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## Population pharmacokinetics of the two enantiomers of tramadol and *O*-demethyl tramadol after surgery in children

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**Background.** Few data are available on the stereoselective pharmacokinetics of tramadol in children. The aim of this study was to develop a population pharmacokinetic model for the (+)- and (–)-enantiomers of tramadol and its *O*-demethyl tramadol metabolite (M1) in children.

**Methods.** Twenty-five children (1–8 yr) were included in this study. Tramadol was administered after surgery by continuous infusion (loading dose, 2 mg kg<sup>-1</sup> i.v. over 10 min followed by continuous infusion of 8 mg kg<sup>-1</sup> over 24 h). If pain relief was inadequate, additional 1 mg kg<sup>-1</sup> i.v. bolus doses of tramadol were given over 10 min. A two-compartment structural model was used with NONMEM.

**Results.** For both enantiomers of tramadol, weight was the only patient characteristic parameter showing significant covariate effects on clearance (CL). CL increased by 5.7–6.1 litre h<sup>-1</sup> between 8–12 and 13–16 kg, and by 2.4–3.3 litre h<sup>-1</sup> between 13–16 and 17–33 kg. The rate constants associated with the metabolite elimination [0.144 h<sup>-1</sup>, (+)-M1 and 0.18 h<sup>-1</sup>, (–)-M1] were smaller than the elimination rate constants of the parent drugs [0.243 h<sup>-1</sup>, (+)-tramadol and 0.241 h<sup>-1</sup>, (–)-tramadol], suggesting that the metabolite disposition was rate-limited by its elimination. The presence of two subpopulations of patients was suspected on the basis of the observed bimodal distributions of the AUC<sub>M1</sub>/AUC<sub>tramadol</sub> ratios.

**Conclusions.** The results of this study combine relationships between tramadol CL and patient covariates that may be useful for dose adjustment. Polymorphism is likely to contribute to the interpatient variability observed in the AUC M1/AUC tramadol ratios.

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Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine containing two chiral centres. This drug is marketed as a racemic mixture of the (+)- and (–)-enantiomers and is classified as a phase IIb analgesic according to the WHO pain score. Tramadol is a centrally acting analgesic and has been recommended recently to relieve mild to moderate postoperative pain in children. Two complementary mechanisms are defined for its mode of action. The opioid activity of tramadol is the result of moderate affinity binding of the (+)-enantiomer to  $\mu$ -receptor. In addition, the (+)-enantiomer inhibits serotonin reuptake and the (–)-enantiomer is a more effective inhibitor of norepinephrine reuptake.<sup>1,2</sup>

Tramadol is rapidly absorbed after oral administration with an absolute bioavailability of 65–70% due to a first-pass metabolism after absorption from the gastrointestinal tract.<sup>1,3</sup> It is rapidly and extensively metabolized in the liver resulting in many phase I and II metabolites. The main metabolic pathways, *O*- and *N*-demethylation, involve cytochrome P-450 iso-enzymes 2D6, 2B6, and 3A4, respectively. Of all the metabolites, the primary *O*-demethyl tramadol (M1) metabolite is the only pharmacologically active metabolite<sup>3</sup> with a greater affinity for the  $\mu$ -receptor than the parent drug.<sup>2,4</sup> The stereoselective pharmacokinetics of tramadol has been described in adults after enteral and parenteral administration.<sup>5–9</sup>

Maturation of metabolic pathways must be kept in mind to allow relevant prescription in children. Metabolic clearance (CL) of drugs is usually very low at birth, then increases to reach a maximum at about 1 yr of age when it can exceed that of adults. However, it has been demonstrated that metabolic CL of tramadol is almost complete by 44 weeks post-conceptual age.<sup>10</sup> Simultaneously, water compartments are significantly larger in children than in adults. Thus, treatment of postoperative pain by drugs extensively metabolized in the liver remains difficult. Although tramadol seems a very promising drug in paediatric pain treatment, few pharmacokinetic data are available.<sup>10–15</sup> They have been described after i.v. infusion,<sup>10–12 15</sup> caudal epidural,<sup>10</sup> oral drop,<sup>14</sup> or rectal<sup>13</sup> administration. Both non-compartmental and compartmental (using one- or two-compartment model) approaches have been used. A population pharmacokinetic/pharmacodynamic modelling of the analgesic effects of tramadol has recently been developed by Garrido and colleagues.<sup>12</sup> In all these studies, non-stereoselective pharmacokinetic analyses were performed.

More recently, Di Patti and colleagues<sup>16</sup> proposed a mathematical model for the kinetics of tramadol to adjust the administered dose, depending on the genetic polymorphisms of CYP2D6.

The present study was carried out to provide data on pharmacokinetics of both enantiomers of tramadol and its active metabolite (M1) in a homogenous paediatric population aged 1–8 yr old. The purpose of this study was (i) to determine accurate population pharmacokinetic parameters of the (+)- and (–)-enantiomers of tramadol and its M1 metabolite by using a two-compartment open model, (ii) to accurately estimate both inter- and intra-individual variability in pharmacokinetic parameters, and (iii) to examine which of the patient physiopathological parameters could have influenced drug disposition.

## Methods

A total of 25 consecutive ASA I–III children, age range 1–8 yr, undergoing laparoscopic fundoplication for gastro-oesophageal reflux at Lapeyronie Hospital (Montpellier, France) were enrolled. Pre-anaesthetic data and results from physical examination and standard laboratory tests including haematological and biochemical tests were recorded before the study. Children with renal dysfunction (creatininaemia  $>1$  mg dl<sup>-1</sup>), or hepatic dysfunction (direct bilirubinaemia  $>2$  mg dl<sup>-1</sup>), were excluded from the study. Also those receiving analgesics or anti-inflammatory drugs the week before surgery were excluded.

One hour before surgery, children were given midazolam (0.4 mg kg<sup>-1</sup>) as rectal premedication. On arrival in the operating theatre, i.v. cannulation was performed and anaesthesia was started with propofol (4 mg kg<sup>-1</sup>) and remifentanyl (1 µg kg<sup>-1</sup>). After tracheal intubation,

**Table 1** Children and infants postoperative pain scale. In the postoperative period, 4 points or more indicate an analgesic demand with increasing urgency<sup>17</sup>

Item	Structure	Points
Crying	None	0
	Moaning	1
	Screaming	2
Facial expression	Relaxed/smiling	0
	Wry mouth	1
	Grimace (mouth and eyes)	2
Posture of the trunk	Neutral	0
	Variable	1
	Rear up	2
Posture of the legs	Neutral, released	0
	Kicking about	1
	Tightened legs	2
Motor restlessness	None	0
	Moderate	1
	Restless	2

anaesthesia was maintained with sevoflurane (1 MAC end-tidal concentration in 50% oxygen) and remifentanyl (0.4 µg kg<sup>-1</sup> min<sup>-1</sup>). Neuromuscular block was obtained with atracurium (0.5 mg kg<sup>-1</sup> to obtain and maintain a train-of-four count of 1) at the beginning of surgery. A second i.v. cannula was inserted into the femoral vein to facilitate subsequent blood sampling. After surgery, children received niflumic acid, a selective inhibitor of cyclooxygenase-2, by rectal route (20 mg kg<sup>-1</sup> twice a day), acetaminophen i.v. (30 mg kg<sup>-1</sup>, four times a day), and tramadol hydrochloride i.v. according to the following protocol: the loading dose, 2 mg kg<sup>-1</sup> over 10 min was given at wound closure followed by continuous infusion of 8 mg kg<sup>-1</sup> over 24 h. In addition, 1 mg kg<sup>-1</sup> bolus doses were infused in 10 min if pain relief was not adequate, but no more than twice within 1 h, and no more than five times for the 24 h study period. If pain remained unacceptable, tramadol would be stopped and rescue analgesia would be provided using i.v. morphine. Pain, evaluated every hour and 30 min after each additional dose of tramadol, was considered unacceptable when the Children and Infants Postoperative Pain Score (CHIPPS)<sup>17</sup> exceeded 2 on a maximum of 10 (Table 1).

The study protocol was reviewed and approved by the Institutional Review Board. The study was performed in accordance with the legal requirements and the Declaration of Helsinki, and with current European Community and US Food and Drug Administration guidelines for good clinical practice. Written consent was obtained from the parents (or legal guardians).

Blood samples (2.5 ml) were obtained at the following times: (i) immediately before and (ii) at the end of the loading dose, (iii) 12 and 24 h after the beginning of infusion, and (iv) 0.25, 0.5, 1, 2, 4, 6, and 12 h after the end of infusion. Immediately after collection, samples were centrifuged (1500g) at 4°C for 10 min, then plasma samples were immediately frozen (–30°C) until assay.

Enantiomers of tramadol and *O*-demethyl tramadol were quantified in human plasma by high-performance liquid chromatography (HPLC) using tandem-mass spectrometry detection. The detection and quantification were carried out in the multiple reaction monitoring mode using ethyl tramadol as an internal standard. The chromatographic separation was performed on a reversed-phase Chiralpack HPLC column (250×4.6 mm, particle size 10 μm) operating at room temperature (21°C), with a Lichrospher 100 diol pre-column (4×4 mm). The mobile phase was a mixture of *n*-hexane/ethanol/diethylamine (94:6:0.1, v/v/v). The flow rate was set to 1.0 ml min<sup>-1</sup>. Samples were extracted using the solid phase extraction (SPE) automate Aspec XL4 on C2 (50 mg, encapped) cartridges. SPE cartridges were first conditioned with 1 ml of methanol and 1 ml of distilled water and then plasma samples were loaded onto the cartridges. The column was then rinsed twice with 1 ml of distilled water. The elution was carried out with 2× 0.5 ml of methanol. The organic phase was evaporated under a stream of nitrogen at 40°C. For all compounds, the assays were linear in the range of 0.50–100 μg litre<sup>-1</sup>. From the analysis of quality control samples (three levels) against calibration curves, the precision was <11% and the accuracy was 97–103%. The lower limit of quantification for all compounds was 0.50 μg litre<sup>-1</sup>, being the lowest concentrations of the standard curves with a precision of 4.0–8.9% and accuracy of 96.8–109%. Dilutions (1:20 and 1:200) did not alter the performances of the method. Extraction efficiency ranged between 90.5% and 102% for the four analyses.

The following patient characteristic data were available for each patient: age, weight, gender, height, and body surface area (BSA). Strong correlations were found between BSA and weight ( $r=0.99$ ) and between age and height ( $r=0.93$ ). Thus, the following potential explanatory patient's covariates, weight, age and gender, were included in the original data files.

#### Pharmacostatistical model (base model)

The pharmacokinetic analysis was performed using the non-linear mixed-effect modelling approach as implemented in the NONMEM computer program (version 5.1)<sup>18</sup> through the Visual-NM graphical interface.<sup>19</sup> For the parent drugs, first-order conditional estimation was used to fit the models because individual data sets were extensive.<sup>18</sup> For the metabolites, as few concentration–time data were collected during the formation phase, the formation rate constant proved to be difficult to estimate; the estimation was markedly improved with first-order estimation. The population characteristics of the pharmacokinetic parameters (fixed and random effects) were estimated using the subroutines ADVAN-1, ADVAN-2, ADVAN-4, or ADVAN-5 from the library of programs provided with the NONMEM-PREDPP package. The compartmental analysis was performed by treating the

parent drug and its metabolites separately. The following structural models were investigated: (i) for the parent drugs: one-, two-, and three-compartment models with zero-order input; and (ii) for the metabolites: one- and two-compartment models with first-order formation of the *O*-demethyl tramadol, with or without a lag time. The structural model was chosen on the basis of changes in  $-2 \log$  likelihood and on graphical analyses of the goodness-of-fit. Because  $-2 \log$  likelihood is approximately  $\chi^2$  distributed and the addition of one compartment increases the degrees of freedom by a factor of two, a change of 5.99 in  $-2 \log$  likelihood was required at the 5% significance level to select the more complex model.

Deviations of each parameter of the  $j$ th individual from the estimated population average values were modelled with the use of an exponential interindividual variability error model:

$$P_j = P_{\text{mean}} \times \exp(\eta_j) \quad (1)$$

where  $P_j$  is the required pharmacokinetic parameter in the  $j$ th individual and  $\eta_j$  a random variable distributed with mean zero and variance of  $\omega_{\eta}^2$  about the average value ( $P_{\text{mean}}$ ) in the population.

Various error models were also tested (additive, exponential, or combined additive and exponential). The smallest  $-2 \log$  likelihood function value was associated with the better model. The error on the concentration measurements of the individual  $j$  was best described by an exponential model for (+)-tramadol, (–)-tramadol, and the (–)-M1 metabolite and a combined additive and exponential model for the (+)-M1 metabolite given below:

$$C_{ij}(t) = f(P_j, D_j, t_{ij}) \times \exp(\varepsilon_{ij}) \quad (2)$$

$$C_{ij}(t) = f(P_j, D_j, t_{ij}) \times \exp(\varepsilon_{1ij}) + \varepsilon_{2ij} \quad (3)$$

where  $P_j$  refers to the parameter vector of the subject  $j$ ;  $t_{ij}$  is the time of the  $i$ th measurement;  $D_j$  the dosing history of the subject  $j$ ;  $f$  the pharmacokinetic model;  $\varepsilon_{1ij}$  and  $\varepsilon_{2ij}$  represent the residual departure of the model from the observations and contain contributions from intra-individual variability, assay error, and model misspecification for the dependent variable.  $\varepsilon_1$  and  $\varepsilon_2$  are assumed to be random Gaussian variables with mean zero and variances of  $\sigma_{\varepsilon_1}^2$  and  $\sigma_{\varepsilon_2}^2$ . The uncertainty (coefficient of variation) in estimating fixed parameter values was determined by expressing the standard error of estimation (calculated in NONMEM) as a percentage of the estimated value.

Because the fraction of the tramadol dose metabolized to *O*-demethyl tramadol ( $f_m$ ) was unknown in this patient population, the volume of distribution and the total CL divided by  $f_m$  were estimated.

In the first step, the population parameters, fixed and random effects together with the individual posterior estimates, were computed assuming that no dependency existed between the pharmacokinetic parameters and the covariates.

The individual predicted plasma concentrations (IPREDs) were calculated for each individual by means of the empirical Bayes estimate of pharmacokinetic parameters using the POSTHOC option in the NONMEM program.

### Covariate inclusion

After selection of the basic structural and statistical models, a preliminary assessment of covariate influence was conducted by plotting individual Bayesian pharmacokinetic estimates against all the preselected potential covariates. On the basis of these results, models were built with use of a stepwise forward addition process followed by a backward elimination process. When a significant relationship was observed, the selected covariates were included individually in the model and tested for statistical significance. The change in the NONMEM objective function produced by the inclusion of a covariate term (asymptotically distributed as  $\chi^2$  with degrees of freedom equal to the number of parameters added to the model) was used to compare alternative models. A change in objective function of at least 3.8 ( $P < 0.05$  with one degree of freedom) was required for statistical significance at the initial covariate screening stage. Finally accepted covariates were added to the model and the population pharmacokinetic parameters were estimated. To demonstrate that retained covariates contributed to an improvement of the fit of the population pharmacokinetic model, each covariate was deleted sequentially from the proposed final model (backward elimination) in order to confirm statistical significance ( $\chi^2$  test). If the objective function did not vary significantly, the relationship between the covariate and the pharmacokinetic parameter was ignored.

### Final model

Only the covariates providing a significant change in the objective function when introduced in the model were retained in the analysis. The final population parameters were estimated considering the relationship with the covariates.

At each step of the model building, diagnostic plots were analysed for closeness to and randomness along the line of identity on observed concentrations (DV) vs predicted (PRED) concentration plot, and randomness along the residual (DV-PRED) and weighted residual zero line on the predicted concentrations or time vs residual or weighted residual plot. Moreover, IPREDs were plotted vs DV, and the results were compared with the reference line of slope=1 and intercept=0. PRED concentrations were computed based on population parameter estimates; IPRED concentrations were computed based on individual parameter estimates. Descriptive statistics were used to compare mean residual values to 0 and to calculate 95% confidence intervals. The model was accepted when: (i) plots showed no systematic pattern and (ii) descriptive

statistics did not show any systematic deviation from the initial hypothesis (mean supposed to be 0).

## Results

Of the 25 patients enrolled in this study, one patient was removed due to an error in the preparation of the drug to be infused (excessive dilution). Characteristics of the children are presented in Table 2. Patients had no other medical history besides their gastro-oesophageal reflux. Eighteen patients received additional doses of tramadol, 17 of these within the first 90 min after the beginning of infusion. Six patients received two to four additional doses. A mean of  $11 \text{ mg kg}^{-1} \text{ day}^{-1}$  was given to achieve adequate pain relief. A maximum of  $14 \text{ mg kg}^{-1} \text{ day}^{-1}$  was administered to one child. No child required morphine rescue analgesia.

Median pain was scored 0 and ranged from 0 to 4 on the CHIPPS scale. No sedation was recorded. Twenty-eight per cent of patients experienced nausea at least once during the postoperative course; however, all of them were able to drink and eat at the end of the study period. No otherwise clinically significant adverse effects were recorded during the study. Overall parents' satisfaction was recorded 3 (range 2–3) on a scale extending from 0 to 3.

### Pharmacokinetics of (+)-tramadol and (–)-tramadol

At the end of infusion, mean (SD) plasma concentrations were  $189 (77.1) \mu\text{g litre}^{-1}$  for (+)-tramadol and  $170 (69.3) \mu\text{g litre}^{-1}$  for (–)-tramadol. Disposition of tramadol in plasma was best characterized by a two-compartment open model. This model significantly improved the objective function compared with the one- or the three-compartment model (Table 3). The four-dimensional vector  $\theta$  of kinetic parameters considered in the population analysis consists of CL, initial volume of distribution ( $V_1$ ), and transfer rate constants ( $k_{12}$  and  $k_{21}$ ). From the individual (Bayesian estimates) primary pharmacokinetic parameters: the volume of distribution at steady state ( $V_{\text{dss}}$ ) and the elimination half-life ( $t_{1/2 \text{ elim}}$ ) were calculated. The goodness-of-fit was evaluated (i) by comparing the regression line estimated on the IPRED vs observed concentrations [(+)-tramadol: slope=0.97 (SE=0.019), intercept=0.18  $\mu\text{g litre}^{-1}$  (SE=4.04) and (–)-tramadol: slope=0.98 (SE=0.018), intercept=2.07

**Table 2** Patient characteristics

	Age (yr)	Weight (kg)	Height (cm)	Body surface area (m <sup>2</sup> )
Mean	3.76	15.8	98.6	0.66
95% CI	2.93–4.55	13.6–18.1	92.4–104.9	0.59–0.72
Minimum	1.17	8.9	68.5	0.41
Maximum	8.17	33	131.5	1.1

**Table 3** Model building steps.  $\Delta$ , difference in the objective function

Models	Number of parameters	Objective function	
		(+)-Tramadol	(-)-Tramadol
Model 1: one-compartment model	2	1892	2004
Model 2: two-compartment model	4	1834	1816
Model 3: three-compartment model	6	2188	2168
Model 4: two-compartment model including a relationship between CL and weight (CL= $a \times \text{weight} + b$ )	5	1816 ( $\Delta=18$ )	1772 ( $\Delta=44$ )
Model 5: two-compartment model including a relationship between CL and age (CL= $a \times \text{age} + b$ )	5	1830 ( $\Delta=4$ )	1800 ( $\Delta=16$ )
Model 6: two-compartment model including weight and age	6	1816 ( $\Delta=18$ )	1772 ( $\Delta=44$ )

$\mu\text{g litre}^{-1}$  (SE=3.45)] to the reference line of slope=1 and intercept=0; no significant difference occurred, and (ii) by comparing the bias [(+)-tramadol:  $-4.65 \mu\text{g litre}^{-1}$ , 95% CI  $-9.68, 0.38$  and (-)-tramadol:  $-3.13 \mu\text{g litre}^{-1}$ , 95% CI  $-7.43, 1.19$ ] with zero; Student's *t*-test showed that these values were not statistically different from zero. In the model building phase, a significant relationship was found between CL and weight [ $P=0.011$  for (+)-tramadol and  $P=0.0042$  for (-)-tramadol] and CL and age [ $P=0.043$  for (+)-tramadol and  $P=0.020$  for (-)-tramadol]. No covariate significantly explained the variability in  $V_1$ . Each covariate was then included individually in the model; each of them significantly improved the fit of the basic model (Table 3). At this stage, weight appeared to be the most important of these factors. In the last step, these two patient covariates were combined in a full regression model for CL. In the final model, only weight was retained. The parameter estimates given by this model are summarized in Table 4.

Consideration of the relationship between CL and weight during modelling also improved (i) the relationship between model-predicted and observed concentrations and (ii) the plot between weighted residuals and model-predicted concentrations, and reduced interindividual variability [(+)-tramadol, from 47.4% to 34.2% and (-)-tramadol, from 39.6% to 30.8%] and residual error when compared with the baseline model. A plot of model-predicted vs observed concentrations for the final model based on population parameter estimates is shown in Figure 1. A plot of weighted residuals vs PRED is shown in Figure 2. The vast majority of weighted residuals lay within 2 units of perfect agreement and were symmetrically distributed around the zero ordinate.

In mean, the total CL of the (+)-enantiomer was 9.5% lower than that of the (-)-enantiomer. The body exposure

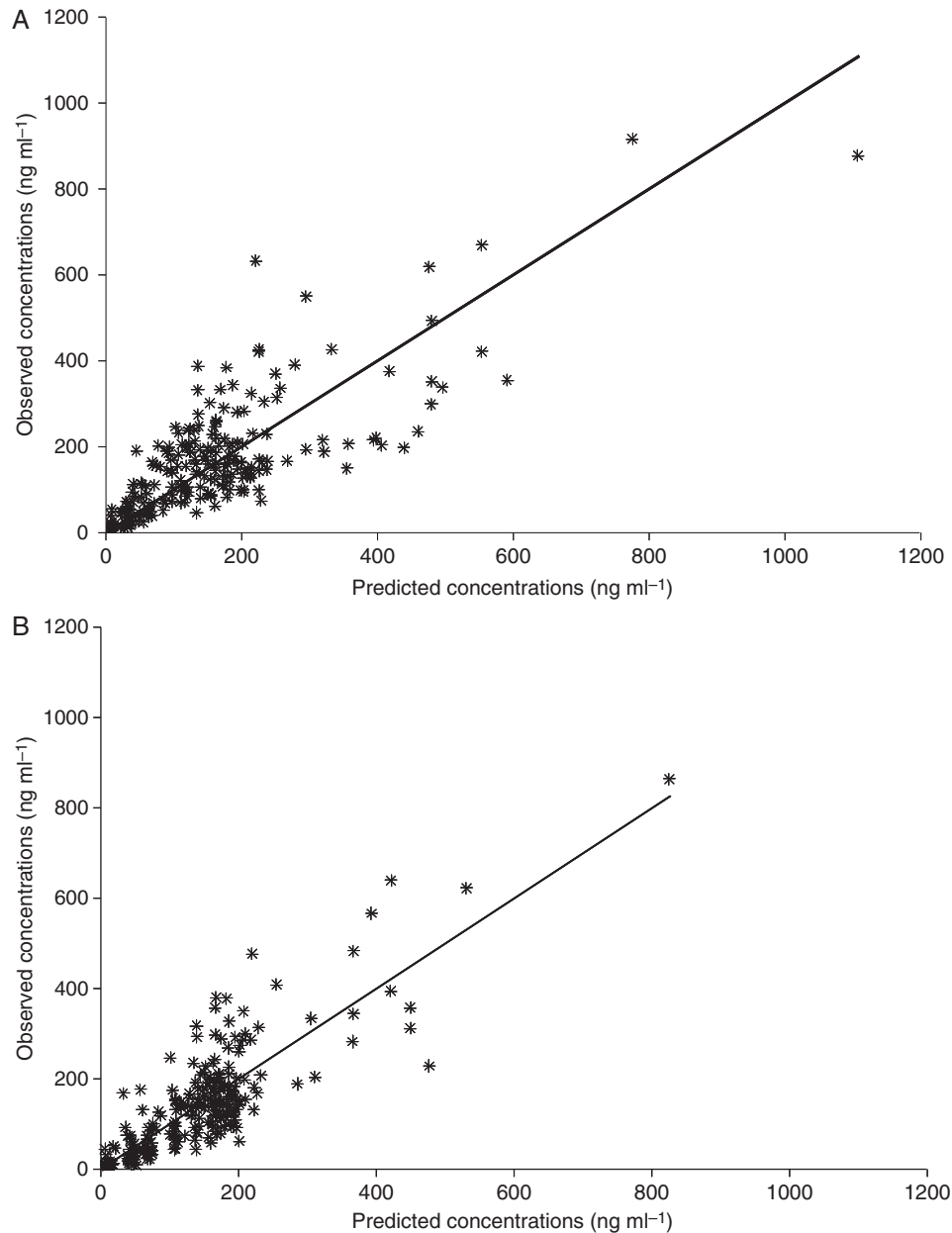
**Table 4** Pharmacokinetic parameters of tramadol and *O*-demethyl tramadol. \*CL= $a \times \text{weight} + b = 13.3 \text{ litre h}^{-1}$  (CV, 36.8%); <sup>†</sup>CL= $a \times \text{weight} + b = 14.7 \text{ litre h}^{-1}$  (CV, 36.6%); <sup>‡</sup>exponential error model; <sup>§</sup>combined additive and exponential model. IIV, interindividual variability; IAV, intraindividual variability; CL, total clearance;  $V_1$ , initial volume of distribution;  $k_{12}$  and  $k_{21}$ , transfer rate constants;  $f_m$ , fraction of the tramadol dose metabolized to *O*-demethyl tramadol;  $k_f$ , formation rate constant;  $V_{\text{dss}}$ , steady-state volume of distribution;  $t_{1/2}$ , half-life of the terminal part of the curve; DV, observed concentrations; IPRED, individual predicted concentrations. Values in parentheses are the error of estimate expressed as coefficient of variation. Values in brackets are the 95% confidence interval

	Mean	IIV (%)	Mean	IIV (%)
	(+)-Tramadol	(+)-Tramadol	(-)-Tramadol	(-)-Tramadol
<i>Population parameters</i>				
$V_1$ (litre)	25.3 (7.19%)	43.1	34.0 (12.2%)	29.9
CL (litre h <sup>-1</sup> )	$a=0.407^*$ (31.0%) $b=6.19^*$ (33.8%)	34.2	$a=0.617^{\dagger}$ (27.2%) $b=3.94^{\dagger}$ (29.9%)	30.8
$k_{12}$ (h <sup>-1</sup> )	0.952 (37.6%)	89.6	0.496 (26.8%)	67.5
$k_{21}$ (h <sup>-1</sup> )	1.28 (24.3%)	5.27	0.919 (26.1%)	1.5
IAV (%)	22.0 <sup>‡</sup>		21.0 <sup>‡</sup>	
Bias (DV vs IPRED) ( $\mu\text{g litre}^{-1}$ )	-3.24 [-8.1; 1.63]		-2.12 [-6.55; 2.30]	
<i>Derived parameters</i>				
$t_{1/2}$ (h)	2.85	23.3	2.88	19.9
$V_{\text{dss}}$ (litre)	55.9	41.4	59.8	37.5
<i>(+)-O-demethyl tramadol</i>				
<i>Population parameters</i>				
$V_1/f_m$ (litre)	331 (43.5%)	40.5	250 (3.35%)	19.3
CL/ $f_m$ (litre h <sup>-1</sup> )	108 (14.1%)	48.9	78.2 (11.4%)	44.5
$k_{12}$ (h <sup>-1</sup> )	0.224 (37.2%)	85.5	0.668 (27.9%)	121
$k_{21}$ (h <sup>-1</sup> )	0.501 (33.5%)	114	1.10 (31.1%)	11.1
$k_f$ (h <sup>-1</sup> )	1.93 (67.0)	93	2.86 (48.2%)	125
IAV (%)	22.2 <sup>‡</sup>		19.3%; 1.99 $\mu\text{g litre}^{-1}$ <sup>§</sup>	
Bias (DV vs IPRED) ( $\mu\text{g litre}^{-1}$ )	-0.283 [-0.83; 0.26]		-0.12 [-0.78; 0.54]	
<i>Derived parameters</i>				
$t_{1/2}$ (h)	4.78	37.6	3.86	30.0
$V_{\text{dss}}/f_m$ (litre)	753	66.3	455	44.7

to (+)-tramadol was greater than that to (-)-tramadol. The half-lives of the terminal part of the curves were similar for the two enantiomers.

#### Pharmacokinetics of (+)-M1 and (-)-M1 metabolites

At the end of the 24 h infusion period, plasma concentration of (-)-M1 metabolite was found higher than that of (+)-M1 metabolite: 32.8 (15.2) vs 26.2 (13.0)  $\mu\text{g litre}^{-1}$ . The basic population pharmacokinetic model was best represented by a two-compartment model with first-order formation from tramadol ( $k_f$ ). Compared with the one-compartment model, the two-compartment model decreased the objective function by 26 for the (+)-enantiomer and by 37.6 for the (-)-enantiomer. The five-dimensional vector  $\theta$  of kinetic parameters considered in the population analysis consists of  $CL/f_m$ ,  $V_1/f_m$ ,  $k_{12}$ ,  $k_{21}$ , and  $k_f$ . During the model building step, a weak relationship was found between  $V_1/f_m$  and weight [(+)-M1,



**Fig 1** Model performance and diagnostic plots. Model-predicted vs observed plasma concentrations based on population parameter estimates (the line represents the line of identity). (A) (+)-Tramadol and (B) (-)-tramadol.

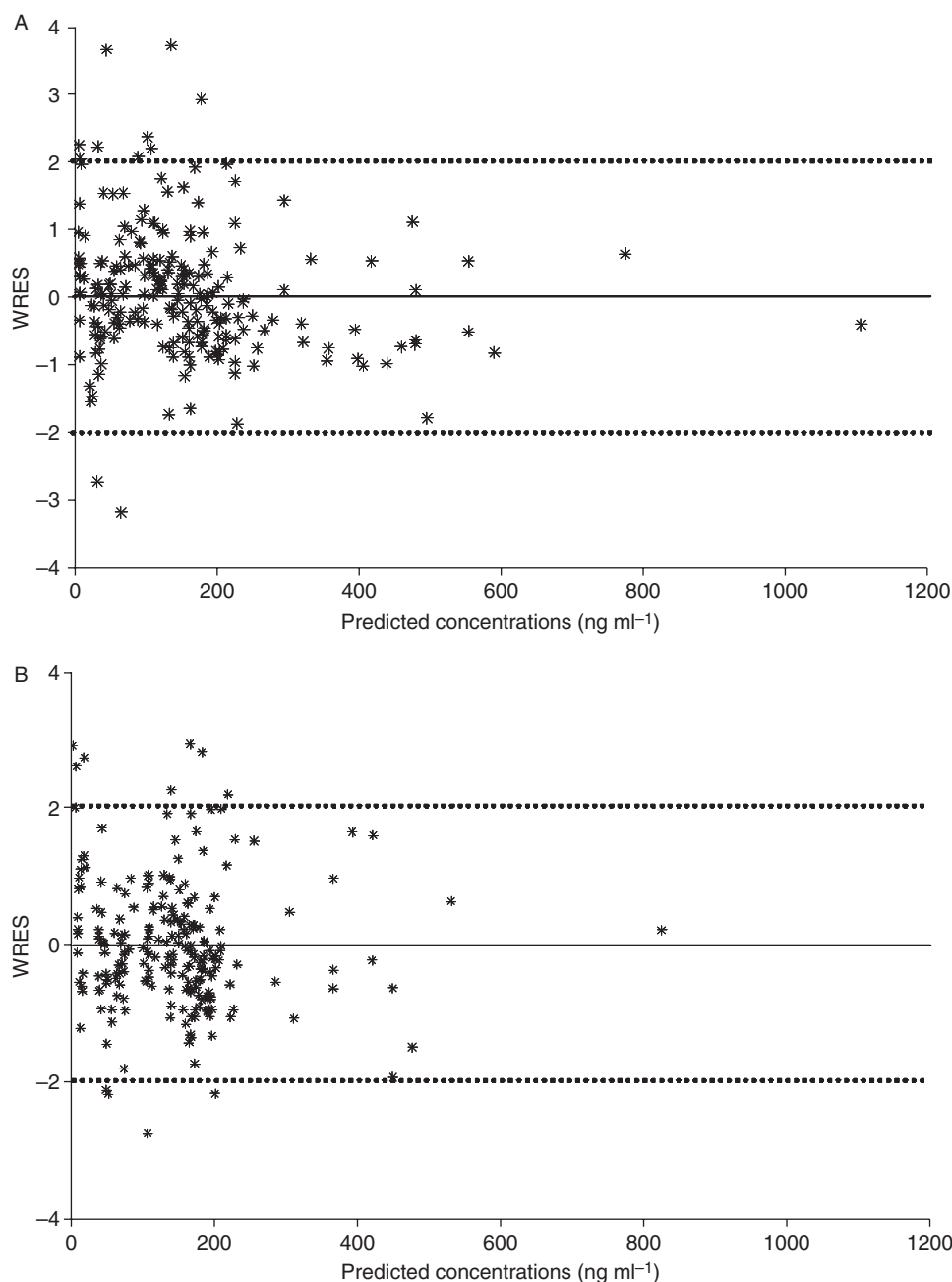
$P=0.0462$  and (-)-M1,  $P=0.0137$ ]. When added to the model, weight did not significantly decrease the objective function. No covariates significantly explained the variability in  $CL/f_m$ . The parameter estimates given by this model are summarized in Table 4.

Predicted and observed plasma concentration–time profiles for (+)-tramadol and (+)-M1 in a child are presented in Figure 3. The terminal disposition phases [(+)-M1, half-life: 4.78 h and (-)-M1, half-life: 3.86 h] were delayed compared with the elimination of tramadol (2.85 and 2.88 h, respectively), suggesting that the metabolite disposition may involve an elimination rate-limitation process. Body exposures to the (+)- and (-)-M1 were 14% and 19%, respectively, that of

the parent compounds; mean AUC ratios (metabolite/parent drug) were 0.141 (range: 0.059–0.27) and 0.185 (range: 0.095–0.31), respectively. Visual inspection of these ratios suggests a bimodal distribution (Fig. 4). No relationship between these ratios and patient’s age was evidenced. Such a bimodal distribution could be attributed to the difference in tramadol metabolism between patients.

## Discussion

Few data are available on the pharmacokinetics of tramadol in children. In most of the previous studies, only the pharmacokinetic profile of the parent drug was described.



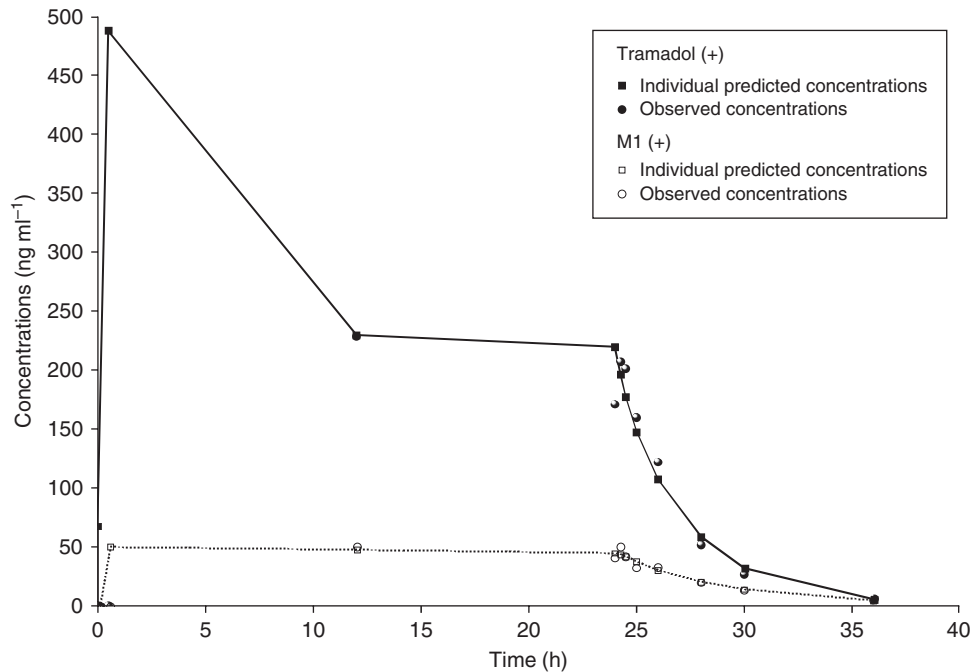
**Fig 2** Model performance and diagnostic plots. Weighted residuals (WRES) vs predicted plasma concentrations. (A) (+)-Tramadol and (B) (-)-tramadol.

This is the first description of the population pharmacokinetics of the (+)- and (-)-enantiomers of tramadol and its M1 metabolite in children (1–8 yr). For both tramadol and its M1 metabolite, the two-compartment model produced the best fit. For the metabolite, most of the data were collected in the post-metabolism phase and the formation constant ( $k_f$ ) could not be accurately estimated; for this reason, high standard errors of estimation were obtained on this parameter.

Only weight showed significant covariate effects on CL of both enantiomers of tramadol. The inclusion of this covariate in the model substantially reduced interindividual

variability in (+)-tramadol and (-)-tramadol CL (13.2% and 8.8%, respectively). CL increased by 5.7–6.1 litre h<sup>-1</sup> between 8–12 and 13–16 kg, and by 2.4–3.3 litre h<sup>-1</sup> between 13–16 and 17–33 kg. Although a weak relationship was found between weight and the initial volume of distribution of the metabolites, this relationship was not retained in the final models. These results were in accordance with those published by Garrido and colleagues.<sup>12</sup> However, in the study of Allegaert and colleagues,<sup>11</sup> a model including age-related changes for tramadol CL and volume of distribution was used. These discrepancies could be explained by the differences in the characteristics of the





**Fig 3** Plasma concentration–time profiles for (+)-tramadol and (+)-M1 in a 4-yr-old child. Lines are obtained from individual predicted concentrations connected point by point.

patients between the two populations. Indeed, in the study published by Allegaert and colleagues, 20 neonates and young infants (0–3 months post-natal age) and 20 adults were included.

The estimates of tramadol CLs observed in the present population pharmacokinetic analysis [ $0.87 \text{ litre h}^{-1} \text{ kg}^{-1}$  for the (+)-enantiomer and  $0.95 \text{ litre h}^{-1} \text{ kg}^{-1}$  for the (–)-enantiomer] were similar to the total CL of the racemic reported by Garrido and colleagues,<sup>12</sup> but higher than that reported by Murthy and colleagues<sup>10</sup> and Payne and colleagues<sup>14</sup> ( $0.37 \text{ litre h}^{-1} \text{ kg}^{-1}$ ) (Table 5). In these last two studies, tramadol was administered before anaesthesia, whereas in the study of Garrido and colleagues<sup>12</sup> and in our study, tramadol was administered after surgery. Thus, alteration in hepatic blood flow during surgery, anaesthesia, or both could have affected some of the pharmacokinetic data.<sup>10 11</sup>

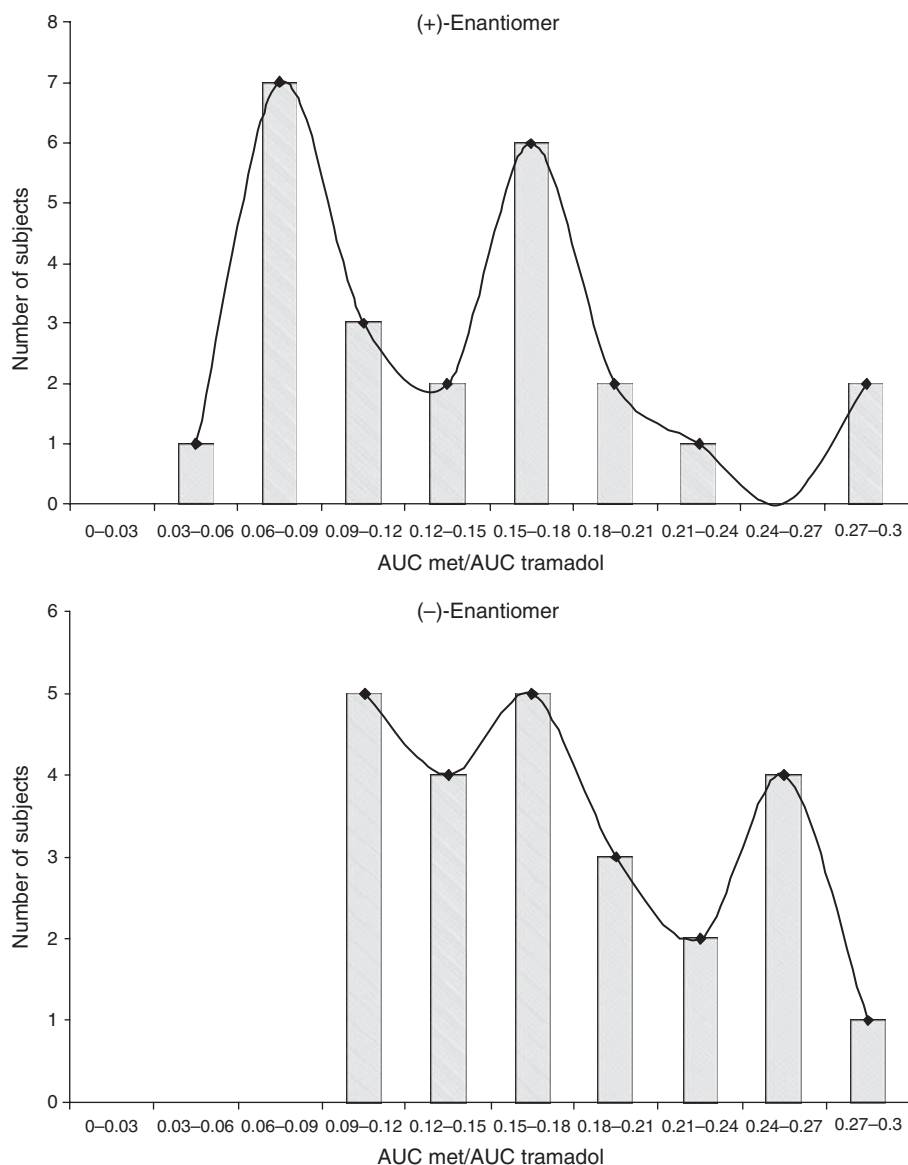
The steady-state volumes of distribution of the (+)- and (–)-enantiomers of tramadol ( $3.4$  and  $3.8 \text{ litre kg}^{-1}$ ) were similar to those reported by others for the racemic (Table 5) and were higher than the physiological water volume.

Tramadol is metabolized via the hepatic cytochrome P450 enzyme system by *O*-demethylation. In adults, M1 plasma concentration was about 25% that of the tramadol concentrations.<sup>20 21</sup> In our study, plasma concentration of the (+)-M1 metabolite was 14% (range: 5.9–27%) that of the parent drug and concentration of the (–)-M1 metabolite was 19% (range: 9.5–31%) that of the parent drug. These results are in accordance with those reported by Murthy and colleagues<sup>10</sup> ( $AUC_{M1}/AUC_{\text{tramadol}}$ , 20%) and

Payne and colleagues<sup>14</sup> ( $AUC_{M1}/AUC_{\text{tramadol}}$ , 18%). In the present study, the presence of two subpopulations of patients was suspected on the basis of the bimodal distribution of the  $AUC_{M1}/AUC_{\text{tramadol}}$  ratios. Tramadol is metabolized by the CYP2D6 enzyme which is affected by a genetic polymorphism in 5–10% of the Caucasian population. Phenotyping and genotyping should certainly allow to clarify the relationship between genetic polymorphism and pharmacokinetics. However, ethical considerations did not allow us to investigate this hypothesis. Further studies are required to confirm these results in a larger population of children.

Formation of the (+)- and (–)-enantiomers of the M1 metabolite from the parent drug was rapid; 12 h after the start of infusion, the steady state was already achieved. The rate constants associated with the metabolite elimination [ $0.144 \text{ h}^{-1}$  for the (+)-M1 and  $0.18 \text{ h}^{-1}$  for the (–)-M1] were smaller than the elimination rate constants of the parent drugs [ $0.243 \text{ h}^{-1}$  for the (+)-tramadol and  $0.241 \text{ h}^{-1}$  for the (–)-tramadol] suggesting that the metabolite disposition was rate-limited by its elimination. In this case, half-life of the metabolite decline represents the true elimination half-life of the metabolite.

In conclusion, we have performed a population approach to estimate individual pharmacokinetic parameters of the two enantiomers of tramadol and *O*-demethyl tramadol. The results of this study combine relationships between tramadol CL and patient covariates that may be useful for dose adjustment. Polymorphism is likely to contribute to the interpatient variability observed



**Fig 4** Distribution of metabolite/tramadol AUC ratios in the 24 children of the study.

**Table 5** Main pharmacokinetic parameters in children reported in the literature. *N*, number of children; T, tramadol; M1, *O*-demethyl tramadol. \*Because the fraction of the tramadol dose metabolized to M1 ( $f_m$ ) was unknown, the volumes of distribution and the total CL divided by  $f_m$  were estimated

<i>N</i>	Age (yr), mean (min–max)		$t_{1/2\text{ elim}}$ (h)	CL (litre h <sup>-1</sup> kg <sup>-1</sup> )	$V_1$ (litre kg <sup>-1</sup> )	$V_{ss}$ (litre kg <sup>-1</sup> )	References
14	3.07 (1–12)	T	6.4	0.37	—	3.1	Murthy and colleagues <sup>10</sup>
		M1	10.6	—	—	—	
24	5.3 (4–7)	T	3.6	0.37	—	4.1	Payne and colleagues <sup>14</sup>
		M1	5.8	—	—	—	
20	0.23 (0–3.2 months)	T	—	0.48	3.27	3.84	Allegaert and colleagues <sup>11</sup>
104	4.55 (2–8)	T	—	0.77	0.40	2.43	Garrido and colleagues <sup>12</sup>
57	0.2 (0–5 months)	T	—	0.53	3.1	—	Allegaert and colleagues <sup>15</sup>
24	3.76 (1.17–8.17)	T(+)	2.85	0.87	1.72	3.42	Our study
		T(–)	2.88	0.95	2.20	3.82	
		M1(+)	4.78	7.28*	22.6*	49.4*	
		M1(–)	3.86	5.61*	16.8*	29.7*	

in the  $AUC_{M1}/AUC_{\text{tramadol}}$  ratios. A mean of 11 mg kg<sup>-1</sup> day<sup>-1</sup> was given to achieve adequate pain relief. A maximum of 14 mg kg<sup>-1</sup> day<sup>-1</sup> was administered to one

child. No children required morphine rescue analgesia. Overall, the treatment was well tolerated by the children and parents' satisfaction was good.

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