

# Comparing the Pharmacokinetics of 2 Novel Intravenous Tramadol Dosing Regimens to Oral Tramadol: A Randomized 3-Arm Crossover Study

Clinical Pharmacology  
in Drug Development  
2020, 9(4) 537–546

© 2019 Avenue Therapeutics. *Clinical Pharmacology in Drug Development* published by Wiley Periodicals, Inc. on behalf of American College of Clinical Pharmacology  
DOI: 10.1002/cpdd.746

Lucy Lu<sup>1</sup>, Michael Ryan<sup>1</sup>, Mark Harnett<sup>1</sup>, George J. Atiee<sup>2</sup>, and Scott A. Reines<sup>1</sup>

## Abstract

Tramadol is a dual-mechanism (opiate and monoamine reuptake inhibition) analgesic. Intravenous (IV) tramadol has been widely prescribed outside the United States. However, there have not been studies comparing the pharmacokinetics (PK) of IV dosing regimens to that of oral tramadol. In this phase 1, open-label, single investigational center, 3-treatment, 3-period, multidose crossover study, we compared 2 novel IV dosing regimens (IV tramadol 75 mg and IV tramadol 50 mg) to oral tramadol 100 mg given every 6 hours (the highest approved oral dosage in the United States). Compared to the oral regimen, IV tramadol 50 mg administered at hours 0, 2, and 4 and every 4 hours thereafter reached initial tramadol peak serum concentration ( $C_{max}$ ) more rapidly, while resulting in similar overall steady-state  $C_{max}$  and area under the plasma concentration–time curve. IV tramadol 75 mg administered at hours 0, 3, and 6 and every 6 hours thereafter had higher  $C_{max}$  and greater fluctuation in peak to trough tramadol concentration. The primary metabolite M1 (a potent  $\mu$  agonist) had lower area under the plasma concentration–time curve and  $C_{max}$  for both IV regimens than for the oral regimen. IV tramadol at both doses was well tolerated, with adverse event profiles consistent with the known pharmacological effects of tramadol. IV tramadol 50 mg is now in phase 3 development in patients with postsurgical pain.

## Keywords

crossover study, intravenous tramadol, pharmacokinetics, postsurgical pain, steady state

Tramadol is a centrally acting synthetic analgesic with a dual mechanism of action, composed of  $\mu$ -opioid activity and monoamine (serotonin and noradrenalin) reuptake inhibition. Tramadol is a member of the phenanthrene group of opium alkaloids, which includes morphine and codeine, to which it is structurally related. Like codeine, there is a substitution of the methyl group on the phenol ring that imparts a relatively weak affinity for opioid receptors.<sup>1,2</sup>

The pharmacokinetic (PK) properties of oral tramadol are well known.<sup>3,4</sup> Following oral administration, tramadol is rapidly and almost completely absorbed. After oral administration of a single dose of 100 mg, peak serum concentration ( $C_{max}$ ) is approximately 300 ng/mL.<sup>5</sup> The absorption is generally 100%, and the bioavailability is approximately 70% following a single dose. The difference between absorption and bioavailability is accounted for by first-pass metabolism.<sup>6</sup> Tramadol is metabolized primarily via N- and O-demethylation in the liver by cytochrome P450 (CYP) 2D6 and CYP3A4 (phase 1 reactions) and by conjugation of these demethylation products (phase 2 reactions). The rate of production of the M1 metabo-

lite is influenced by the polymorphic CYP2D6 enzyme.<sup>7</sup> There are several metabolites, but the key metabolite that is pharmacodynamically active is O-desmethyltramadol (M1), which is converted from the parent compound by CYP2D6.<sup>1</sup> Quinidine, a CYP2D6 inhibitor, can inhibit this biotransformation.<sup>8,9</sup> Phenotypically, <10% of Caucasians are “poor metabolizers,” while the rest are “extensive metabolizers.” M1 production is markedly reduced in “poor metabolizers.”<sup>10</sup>

<sup>1</sup> Avenue Therapeutics, Inc., New York, New York, USA

<sup>2</sup> Worldwide Clinical Trials, San Antonio, Texas, USA

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Submitted for publication 26 June 2019; accepted 25 September 2019.

## Corresponding Author:

Lucy Lu, MD, 2 Gansevoort Street, 9th Floor, New York, NY 10044  
(e-mail: llu@Avenuetx.com)

[The copyright line for this article was changed on 25 October after original online publication.]

M1 has significantly higher affinity for opioid receptors, and the expression of the opioid component of tramadol is primarily due to M1.<sup>11</sup> The affinity of tramadol for cloned human  $\mu$ -opioid receptors is 2.4  $\mu$ M, much weaker than the affinity of M1 (5.4 nM) or morphine (0.62 nM).<sup>12</sup>

Upon multiple dose administration and with the saturation of the metabolizing enzymes, serum levels of tramadol as well as oral bioavailability increase to approximately 90% to 100%. As a result, both  $C_{\max}$  and area under the plasma concentration–time curve (AUC) are higher following multiple dose administration.<sup>13</sup>

Tramadol's analgesic effects are produced by both opioid and nonopioid mechanisms, based on results from multiple studies in both animals and humans.<sup>14</sup> Both enantiomers and their metabolites contribute to pain control via different mechanisms, which include both binding of M1 to  $\mu$ -opioid receptors and inhibition of serotonin and norepinephrine reuptake. In preclinical models, pretreatment with either yohimbine or idazoxan (both  $\alpha_2$ -adrenoceptor antagonists) can significantly reduce the antinociceptive effect of intravenous (IV) tramadol.<sup>15,16</sup>

Effective postoperative pain control is a critical need, as most patients undergoing surgical procedures experience pain immediately following the procedure and require treatment for several days during the immediate postoperative period. In this setting, intravenous analgesics play an important role, as patients may not tolerate oral medicine or need a more rapid onset of action than oral medications typically offer. IV tramadol has the potential to become a useful analgesic in this setting.

Tramadol was originally developed by the German pharmaceutical company Grünenthal GmbH in the late 1970s and is marketed globally. Parenteral tramadol injection (IV, intramuscular, and/or subcutaneous) is approved and available in 73 countries in several geographic regions, including Europe, Asia, and Australia/New Zealand. The approved doses of tramadol are 50 mg and 100 mg administered as a slow injection every 4 to 6 hours. While in the United States oral tramadol is approved by the Food and Drug Administration and widely prescribed, IV tramadol has not been approved and is therefore not available. To address this need, we conducted a study comparing the PK of 2 different regimens of IV tramadol to that of oral tramadol.

Initial PK modeling simulations were performed to determine IV regimens that might produce tramadol exposure similar to that of the highest US approved oral dosage (100 mg q6h), but with earlier drug levels in the therapeutic range. Two IV dosing regimens were identified for inclusion in the subsequent clinical trial: 50 mg

infused at hours 0, 2, and 4 and once every 4 hours thereafter, and 75 mg infused at hours 0, 3, and 6 and once every 6 hours thereafter. The IV formulation of tramadol is in use outside the United States; however, the dosing regimens tested in the current study have not been used or reported before. This study provided insight into the comparative PK of oral vs IV tramadol over a period of 48 hours and defined both acute and steady-state PK, thus facilitating clinical studies of IV tramadol in the treatment of pain in the postoperative setting.

## Methods

The protocol and other study documents were reviewed and approved by an institutional review board, IntegReview Institutional Review Board (Austin, Texas). Written informed consent was obtained from each subject before any baseline study specific evaluations were performed. This research was carried out in accordance with the clinical research guidelines established by the Basic Principles defined in the United States, 21 CFR Parts 50, 56, and 312; the principles enunciated in the Declaration of Helsinki (and its amendments); and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The single investigational center was Worldwide Clinical Trials Early Phase Services, LLC (San Antonio, Texas).

This study design was a phase 1, open-label, single-center, 3-treatment, 3-period, multidose crossover. A crossover design is a powerful tool to assess comparative PK as subjects serve as their own control, greatly diminishing the influence of confounding covariates and precluding the need for a separate control group. Crossover studies also provide optimal power as compared to parallel designs and therefore allow, for a given sample size, more precise estimates of the measurement of interest.

This study had 2 phases:

- Screening phase: Each subject underwent a screening visit (day –28 to day –1).
- Treatment phase: Subjects remained in the clinic for the duration of the treatment phase of the study, from day –1 (the day of admission to the clinic) to the day of discharge from the clinic (day 13). During the course of this treatment phase, patients received each of the 3 treatment regimens, with at least 3 days' "washout" between regimens.

The following treatment regimens were evaluated:

1. IV tramadol 50 mg at hour 0, followed by 50 mg at hour 2, 50 mg at hour 4 and 50 mg every 4 hours

- thereafter through hour 44. This regimen resulted in a total tramadol dosage of 350 mg from hour 0 to hour 24, 300 mg from hour 24 to hour 48, and 650 mg over the full 48 hours in total.
2. IV tramadol 75 mg at hour 0, followed by 75 mg at hour 3 and hour 6 and 75 mg every 6 hours thereafter through hour 42. This regimen resulted in a total tramadol dosage of 375 mg from hour 0 to hour 24, 300 mg from hour 24 to hour 48, and 675 mg over the full 48 hours in total.
  3. Oral tramadol 100 mg (50 mg tablets  $\times$  2) at hour 0 and hour 6 and every 6 hours thereafter through hour 42. This regimen resulted in a total tramadol dosage of 400 mg from hour 0 to hour 24, 400 mg from hour 24 to hour 48, and 800 mg over the full 48 hours in total.

Subjects were assigned patient numbers in an ascending order after successful completion of the screening process, and those who met eligibility criteria were randomized to 1 of 6 treatment sequences to ensure uniformity and balance of the treatments across the treatment periods (and thus to allow for control of sequence and/or period effects). The subjects were allocated to sequences such that at least 1 male and at least 1 female were in each sequence. A randomization schedule was prepared by Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, Inc. using SAS (Version 9.3, SAS Institute Inc., Cary, North Carolina).

Following a fast of at least 8 hours, subjects received their first randomized tramadol formulation in period 1. Fasting was required only for the first dose within each period; throughout the study, standardized meals and beverages were served. Meals were the same in content and quantity for all subjects during the confinement period. The oral drug product was administered with water at each dose. Subjects underwent a minimum 72-hour washout period between the end of period 1 (hour 48) and initiation of dosing in period 2, and between the end of period 2 (hour 48) and initiation of dosing in period 3. Subjects remained in the clinic for observation for a minimum of 24 hours after the final dose of period 3 (day 13).

PK sampling commenced immediately before the first dose and included blood samples at the following time points:

Blood sampling for IV tramadol 50 mg was as follows:

- Immediately before dosing and at hours 0.15, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.25, 2.5, 4, 4.25, 4.5, 5, 6, 8, 12, 16, 20, 24, 32, 40, 44, 44.25, 44.5, 44.75, 45, 45.5, 46, 47, and 48.

Blood sampling for IV tramadol 75 mg was as follows:

- Immediately before dosing and at hours 0.15, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 3.25, 3.5, 4, 6, 6.25, 6.5, 7, 9, 12, 18, 24, 30, 36, 42, 42.25, 42.5, 42.75, 43, 43.5, 46, 47, and 48.

Blood sampling for oral dosing was as follows:

- Immediately before dosing and at hours 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 12, 18, 24, 36, 42, 42.25, 42.5, 42.75, 43, 43.5, 44, 46, and 48.

Samples were sequentially collected by direct venipuncture and processed in a timely manner. All blood samples were stored on ice or at 4°C for no more than 60 minutes until plasma was centrifuged. Blood samples were centrifuged in a refrigerated centrifuge (approximately 4°C) at 3000 rpm for 10 minutes. The harvested plasma was split into 2 approximately equal aliquots and stored in 2 mL or appropriate-size cryovial tubes at -20°C in a freezer pending shipment for analysis. The plasma samples were frozen within approximately 60 minutes of centrifugation.

The plasma analyses were performed at Worldwide Clinical Trials, a private contract laboratory, using a proprietary liquid chromatography-tandem mass spectrometry method. Study samples were analysed on a Sciex API 4000 equipped with a high-performance liquid chromatography column using Analyst (Version 1.6.1; Applied Biosystems/MDS SCIEX [Ontario, Canada]) and Watson Laboratory Information Management System (LIMS, Version 7.2.0.03; Thermo Fisher Scientific, Waltham, Massachusetts) software. Human plasma samples were analyzed for tramadol and O-desmethyltramadol using a method validated for a range of 4.00 to 2000 ng/mL for tramadol and 0.800 to 400 ng/mL for O-desmethyltramadol based on the analysis of 0.200 mL of plasma. Plasma samples were extracted with an organic solvent (liquid-liquid extraction) and the organic layer removed, evaporated, and reconstituted in a solvent mixture for injection. The chromatographic conditions utilized a normal-phase high-performance liquid chromatography silica column under an isocratic elution scheme. An acidified methanol/high organic mobile phase was used for chromatographic separation. Quantitation was performed using separate weighted 1/ $\times$ 2 (for each analyte) linear least squares regression analyses generated from calibration standards.

The validated bioanalytical assay variability was as follows:

- Tramadol: Interday accuracy ranged from -1.3% to 7.9%; interday precision ranged from

5.6% to 10.9%. Intraday accuracy ranged from -8.0% to 15.0%; intraday precision ranged from 2.9% to 13.6%.

- O-desmethyltramadol: Interday accuracy ranged from -11.8% to 1.4%; interday precision ranged from 3.2% to 14.0%. Intraday accuracy ranged from 1.4% to 16.7%.

Individual plasma tramadol and O-desmethyltramadol were summarized by treatment. Plasma concentration-time data were summarized by treatment and nominal time point for the PK analysis set using descriptive statistics: sample size (N), arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum. All subjects' plasma concentration-time data were presented in 1 plot per treatment using actual time points on linear and semilog scales. Mean plasma concentration-time data were presented graphically by nominal time points using linear and semilog scales.

Concentration time data that were below the limit of quantification (BLQ) were treated as zero in the data summarization and descriptive statistics. In the PK analysis, BLQ concentrations were treated as zero from time zero up to the time at which the first quantifiable concentration was observed; embedded (a BLQ value that is flanked at adjacent time points by quantifiable concentrations) and/or terminal BLQ concentrations were treated as "missing." PK parameters for plasma tramadol and O-desmethyltramadol were computed using noncompartmental methods in Phoenix WinNonlin (Version 6.3, Pharsight Corporation, Mountain View, California). All PK analyses, summaries, and listings were generated using the PK analysis set. Actual sample times were used for the PK and statistical analyses. PK parameter values were summarized by treatment using descriptive statistics: sample size (N), arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum.

As identification of the optimal dosing regimen was of primary interest in this study, the primary comparison of interest was the pairwise assessments of the IV regimens to the oral regimen. Comparison between the IV regimens was also performed to determine the optimal dosing regimen for the IV formulation. Comparisons between treatments were evaluated by an analysis of the PK parameters by performing an analysis of variance, with terms for sequence, subject within sequence, period, and treatment effects, on log-transformed values of the overall  $C_{max}$ ,  $AUC_{0-24}$ ,  $AUC_{24-48}$ , and  $AUC_{0-48}$  and the trough levels at the end of the last dosing interval ( $C_{48}$ ). From these analyses, least squares (LS) means, LS treatment differences, and 90% confidence interval (CI) for the treatment differences on log-scale were obtained. The

**Table 1.** Demographic Data of Study Population at Screening

Parameter	Statistic	Overall (N = 18)
Age (y) at first dose	Mean (SEM)	34.9 (1.98)
	Median	34.5
	SD	8.41
	Min, Max	24, 55
Gender		
Male	N (%)	11 (61.1)
Female	N (%)	7 (38.9)
Ethnicity		
Hispanic or Latino	N (%)	3 (16.7)
Not Hispanic or Latino	N (%)	15 (83.3)
Race		
Black or African American	N (%)	12 (66.7)
White	N (%)	6 (33.3)
Height (cm) at screening	Mean (SEM)	171.36 (2.115)
	Median	171.50
	SD	8.973
	Min, Max	153.0, 191.5
Weight (kg) at screening	Mean (SEM)	80.50 (2.363)
	Median	81.65
	SD	10.024
	Min, Max	62.5, 102.6
BMI (kg/m <sup>2</sup> ) at screening	Mean (SEM)	27.38 (0.572)
	Median	27.65
	SD	2.429
	Min, Max	23.5, 31.1

BMI, body mass index; Max, maximum; Min, minimum; SD, standard deviation; SEM, standard error of the mean.

reference treatment was the oral formulation for all comparisons. The results were transformed back to the original scale by exponentiation to provide treatment geometric LS means, point estimates of the LS mean ratios (test/reference, i.e., T/R) and 90%CI for these ratios. Note that numerical comparison of the first and last dosing intervals of each regimen was also provided via the  $AUC_{tau 1}$  (first dose for each regimen) and  $AUC_{tau n}$  (last dose for each regimen).  $AUC_{tau 1}$  was calculated from actual data for the oral dosing regimen. Due to the second dose midway through the first dosing intervals for the IV regimens (at 3 hours for 75 mg IV, at 2 hours for 50 mg IV),  $AUC_{tau 1}$  was estimated as  $AUC_{0-6} \times 0.5$  for 75 mg IV and  $AUC_{0-4} \times 0.5$  for 50 mg IV (to scale the AUC to that for half the actual administered dose).  $C_{max}$  and time to maximum plasma concentration for each regimen are also provided for the first and last dosing intervals. Accumulation from the first dose to the last dose is provided as ratio of accumulation ( $AUC_{tau}$ ). Bioavailability for the parent was calculated for each IV regimen to the oral formulation using the group-mean AUCs from the last dosing interval. The accumulation ratio of the last dose as compared to the first dose (ratio of accumulation) was

**Table 2.** Plasma Pharmacokinetic Parameters of Tramadol

Tramadol Parameter	75 mg IV				50 mg IV				100 mg Oral			
	n	Mean	SD	%CV	n	Mean	SD	%CV	n	Mean	SD	%CV
t <sub>max</sub> (h)	14	15.93	17.36	108.96	14	30.02	19.89	66.27	17	44.03	1.01	2.29
C <sub>max</sub> (ng/mL)	14	932	199	21.30	14	736	152	20.60	17	701	178	25.44
C <sub>1h</sub> (ng/mL)	14	361	63.8	17.65	14	243	45.2	18.56	17	278	77.0	27.72
t <sub>2</sub> (ng/mL)	...	...	...	...	14	203	31.6	15.59	...	...	...	...
t <sub>3</sub> (ng/mL)	14	237	41.6	17.53	...	...	...	...	...	...	...	...
t <sub>6</sub> (ng/mL)	...	...	...	...	...	...	...	...	17	197	55.0	27.93
t <sub>max(0-2)</sub> (h)	...	...	...	...	14	0.54	0.22	40.34	...	...	...	...
C <sub>max(0-2)</sub> (ng/mL)	...	...	...	...	14	294	68.5	23.27	...	...	...	...
t <sub>max(0-3)</sub> (h)	14	0.50	0.28	55.47	...	...	...	...	...	...	...	...
C <sub>max(0-3)</sub> (ng/mL)	14	484	155	31.93	...	...	...	...	...	...	...	...
t <sub>max(0-6)</sub> (h)	...	...	...	...	...	...	...	...	17	1.54	0.33	21.60
C <sub>max(0-6)</sub> (ng/mL)	...	...	...	...	...	...	...	...	17	377	68.9	18.31
t <sub>max(2-4)</sub> (h)	...	...	...	...	14	2.36	0.13	5.40	...	...	...	...
C <sub>max(2-4)</sub> (ng/mL)	...	...	...	...	14	479	77.7	16.23	...	...	...	...
t <sub>max(3-6)</sub> (h)	14	3.31	0.11	...	...	...	...	...	...	...	...	...
C <sub>max(3-6)</sub> (ng/mL)	14	756	141	18.65	...	...	...	...	...	...	...	...
t <sub>max(42-48)</sub> (h)	14	42.38	0.19	0.45	...	...	...	...	17	44.03	1.01	2.29
C <sub>max(42-48)</sub> (ng/mL)	14	827	234	28.24	...	...	...	...	17	701	178	25.44
t <sub>max(44-48)</sub> (h)	...	...	...	...	14	44.30	0.11	0.24	...	...	...	...
C <sub>max(44-48)</sub> (ng/mL)	...	...	...	...	14	711	152	21.40	...	...	...	...
t <sub>48</sub> (ng/mL)	14	354	85.9	24.31	14	448	131	29.36	17	497	144	29.09
AUC <sub>tau 1</sub> (ng • h/mL)	14	1251	165.4	13.22	15	624.2	85.06	13.64	17	1494	282.3	18.90
AUC <sub>0-24</sub> (ng • h/mL)	14	9932	1958	19.72	14	9520	2106	22.12	17	7491	1936	25.85
AUC <sub>24-48</sub> (ng • h/mL)	14	9402	2511	26.71	14	11020	2852	25.88	17	11650	3387	29.07
AUC <sub>0-48</sub> (ng • h/mL)	14	19330	4427	22.90	14	20540	4906	23.89	17	19140	5172	27.02
AUC <sub>tau n</sub> (ng • h/mL)	14	3036	608.3	20.04	14	2228	525.6	23.60	17	3475	902.2	25.97
RAC(C <sub>max</sub> )	14	1.7828	0.4975	27.91	14	2.4663	0.4953	20.08	17	1.8588	0.2858	15.37
RAC <sub>(trough)</sub>	14	1.5026	0.3613	24.05	14	2.1937	0.4768	21.74	17	2.5580	0.4577	17.89
RAC(AUC <sub>tau</sub> )	14	2.4314	0.4060	16.70	14	3.5359	0.4662	13.18	17	2.3211	0.3437	14.81
C <sub>ss</sub> (ng/mL)	14	506	101	20.03	14	557	131	23.60	17	579	150	25.96
P/T ratio first	14	2.0658	0.6131	29.68	14	1.4566	0.2812	19.31	17	1.9824	0.3664	18.48
P/T ratio last	14	2.3692	0.5090	21.48	14	1.6370	0.2655	16.22	17	1.4400	0.2286	15.87

AUC, area under the plasma concentration–time curve; C, concentration; C<sub>max</sub>, maximum plasma concentration; C<sub>ss</sub>, average concentration at steady state; CV, coefficient of variation; IV, intravenous; P/T, peak to trough; RAC, accumulation ratio of last dose to first dose; SD, standard deviation; t, time; t<sub>max</sub>: time to maximum plasma concentration.

calculated based on C<sub>max</sub>, trough, and AUC<sub>tau</sub> (based on AUC<sub>tau 1</sub> and AUC<sub>tau n</sub>) for each regimen.

An assessment of whether steady state is attained by the last dose (within each dosing regimen) was performed using Helmert contrasts,<sup>17</sup> in which the first contrast tested compares the mean concentration at the first time point to the pooled mean over all remaining time points. The second contrast compares the mean at the second time point to the pooled mean over all remaining time points. Testing continues until the contrast is not statistically significant. The first time point included in this last contrast is concluded to be the dosing interval on which steady state is attained. The trough concentrations taken at 48, 42, 36, 24, 18, and 12 hours for the oral formulation; 48, 44, 40, 32, 24, 20, and 16 hours for IV tramadol 50 mg; and 48, 42,

36, 30, 24, 18, and 12 hours for IV tramadol 75 mg will be included in the steady-state analysis.

## Results

A total of 18 subjects were enrolled and randomly allocated to the treatment sequences. Subjects were male (11 [61.1%]) or female (7 [38.9%]), ranged in age from 24 to 55 years with body mass index between 23.5 and 31.1 kg/m<sup>2</sup> (Table 1). Seventeen subjects had PK parameters for at least 2 treatments and therefore were included in the pharmacokinetic and statistical analyses.

Table 2 (tramadol) and Table 3 (O-desmethyltramadol; ie, M1) present the PK parameters for each treatment regimen. Figure 1 demonstrates that mean plasma tramadol concentrations shortly after



**Table 3.** Plasma Pharmacokinetic Parameters of O-Desmethyltramadol

O-Desmethyltramadol Parameter	75 mg IV				50 mg IV				100 mg Oral			
	n	Mean	SD	%CV	n	Mean	SD	%CV	n	Mean	SD	%CV
t <sub>max</sub> (h)	14	32.99	16.50	50.01	14	44.95	1.59	3.53	17	43.97	1.12	2.54
C <sub>max</sub> (ng/mL)	14	99.2	25.6	25.85	14	96.6	24.5	25.35	17	146	37.4	25.62
C <sub>1h</sub> (ng/mL)	14	19.9	6.65	33.32	14	11.8	4.57	38.82	17	41.4	19.7	47.47
t <sub>2</sub> (ng/mL)	...	...	...	...	14	16.9	6.47	38.32	...	...	...	...
t <sub>3</sub> (ng/mL)	14	29.5	10.0	33.87	...	...	...	...	...	...	...	...
t <sub>6</sub> (ng/mL)	...	...	...	...	...	...	...	...	17	42.3	13.6	32.19
t <sub>max(0-2)</sub> (h)	...	...	...	...	14	1.85	0.19	10.34	...	...	...	...
C <sub>max(0-2)</sub> (ng/mL)	...	...	...	...	14	17.1	6.46	37.91	...	...	...	...
t <sub>max(0-3)</sub> (h)	14	2.71	0.49	18.03	...	...	...	...	...	...	...	...
C <sub>max(0-3)</sub> (ng/mL)	14	29.7	10.2	34.28	...	...	...	...	...	...	...	...
t <sub>max(0-6)</sub> (h)	...	...	...	...	...	...	...	...	17	2.04	0.87	42.42
C <sub>max(0-6)</sub> (ng/mL)	...	...	...	...	...	...	...	...	17	60.3	22.7	37.60
t <sub>max(2-4)</sub> (h)	...	...	...	...	14	3.95	0.00	0.00	...	...	...	...
C <sub>max(2-4)</sub> (ng/mL)	...	...	...	...	14	37.8	15.5	40.86	...	...	...	...
t <sub>max(3-6)</sub> (h)	14	5.81	0.52	8.98	...	...	...	...	...	...	...	...
C <sub>max(3-6)</sub> (ng/mL)	14	59.4	18.6	31.34	...	...	...	...	...	...	...	...
t <sub>max(42-48)</sub> (h)	14	43.10	0.36	0.84	...	...	...	...	17	43.97	1.12	2.54
C <sub>max(42-48)</sub> (ng/mL)	14	96.7	25.1	25.99	...	...	...	...	17	146	37.4	25.62
t <sub>max(44-48)</sub> (h)	...	...	...	...	14	45.31	0.68	1.50	...	...	...	...
C <sub>max(44-48)</sub> (ng/mL)	...	...	...	...	14	96.2	24.5	25.46	...	...	...	...
t <sub>48</sub> (ng/mL)	14	75.9	22.4	29.48	14	81.7	20.2	24.68	17	111	31.5	28.33
AUC <sub>tau 1</sub> (ng • h/mL)	14	108.3	35.79	33.06	15	39.93	15.89	39.77	17	272.1	97.32	35.77
AUC <sub>0-24</sub> (ng • h/mL)	14	1608	428.2	26.63	14	1425	405.4	28.44	17	1655	476.6	28.79
AUC <sub>24-48</sub> (ng • h/mL)	14	1896	524.5	27.66	14	2002	514.9	25.72	17	2693	750.0	27.85
AUC <sub>0-48</sub> (ng • h/mL)	14	3504	931.2	26.58	14	3427	889.9	25.97	17	4349	1139	26.20
AUC <sub>tau n</sub> (ng • h/mL)	15	519.8	142.7	27.45	14	355.6	89.39	25.14	17	768.4	209.4	27.26
RAC(C <sub>max</sub> )	14	3.4575	0.8063	23.32	14	6.0794	1.4574	23.97	17	2.7316	1.2718	46.56
RAC <sub>(trough)</sub>	14	2.7237	0.7000	25.70	14	5.2872	1.4637	27.68	17	2.7839	1.0135	36.41
RAC(AUC <sub>tau</sub> )	14	5.0884	1.2051	23.68	14	9.7100	2.6019	26.80	17	3.1287	1.5078	48.19
C <sub>ss</sub> (ng/mL)	14	86.6	23.8	27.44	14	88.9	22.3	25.14	17	128	34.9	27.25
P/T ratio first	14	1.0049	0.0185	1.84	14	1.0122	0.0327	3.23	17	1.3982	0.1890	13.52
P/T ratio last	14	1.2878	0.1073	8.33	14	1.1782	0.0772	6.55	17	1.3302	0.1635	12.29
M/P ratio C <sub>1h</sub>	14	0.0571	0.0232	40.64	14	0.0503	0.0224	44.54	17	0.1579	0.0798	50.54
M/P ratio T <sub>48</sub>	14	0.2266	0.0796	35.14	14	0.2002	0.0794	39.67	17	0.2423	0.0929	38.33

AUC, area under the plasma concentration–time curve; C, concentration; C<sub>max</sub>, maximum plasma concentration; C<sub>ss</sub>, average concentration at steady state; CV, coefficient of variation; IV, intravenous; M/P, metabolite to parent; P/T, peak to trough; RAC, accumulation ratio of last dose to first dose; SD, standard deviation; t, time; t<sub>max</sub>, time to maximum plasma concentration.

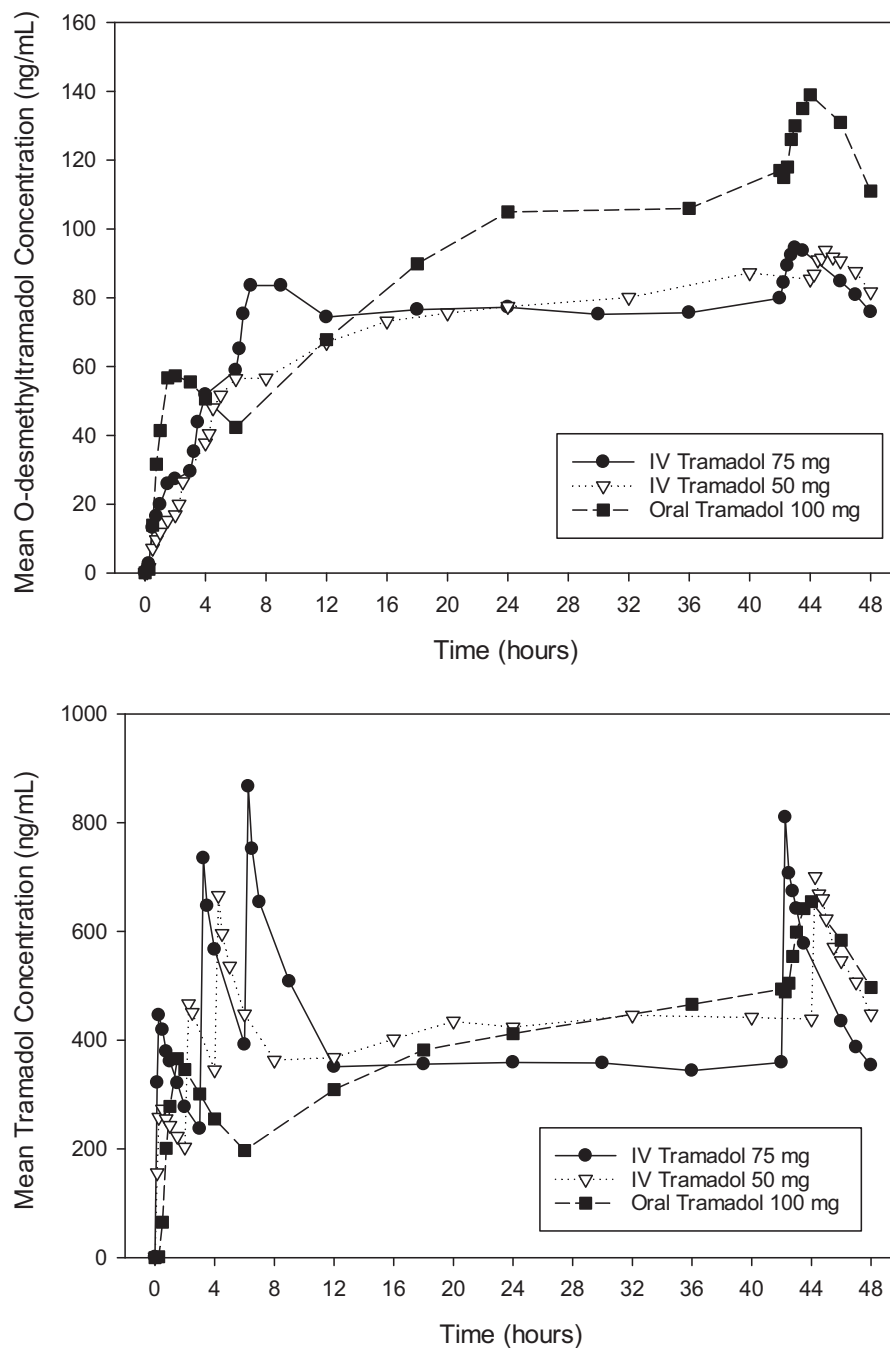
administration of each dose (eg, at 3, 6, and 42 hours) were higher with 75 mg IV every 6 hours (q6h) compared to 50 mg IV every 4 hours (q4h) and 100 mg PO q6h. While the curves reflect the dosing routes (with the rapid uptick in concentrations from the IV route vs more gradual increases from the oral route), mean trough tramadol concentrations were similar for 50 mg IV q4h and 100 mg PO q6h but somewhat lower for 75 mg IV q6h between 24 and 42 hours. During the latter dosing intervals, the mean tramadol concentrations for 50 mg IV q4h and 100 mg PO q6h were very similar.

Mean plasma O-desmethyltramadol (M1) concentrations were initially higher after oral tramadol 100 mg

as compared to the IV doses, due to first-pass effect via the oral route, and generally remained higher throughout the dosing period.

The 75 mg IV q6h regimen resulted in the greatest fluctuation in tramadol concentrations. Administration of the 50 mg IV dose, given at 4-hour intervals, resulted in less fluctuation between peak and trough and a PK profile similar to the 100-mg oral dose. With the exception that tramadol concentrations rose more rapidly after IV dosing, exposure to tramadol based on C<sub>max</sub>, AUC<sub>24-48</sub>, and AUC<sub>0-48</sub> was not significantly different between 50 mg IV q4h and 100 mg PO q6h (Table 4).

The 75 mg IV/100 mg PO ratios for C<sub>max</sub> was 137.94%, indicating higher peak exposure to tramadol



**Figure 1.** Pharmacokinetic concentrations of tramadol and O-desmethytramadol during 48-hour dosing regimens of IV tramadol 50 mg, IV tramadol 75 mg, and oral tramadol 100 mg. IV, intravenous.

after 75 mg IV q6h compared to 100 mg PO q6h in general, most apparent through 24 hours (Table 3). Based on the 80.00% to 125.00% acceptance criteria for the 90% confidence intervals,  $AUC_{0-48}$  was not significantly different between these treatments. The 50 mg IV/100 mg PO ratios ranged from 89.82% to 127.81%, and only  $AUC_{0-24}$  had 90% CIs outside the 80.00% to 125.00% range;  $C_{max}$ ,  $AUC_{24-48}$ ,  $AUC_{0-48}$ , and  $C_{48}$  were

not significantly different between these treatments. The 75 mg IV/50 mg IV ratios ranged from 83.13% to 129.16%; although the AUCs were not significantly different across these treatments, the  $C_{max}$  and  $C_{48}$  concentrations were, reflecting the more pronounced fluctuation in tramadol concentrations for the 75 mg IV q6h arm. For the metabolite, given that there is no first-pass metabolism resulting from the IV route, the ratios

**Table 4.** Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Tramadol and O-Desmethyltramadol

Tramadol	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (75 mg IV/100 mg Oral)	90%CI <sup>c</sup>	
		75 mg IV	100 mg Oral		Lower	Upper
	ln(C <sub>max</sub> )	933.2	676.5	137.94	127.99	148.66
	ln(AUC <sub>0-24</sub> )	9985	7243	137.85	130.09	146.06
	ln(AUC <sub>24-48</sub> )	9375	11160	83.98	79.49	88.73
	ln(AUC <sub>0-48</sub> )	19433	18447	105.34	100.45	110.48
	ln(t <sub>48</sub> )	355.1	475.6	74.67	69.84	79.83
	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (50 mg IV/100 mg Oral)	90%CI <sup>c</sup>	
		50 mg IV	100 mg Oral		Lower	Upper
	ln(C <sub>max</sub> )	722.5	676.5	106.80	99.20	114.98
	ln(AUC <sub>0-24</sub> )	9258	7243	127.81	120.72	135.32
	ln(AUC <sub>24-48</sub> )	10600	11160	95.00	89.99	100.28
	ln(AUC <sub>0-48</sub> )	19860	18450	107.64	102.71	112.81
	ln(t <sub>48</sub> )	427.2	475.6	89.82	84.09	95.94
	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (75 mg IV/50 mg IV)	90%CI <sup>c</sup>	
		75 mg IV	50 mg IV		Lower	Upper
	ln(C <sub>max</sub> )	933.2	722.5	129.16	119.16	139.99
	ln(AUC <sub>0-24</sub> )	9985	9258	107.85	101.33	114.80
	ln(AUC <sub>24-48</sub> )	9375	10600	88.41	83.32	93.80
	ln(AUC <sub>0-48</sub> )	19430	19860	97.87	92.97	103.02
	ln(t <sub>48</sub> )	355.1	427.2	83.13	77.35	89.34
O-Desmethyltramadol	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (75 mg IV/100 mg Oral)	90%CI <sup>c</sup>	
		75 mg IV	100 mg Oral		Lower	Upper
	ln(C <sub>max</sub> )	95.92	141.4	67.81	63.86	72.01
	ln(AUC <sub>0-24</sub> )	1516	1595	95.04	91.27	98.96
	ln(AUC <sub>24-48</sub> )	1837	2599	70.69	66.58	75.04
	ln(AUC <sub>0-48</sub> )	3372	4210	80.10	76.39	83.98
	ln(t <sub>48</sub> )	72.91	107.0	68.13	64.21	72.30
	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (50 mg IV/100 mg Oral)	90%CI <sup>c</sup>	
		50 mg IV	100 mg Oral		Lower	Upper
	ln(C <sub>max</sub> )	93.53	141.4	66.12	62.32	70.15
	ln(AUC <sub>0-24</sub> )	1377	1595	86.35	82.98	89.86
	ln(AUC <sub>24-48</sub> )	1946	2599	74.87	70.58	79.41
	ln(AUC <sub>0-48</sub> )	3326	4210	79.00	75.40	82.77
	ln(t <sub>48</sub> )	79.97	107.0	74.73	70.49	79.23
	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (75 mg IV/50 mg IV)	90%CI <sup>c</sup>	
		75 mg IV	50 mg IV		Lower	Upper
	ln(C <sub>max</sub> )	95.92	93.53	102.56	96.13	109.42
	ln(AUC <sub>0-24</sub> )	1516	1377	110.06	105.36	114.97
	ln(AUC <sub>24-48</sub> )	1837	1946	94.42	88.52	100.71
	ln(AUC <sub>0-48</sub> )	3372	3326	101.39	96.34	106.70
	ln(t <sub>48</sub> )	72.91	79.97	91.17	85.52	97.19

AUC, area under the plasma concentration–time curve; CI, confidence interval; C<sub>max</sub>, maximum plasma concentration; IV, intravenous; ln, natural log; t, time.



of each IV formulation to oral for the metabolite were approximately 65% to 75%, reflecting the lower exposure for the metabolite.

From the steady-state assessment using Helmert contrasts, the *P* values for all contrasts in the 75-mg IV and 50-mg IV regimens were greater than .05. Therefore, it can be concluded that steady state was reached at the earliest time points in the model, that is, by 12 hours for 75 mg IV and by 16 hours for 50 mg IV. For the 100-mg oral regimen, steady state was reached by 24 hours.

Compared to the IV tramadol 75-mg dose, steady-state bioavailability of the parent for the oral regimen was estimated as 85.8%. Compared to the IV tramadol 50-mg dose, steady-state bioavailability of the parent for the oral regimen was estimated as 78.0%.

Overall, tramadol was well tolerated in this study, both as an IV infusion and as an oral tablet. There were no unusual or unexpected adverse events (AEs) related to the study medication. The most commonly reported AEs reported were nausea (3 subjects), dizziness (2 subjects), and urinary hesitation (2 subjects) following administration of the 75-mg IV regimen; pruritus (2 subjects) following administration of the 50-mg IV regimen; and nausea (2 subjects) following the oral regimen. One AE, constipation, reported by 1 subject following the 50-mg IV regimen, was moderate in severity. All other AEs were mild in severity.

## Discussion

This study was designed to find an IV route of tramadol administration possessing PK properties similar to those of oral tramadol 100 mg q6h (the maximum dosage approved in the United States), but with earlier appearance of plasma levels within the presumed therapeutic range. Such a regimen has potential for use in postoperative situations in which rapid pain relief is required, or in which patients are not able to take oral medications. The 50-mg IV regimen resulted in a PK profile very similar to that of the 100-mg oral dose at steady state, with the exception of the more rapid increase in parent drug concentrations during the IV infusion as compared to the oral formulation. Exposure to tramadol based on steady-state  $C_{max}$  and AUC were not appreciably different between the 50-mg IV regimen and the oral 100-mg q6h regimen. In addition, the IV tramadol 50-mg dosing regimen resulted in lower exposure of M1, a stronger  $\mu$  opioid agonist than the parent compound, and resulted in a slower onset of exposure to M1, as compared to oral tramadol 100 mg q6h. The slower onset and overall lower exposure of M1 via the IV route should ensure that the abuse liability of tramadol is not increased by IV administration.

## Conclusions

The primary objective of this study was to evaluate the PK properties of 2 different regimens of IV tramadol hydrochloride versus a standard regimen of oral tramadol tablets during 48 hours of treatment. PK concentrations were the primary end point, and safety was assessed. The IV tramadol 50-mg regimen evaluated in this study, consisting of q4h administration plus a loading dose at hour 2, was identified as having a similar PK profile to the approved oral formulation. Furthermore, the 50-mg regimen demonstrated an excellent tolerability profile, and therefore was selected for further assessment in a phase 3 development program in postsurgical pain.

## Acknowledgments

Special thanks for bioanalytical contributions from Bhasha Desai and pharmacokinetic analysis contributions from Jeff Stark at Worldwide Clinical Trials, LLC (WCT) (2455 NE Loop 410, Suite 150, San Antonio, Texas 78217, USA). WCT conducted the study and performed the bioanalytical and PK analyses. Robert Criscola (Avenue Therapeutics, Inc.) oversaw data management activities and participated in study management.

## Conflicts of Interest

The authors are either employees or paid consultants of Avenue Therapeutics, Inc., a pharmaceutical company developing intravenous tramadol for the US market.

## Funding

This study was funded by Avenue Therapeutics, Inc.

## Author Contributions

M.H., S.R., and L.L. wrote the manuscript; L.L. and S.R. designed the research; M.R. led the clinical research; M.H. analyzed the data; G.A. was the principal investigator for the trial.

## References

1. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet*. 2004;43:879-923.
2. Hennies HH, Friderich E, Schneider J. Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. *Arzneimittelforschung*. 1988;38:877-880.
3. Lintz W, Barth H, Becker R, et al. Pharmacokinetics of tramadol and bioavailability of enteral tramadol formulations. 2nd communication: drops with ethanol. *Arzneimittel Forschung*. 1998;48(5):436-445.

4. Lintz W, Becker R, Gerloff J, et al. Pharmacokinetics of tramadol and bioavailability of enteral tramadol formulations. 4th communication: drops (without ethanol). *Arzneimittel Forschung*. 2000;50(2):99-108.
5. Lintz W, Barth H, Osterloh G, et al. Pharmacokinetics of tramadol and bioavailability of enteral tramadol formulations. 3rd communication: suppositories. *Arzneimittel Forschung*. 1998;48(9):889-899.
6. Scott L, Perry C. Tramadol: a review of its use in perioperative pain. *Drugs*. 2000;60(1):139-176.
7. Likar R, Schalk HV, Sittl R. Tramadol - acute postoperative pain management. In: Gullo A. ed. *Anaesthesia, Pain, Intensive Care and Emergency Medicine - A.P.I.C.E.* Milan:Springer; 1998.
8. Subrahmanyam V, Renwick AB, Walters DG, et al. Identification of cytochrome P-450 isoforms responsible for cis-tramadol metabolism in human liver microsomes. *Drug Metab Dispos*. 2001;29(8):1146-1155
9. Lledo P. Variations in drug metabolism due to genetic polymorphism: a review of the debrisoquinidine/sparteine type. *Drug Invest*. 1993;5:19-34
10. Collart L, Luthy C, Dayer P. Multimodal analgesic effect of tramadol [abstract]. *Clin Pharmacol Ther*. 1993;53:223.
11. Raffa RB. Basic pharmacology relevant to drug abuse assessment: tramadol as example. *J Clin Pharm Ther*. 2008;33:101-108.
12. Gillen C, Haurand M, Kobelt DJ, Wnendt S. Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor. *Naunyn Schmiedebergs Arch Pharmacol*. 2000;362(2):116-121.
13. Lee CR, McTavish D, Sorkim EM. Tramadol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs*. 1993;46(2):313-340.
14. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exper Ther*. 1992;260(1):275-285.
15. Desmeules JA, Piguel V, Collart L, et al. Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br J Clin Pharmacol*. 1996;41:7-12.
16. Codd EE, Shank R, Schupsky J, et al. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesic. Structural determinants and role in antinociception. *J Pharmacol Exper Ther*. 1995;274:1263-1270.
17. Maganti L, Panebianco D, Maes A. Evaluation of methods for estimating time to steady state with examples from Phase 1 studies. *APPIS J*. 2008;10(1):141-147.