute and postoperative chronic pain of intermediate or severe intensity in children, and is as equally effective as nalbuphine, pethidine, or oxycodone.2–6

It thus seems that tramadol may be suitable to treat postoperative pain in children. However, after i.v. and oral administration, peak concentrations are reached rapidly and this has been associated with postoperative nausea and vomiting.7 This limits the use of tramadol as a postoperative analgesic especially in day surgery. Rectal administration of tramadol may be an alternative in this situation. It is convenient to use, and is established treatment for postoperative pain in adults.8

However, both the pharmacokinetics and effects of rectal tramadol in children are unknown.

We developed a tramadol suppository and investigated its pharmacokinetics. Particular interest was paid to the variability in absorption and the concentration–time profiles. These data were also used to estimate the therapeutic dose. For this last objective, the requirement was that plateau tramadol concentrations were at least 100 ng ml⁻¹, which is the lower end of the effective concentration range in adults.9

Patients and methods

The study was an open study performed in 12 children. The Ethics Committees of the Leiden University Medical Center (LUMC) and the Juliana’s Children Hospital (The Hague) approved the study protocols. The study was carried out in the Juliana’s Children Hospital, and conducted according to the principles of the ‘Declaration of Helsinki’. Parents or guardians of the patients gave written informed consent before study enrolment.
Patients

Patients were included in the study if they were admitted to the hospital for minor surgery and it was planned that they had to stay for postoperative care in the hospital for at least 24 h. Their body weight had to be between 12.5 and 25 kg. Postoperative analgesia would otherwise have included acetaminophen and/or a non-steroidal anti-inflammatory drug. Patients were excluded if they had to undergo abdominal surgery or surgery for which postoperative treatment with opioids was planned. Induction of general anaesthesia was carried out using propofol and alfentanil, sufentanil or remifentanil. In some patients, vecuronium (for intubation) and midazolam (premedication) were used. Maintenance of anaesthesia was with isoflurane or sevoflurane, and if necessary an opiate. Regional block or infiltration was carried out with bupivacaine or lidocaine.

Patients receiving enzyme inhibitors or inducers (CYP450 2D6) and/or drugs acting on the CNS, other than those necessary for anaesthesia, were excluded.

Experimental medication

In the study, suppositories consisting of tramadol 25 mg in hard fat (Witepsol H15) were used. The suppositories were prepared in the LUMC hospital pharmacy and analysed for tramadol content and content uniformity by the quality assurance laboratory of the LUMC hospital pharmacy.

Study days

The suppository was inserted immediately after induction of anaesthesia. Venous blood samples (1 ml; plain tubes) were taken at 0, 0.45, 2, 4, 6, 9 and 24 h after drug administration through an i.v. cannula. The samples were centrifuged for 5 min (speed 4000 rounds min⁻¹), and the serum was stored at −20°C until analysis.

Analytical procedures

Serum samples were analysed for tramadol and O-desmethyltramadol using a modified high pressure liquid chromatography method. To 200 µl homogenized serum, 10 µl verapamil (internal standard, 5 µg ml⁻¹), 100 µl ammonium hydroxide (25%), and 2 ml methyl tertbutylether were added. After vortex mixing for 15 s and centrifugation (5 min, 4000 rounds min⁻¹), the organic layer was removed and evaporated under nitrogen (40°C). The dry extract was reconstituted in 100 µl of methanol and transferred into the microvial of the autosampler (Gynkotek). Subsequently, 40 µl was injected onto the analytical column (Hypersil silica 3 µm, 125 × 4.6 mm ID, Shandon). The signal was quantified using fluorescence detection (excitation wavelength: 275 nm; emission wavelength of 310 nm; Waters). The mobile phase consisted of perchloric acid (70%, 25 µl) in methanol (500 ml), and the flow-rate was 1 ml min⁻¹. Calibration curves were obtained by adding tramadol and O-desmethyltramadol to drug-free human serum in the range 25–500 ng ml⁻¹ with a fixed amount of internal standard. Precision and accuracy studies in plasma showed the coefficient of variation to be less than 10%, with a high accuracy for both within-day (n=6) and day-to-day (n=7) assays (<8%). Total recovery of verapamil, tramadol, and O-desmethyl-tramadol was 100, 95, and 89%, respectively. The lower limit of quantification for tramadol and O-desmethyltramadol was 5 and 3 ng ml⁻¹, respectively.

Data analysis

The serum concentration–time profiles of tramadol and O-desmethyltramadol were analysed using a population pharmacokinetic approach with non-linear mixed effect modelling (Version V; NONMEM Project Group, UCSF, San Francisco, CA). First order conditional estimation was used with the ‘interaction’ option, assuming multiplicative inter- and intra-subject error distributions. The parameters that were estimated were the absorption half-life, the elimination half-life, and the apparent clearance (CL/F), in which F is the fractional bioavailability. The resulting empirical Bayes estimates were used in a simulation to predict maximal concentrations, and the time interval during which tramadol concentrations would exceed 100 ng ml⁻¹ after administration of doses of 1 or 2 mg kg⁻¹ in the population were included in this study.

Results

The data set of the study comprised samples from 12 evaluable patients (one girl, 11 boys). The patients were admitted to the hospital for surgical correction of hypospadias (seven), cryptorchidism (two), palatoschisis (one), orthopaedic surgery (one), and cholesteatoma (one). The median age was 3.3 yr (range: 1–6 yr) and the median weight was 17.1 kg (range: 12.9–25.0 kg). This resulted in a median dose of tramadol 1.5 mg kg⁻¹.

One patient expelled the suppository shortly after administration. The data of this patient were not analysed and replaced by data from a newly recruited subject. Three subjects had minor gastrointestinal complaints during the postoperative course, resulting in vomiting in two patients (at ~5–6 h after administration). Depression of respiration was not observed.

Tramadol pharmacokinetics

The average concentration–time curves of tramadol and O-desmethyltramadol are shown in Figure 1. Mean (sd) maximal plasma concentrations of tramadol and its metabolite were 200 (60) and 35 (15) ng ml⁻¹. The mean time of the maximal serum concentrations of tramadol and its metabolite was 2.4 (1.0) and 3.9 (1.1) h after administration. Two models were examined to describe the pharmacokinetics of tramadol. Although the data from two subjects indicated that a two-compartment pharmacokinetic model with first order absorption would be necessary to describe all aspects of the pharmacokinetics of tramadol, it was not
possible to reach adequate convergence for this model. Therefore, a one-compartment model with first order absorption was used. The pharmacokinetic parameters are summarized in Table 1 and these indicate that a low variability was present.

Using the derived parameters, the pharmacokinetics for rectal doses of tramadol 1 and 2 mg kg\(^{-1}\) were calculated. It was estimated that in this group of patients, this would result in a mean (SD) maximum concentration of 115 (24) and 230 (48) ng ml\(^{-1}\), respectively. For the 2 mg kg\(^{-1}\) dose, this was associated with a body weight corrected apparent clearance of 0.93 litre kg\(^{-1}\) h\(^{-1}\) (an inter-individual coefficient of variation (CV): 19%) and an apparent volume of distribution of 6.1 litre kg\(^{-1}\) (CV: 20%). The time interval during which tramadol concentrations would be at least 100 ng ml\(^{-1}\) could not be calculated after a dose of 1 mg kg\(^{-1}\) as this concentration will not be reached in 25% of subjects. After administration of the 2 mg kg\(^{-1}\) dose, the time interval would be 8.6 (1.1) h.

Discussion

In this study, the pharmacokinetic variables of rectally administered tramadol were determined, in order to refine post-operative analgesic treatment in children. A tramadol suppository was developed and its pharmacokinetics were investigated. Particular interest was paid to the variability in absorption and the concentration–time profiles. The study was carried out during routine clinical care so that the burden on the children was not unduly increased. To meet our objectives, a known analytical method\(^{10,11}\) was modified to increase the sensitivity per unit volume, as necessary for the determination of tramadol and its active metabolite in small amounts of serum. Secondly, a population pharmacokinetic approach was used to determine the pharmacokinetics of tramadol and its active metabolite. This approach minimizes the amount of sampling required from each patient.

This study showed that after rectal administration, tramadol was well absorbed and showed a relatively low variability in absorption and clearance. It may have been preferable to perform a study with both i.v. and rectal administration of tramadol to fully characterize the kinetics (especially the fractional bioavailability). This would however, have also required us to study the pharmacokinetics of an i.v. dose of tramadol, in the same children. Because of the additional burden on the children for research purposes only, we decided against this for ethical reasons. Notwithstanding, some important observations could be made.

The study showed again that it is not justified to extrapolate data from adults to (young) children. Both primary pharmacokinetic parameters, clearance and volume of distribution, were different from those reported in adults. The apparent clearance (CL/F) in children (0.93 litre kg\(^{-1}\) h\(^{-1}\)) was twice as high as in adults (0.49 litre kg\(^{-1}\) h\(^{-1}\)), and the apparent volume of distribution (V/F) in children (6.1 litre kg\(^{-1}\)) was slightly higher than in adults (4.0 litre kg\(^{-1}\)).\(^{12}\) The latter may be attributed to the higher water to fat ratio in children. Although comparisons between studies in different groups of patients should be made with care, these findings indicate that the shorter elimination half-life in children is likely as a result of a higher tramadol clearance. This is in agreement with the observation of a relationship between liver size and the rate of metabolism of hepatically metabolized drugs, which cannot be explained by an increased activity of cytochrome P450.\(^{13}\) The difference in tramadol clearance between children and adults after rectal administration is in contrast to the finding that after i.v. administration no difference in clearance between the two age groups was found.\(^{14}\) Apparently, there are differences in the degree of absorption after rectal administration between children and adults. One likely explanation for this is a more alkaline pH of the rectal mucosa in children.\(^{15}\) It is important to stress that rectal absorption of tramadol showed low variability, which is in contrast to the rectal absorption of morphine, which can be poor and variable in children.\(^{16,17}\)

The analgesic activity of O-desmethyltramadol (M1) is one to four times higher than the parent compound,\(^{9}\) which is reflected by the lower analgesic efficacy of tramadol in patients with low serum concentrations of M1.\(^{18}\) The mean maximum serum concentration of the active metabolite in our patients was 35 ng ml\(^{-1}\), which is roughly similar to concentrations found in adults\(^{9}\) and older children.\(^{19}\) It is
likely that in young children, O-desmethyltramadol also contributes to the analgesic effect of rectally administered tramadol. The contribution of the metabolite to the analgesic effect may be even larger, as the ratio of the AUC of the metabolite over the AUC of parent tramadol is twice as high in children (28%) as in adults (14%).

Tramadol is metabolized primarily by cytochrome P4502D6 for which polymorphisms have been described. Variability in enzyme capacity may thus play a role in the disposition and effects of tramadol. Variability in the AUC in this pharmacokinetic study was limited, but it must be appreciated that only a limited population was studied. In future studies of rectal tramadol in children, this issue should be considered.

The population model was also used to simulate the pharmacokinetics of different doses of tramadol and to estimate the period during which analgesia was likely to be achieved. This simulation suggested that rectal administration of tramadol 1 mg kg\(^{-1}\) is unlikely to result in therapeutic concentrations. This is corroborated by the observation that the analgesic effect of i.v. tramadol 2 mg kg\(^{-1}\) is superior to a dose of 1 mg kg\(^{-1}\) in children.

The design of the study only allows the reporting of major adverse events. In two patients vomiting occurred. However, it is important to realise that vomiting is frequently reported after anaesthesia and that this study was not appropriate to assess the true incidence of vomiting.

In conclusion, the results of this study indicate that in small children, rectally administered tramadol is absorbed with low variability and shows limited variability in its clearance. Simulations suggest that at least tramadol 1.5 mg kg\(^{-1}\) is necessary to reach therapeutic concentrations. Further prospective studies are warranted in which the efficacy of rectal tramadol vs standard treatment analgesic in children is investigated.

References
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