

# Population Pharmacokinetic/Pharmacodynamic Modelling of the Analgesic Effects of Tramadol in the Paediatric Population

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## INTRODUCTION

Tramadol (T) is an analgesic widely used in the treatment of pain.<sup>1</sup> T is administered as a racemic mixture of (+)- and (-)-T, both of which are metabolized in the liver given among others the active metabolites (+)-, and (-)-O-demethyltramadol (M1) via CYP2D6.<sup>2</sup> The pharmacodynamic properties of T enantiomers and their M1 metabolites are very different: (+)-M1 shows moderate affinity for the  $\mu$ -opioid receptors, (+)-T is capable of inhibiting the serotonin re-uptake, and (-)-T and (-)-M1 inhibit noradrenaline re-uptake.<sup>3</sup> Although these other mechanisms enhance the inhibitory effects elicited by  $\mu$ -opioid agonists on pain transmission in the spinal cord,<sup>4</sup> is accepted in the literature that (+)-M1 is the major agents responsible for T effects<sup>5</sup>. Taking into account that the ability of young children to form M1 is still not characterised, the propose of this work is the development of a population pharmacokinetic/pharmacodynamic (PK/PD) model for T in paediatrics, to identify the main responsible of drug effects.

## METHODS

104 children [mean age (range) = 4.55 (2-8) years; mean weight (range) = 19.65 (10-43 kg)] received postoperatively an initial 2.5 min i.v. infusion of T at 1 mg/kg. Depending on pain relief one third of the initial dose was given at 15, 30 and/or 45 min. A number between one and three blood

samples were withdrawn per patient for determination of racemic T and M1. The first blood sample was taken within the first hour and before the first re-injection of T, and the rest in the interval from 2 to 6 h after the start of the initial infusion. Several response variables, such as movement, agitation, sedation, verbal evaluation, crying and increase in systolic blood pressure, related all of them to pain relief were recorded for a period of 6 h. Rescue medication with other analgesics was allowed 60 min after the start of the first infusion of T. Pain related response measurements were treated as ordered categorical variables and were analyzed by logistic regression. All analyses were performed using NONMEM V.

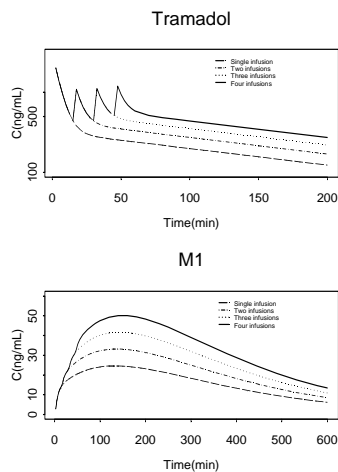
The effect of some continuous (age, height, weight, and duration of surgery) or categorical (sex, type of surgery, anesthetics and drugs given during the anesthesia, and co-medications given after surgery) covariates were also explored for significance.

## RESULTS

### *Pharmacokinetics*

Disposition of T and M1 was described with a two and a one-compartment model, respectively. Weight showed significant effects ( $P < 0.001$ ) on T and M1 distribution and on elimination of T, respectively. Inter-subject variability did not exceed 52%.

The mean (range) predicted maximum plasma concentration values for T and M1 were: 1914.7 (1067.6 – 3310) and 25 (9.7 – 87.4) ng/mL, respectively.



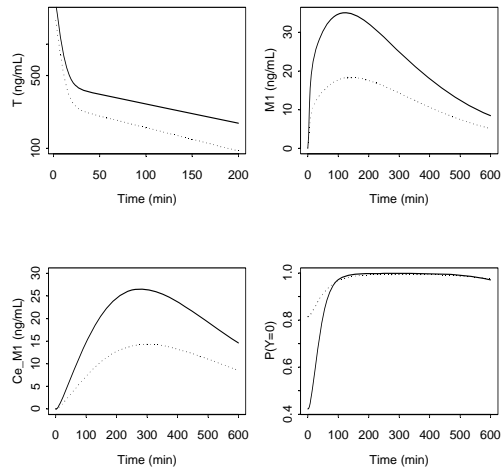
**Figure 1:** Typical pharmacokinetic profiles for tramadol and M1 corresponding to a 20 kg child receiving tramadol in a single, two, three, or four infusion regimen. The initial dose was 1 mg/kg and the rest one third of the initial dose.

### Pharmacokinetic/Pharmacodynamic

During the pharmacodynamic modelling it was found that for all the responses analyzed, models relating drugs effects with effect site concentrations behave significantly better ( $P < 0.05$ ).

Model predicted concentrations of M1 in the effect site was the best predictor to describe crying response. Weight was found to have a significant ( $P < .05$ ) effect on the baseline pain relief of crying.

Figure 2 shows the complete typical population pharmacokinetic model including kinetics of M1 in the effect site. Typical steady-state plasma concentration levels of M1 and T of 10 and 120 ng.mL<sup>-1</sup> in a 20 kg child, were associated with a 95 % probability of achieving complete pain relief.



**Figure 2:** Typical model predicted serum T (upper right panel), serum M1 (upper left panel), effect site M1 (lower left panel) and  $P(Y = 0)$ ; crying [lower right panel], vs time profiles as a function of body weight: solid, 14 kg; dashed, 26 kg.

**Conclusions.** T and M1 show predictable PK. M1 is the major predictor of T induced analgesia.

Children have the ability to produce enough M1 to achieve adequate pain relief safely.

### References

1. Scott LJ, Perry CM. *Drugs* 60: 139, (2000)
2. Paar WD , Poche S, Gerloff J, Dengler HJ. *Eur J Clin Pharmacol* 53: 235, (1997)
3. Guillen C, Haurand M, Kobelt DJ, Wnendt S. *Naunyn Schmiedebergs Arch Pharmacol* 362: 116, (2000)
4. Fairbanks CA, Wilcox GL. *J Pharmacol Exp Ther* 288: 1107, (1999)
5. Poulsen L, Arendt-Nielsen L, Brøsen K, Sindrup SH. *Clin Pharmacol Ther* 60: 636, (1996)

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