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# Population pharmacokinetic modelling of tramadol using inverse Gaussian function for the assessment of drug absorption from prolonged and immediate release formulations

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ABSTRACT

This study aimed to develop a population pharmacokinetic model for tramadol that combines different input rates with disposition characteristics. Data used for the analysis were pooled from two phase I bioavailability studies with immediate (IR) and prolonged release (PR) formulations in healthy volunteers. Tramadol plasma concentration–time data were described by an inverse Gaussian function to model the complete input process linked to a two-compartment disposition model with first-order elimination. Although polymorphic CYP2D6 appears to be a major enzyme involved in the metabolism of tramadol, application of a mixture model to test the assumption of two and three subpopulations did not reveal any improvement of the model. The final model estimated parameters with reasonable precision and was able to estimate the interindividual variability of all parameters except for the relative bioavailability of PR vs. IR formulation. Validity of the model was further tested using the nonparametric bootstrap approach. Finally, the model was applied to assess absorption kinetics of tramadol and predict steady-state pharmacokinetics following administration of both types of formulations. For both formulations, the final model yielded a stable estimate of the absorption time profiles. Steady-state simulation supports switching of patients from IR to PR formulation.



## 1. Introduction

Tramadol hydrochloride is a centrally acting analgesic that is widely used in the treatment of moderate to severe chronic and acute pain (Grond and Sablotzki, 2004). Its analgesic efficacy ranges between that of weak opioids and morphine (Raffa et al., 1995). Analgesic action of tramadol involves two complementary and synergistic mechanisms: opioid activity through activating the μ-opioid receptor by the parent drug and its principal metabolite, *O*-desmethyltramadol (M1), and a separate non-opioid mechanism through inhibiting neuronal noradrenaline and serotonin reuptake by the parent drug (Grond and Sablotzki, 2004). This dual mode of action of tramadol results in the 'atypical' nature of the clinical analgesic efficacy and favourable side-effect profile, with respect to other opioids of comparable efficacy (Grond and Sablotzki, 2004; Raffa et al., 1995).

Following oral administration, tramadol is rapidly and almost completely absorbed (Lintz et al., 1981, 1986, 1998a). While the extent of oral absorption amounts to about 90% of the dose (Lintz et al., 1981, 1986, 1998a), the absolute bioavailability of tramadol is only about 70% (reported mean values range from 64 to 86%) (Lintz, 1980; Lintz et al., 1986, 1998a, 2000; Pedersen et al., 2006). The difference between absorption and bioavailability is attributed to the first-pass metabolism (Lintz, 1980; Lintz et al., 1986, 1998a; Pedersen et al., 2006).

In addition to immediate release (IR) formulations, which normally require oral administration four to six times daily (capsules, drops, dispersible and orodispersible tablets), tramadol is available in various prolonged release (PR) formulations (capsules and tablets), allowing once- or twice-daily dosing (Summaries of Product Characteristics, 2014). Systemic exposure after administration of various PR formulations in terms of AUC is comparable with IR formulations (Bodalia et al., 2003; Eradiri et al., 2006; Grond and Sablotzki, 2004; Karhu et al., 2010; Lai et al.,

*Abbreviations:* AIC, Akaike information criteria; BCS, Biopharmaceutics Classification System; BLQ, below the limit of quantification; CI, confidence interval; CYP2D6, cytochrome P450 2D6; GC–MS, gas chromatography coupled to mass spectrometry; IIV, interindividual variability; IR, immediate release; IVIVC, *in vitro–in vivo* correlation; LC–MS/MS, liquid chromatography coupled to mass spectrometry; M1, *O*-desmethyltramadol; OFV, objective function value; PR, prolonged release; VPC, visual predictive check.

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2003; Malonne et al., 2004; Raber et al., 1999a,b) following single- and multiple-dose administration.

Within therapeutic dose range, tramadol exhibits linear pharmacokinetic (PK) profile for IR (Grond and Sablotzki, 2004; Raffa et al., 1995) and PR dosage forms (Grond and Sablotzki, 2004; Schulz et al., 1999; Sista et al., 2003) following single and multiple dosing.

Tramadol has a high tissue affinity with a mean volume of distribution of about 260–320 l (Lintz et al., 1986; Murthy et al., 2007; Salman et al., 2011; Skinner-Robertson et al., 2011) and 190–270 l (Allegaert et al., 2005; Lintz, 1980; Lintz et al., 1986, 1998a,b, 1999, 2000) reported after oral and intravenous administration, respectively. Plasma protein binding of tramadol is about 20% (Grond and Sablotzki, 2004).

Tramadol is extensively metabolized in the liver resulting in many phase I and phase II metabolites. The primary metabolic route via *O*-demethylation to produce M1 is catalysed by the polymorphic isoenzyme cytochrome P450 2D6 (CYP2D6) (Lintz et al., 1981; Subrahmanyam et al., 2001; Wu et al., 2002). Tramadol and its metabolites are primarily excreted by the kidneys (90%), with the remaining 10% appearing in the faeces (Lintz et al., 1981).

The mean total clearance of tramadol is reported to be about 24–36 l/h (Allegaert et al., 2005; Lintz, 1980; Lintz et al., 1986, 1998a,b, 1999, 2000) and 25–52 l/h (Ardakani and Rouini, 2009; Lintz et al., 1986, 1998a, 2000; Murthy et al., 2007; Salman et al., 2011; Skinner-Robertson et al., 2011) following intravenous and oral administration, respectively.

Tramadol disposition is most often described by a two-compartment PK model (Allegaert et al., 2005; Lintz, 1980; Lintz et al., 1986, 1998a,b, 2000) with the reported terminal half-life ($t_{1/2,\beta}$) of about 5–7 h (Ardakani and Rouini, 2009; Lintz, 1980; Lintz et al., 1986, 1998a,b, 1999).

Several population PK models of tramadol have been reported in the literature for adults (Allegaert et al., 2005; Gan et al., 2004; Murthy et al., 2007; Skinner-Robertson et al., 2011) as well as children (Allegaert et al., 2005; Bressolle et al., 2009; Garrido et al., 2006; Zwaveling et al., 2004), infants (Allegaert et al., 2005, 2008), neonates (Allegaert et al., 2005), preterm neonates (Allegaert et al., 2008) and lactating women (Salman et al., 2011) following either intravenous, rectal or oral administration.

The population PK analyses focused mainly on assessing tramadol disposition in various populations and on the contribution of various covariates (e.g. age, body weight, *CYP2D6* polymorphism and smoking) to variability in clearance and volume of distribution. However, with the exception of the population PK model developed by Murthy et al. (2007), no reports were found on modelling the absorption and disposition of tramadol following oral administration of different tramadol formulations.

In the present study, a population PK model of tramadol was developed using pooled data from bioavailability studies with IR and PR formulations in healthy volunteers. The combined IR/PR PK model was used to assess absorption kinetics of tramadol and predict steady-state pharmacokinetics following administration of both types of formulations.

To our knowledge, the present study and the study by Murthy et al. (2007) are the only studies to report population PK modelling of tramadol using bioavailability data obtained following administration of IR and PR formulations.

## 2. Material and methods

### 2.1. In vivo *studies*

Data were obtained from two phase I comparative bioavailability studies (Study I and Study II). Only the data on the reference formulations were used in the present analysis.

Both studies were conducted with approval of the appropriate local ethics committees in compliance with the guideline of the International Committee on Harmonisation on Good Clinical Practice, local regulatory requirements, the ethical requirements of Directive 2001/20/EC and the principles enunciated in the Declaration of Helsinki and its revisions. Written informed consent was obtained from all subjects before they underwent any study-specific procedures.

#### 2.1.1. Study population

Healthy, Caucasian, non-smoking adult (age 18–42 years) male volunteers with a body mass index (BMI) between 19 and 29 $kg/m^2$ were enrolled in the studies. All subjects met the inclusion criteria and no exclusion criteria described in the protocol and were judged eligible for enrolment in the studies based on medical and medication histories, demographic data (including gender, age, body weight, height, BMI), vital signs measurements (blood pressure, heart rate), electrocardiogram, physical examination, urine drug screen, alcohol screen and clinical laboratory tests (hematology, biochemistry, urinalysis, human immunodeficiency virus test, hepatitis C antibodies, hepatitis B surface antigen).

A total of 52 subjects were included, 26 in each study.

#### 2.1.2. Study procedures

Both trials were designed as an open-label, randomised, 2-period, 2-sequence cross-over studies under fasting conditions.

*2.1.2.1. Study I.* Study I was a single-dose study, in which subjects were administered test and reference (Tramal® 50 mg capsules, Grünenthal GmbH, Germany) IR capsule formulation containing 50 mg of tramadol hydrochloride. There was a 7-day washout period between the doses.

Study drugs were administered with 200 ml of water. After an overnight fast of at least 10 h prior to drug administration, standard meals were provided at approximately 6, 10 and 14 h after dosing and were identical for both periods. Water was not permitted from 2 h before dosing until 2 h following dosing.

5 ml blood samples were collected in blood collection tubes containing heparin before dosing and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 14.0, 16.0, 24.0 and 36.0 h post-dose. After collection blood samples were immediately centrifuged, divided into 2 aliquots and frozen for storage at −20 °C pending sample analysis.

Plasma concentrations of tramadol were determined using LC–MS/MS method with the lower limit of quantification of 4 ng/ml and upper limit of quantification of 256 ng/ml. Analytical method was fully validated and was in accordance with appropriate guidelines.

*2.1.2.2. Study II.* In Study II, PR tablet formulation containing 200 mg of tramadol hydrochloride was dosed to the subjects every 12 h (a total of 5 doses) as either test or reference (Tramal® 200 mg PR tablets, Grünenthal GmbH, Germany) product. The treatment periods were separated by a washout period of 5 days.

All doses were administered with 200 ml of water. Subjects fasted for 10 h before every morning drug administration. On days 1 and 2, subjects received a standardised breakfast, lunch and snack 1, 6 and 9 h after the morning dose, respectively, and a standardized dinner was provided 1 h after the evening dose. On day 3, standardised meals were provided to trial subjects 4, 7 and 10 h post-dose. Post-dose meals were identical for both periods. With the exception of water administered at the time of each dosing, fluids were not permitted from 1 h before dosing to 1 h after dosing on days 1 and 2 and until 2 h after dosing on day 3.