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Bioavailability of Long Acting Tramadol in Mexican Healthy Volunteers

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Abstract

Tramadol hydrochloride is a synthetic, centrally acting analgesic, used for the relief of moderate to severe acute and chronic pain. Immediate-release tramadol have a short duration of therapeutic effect and are generally less effective for pain control than other opioid derivatives. The aim of this study was to investigate the pharmacokinetic profile of long release formulation of tramadol. Twelve healthy volunteers were included into the study. After 12-hour (overnight) fast, subjects received a single capsule of long release of tramadol 100 mg dose. For the analysis of pharmacokinetic properties, blood samples were drawn at baseline, 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hours after dosing. The tramadol pharmacokinetic values were C_{max} of 245.60 ± 54.26 ng/mL, t_{max} of 3.79 ± 0.50 h, AUC_{0-t} of 2,621.39 ± 780.21 hr.ng/mL, $AUC_{0-\infty}$ of 2,917.16 ± 980.29 hr.ng/mL, $t_{1/2}$ of 6.24 ± 1.12 h, Cl of 38.18 ± 13.14 L/h and Vd of 328.71 ± 74.44 L. The pharmacokinetic (PK) values of long acting tramadol of our study were consistent with PK results of other populations that used the extended release formulation of tramadol.

Keywords: Tramadol; Pharmacokinetics; Human; HPLC; MS-MS; Long release capsules

Introduction

Tramadol hydrochloride is a synthetic, centrally acting analgesic, which has been used since 1977 for the relief of moderate to severe acute and chronic pain. Tramadol is rapidly and almost completely absorbed after an oral administration. However, its mean absolute bioavailability is only 65–70% due to the first-pass hepatic metabolism [1,2]. The extent of bioavailability increases to 77% after the rectal administration of tramadol suppositories [3] and to 100% after an intramuscular administration [4]. The peak plasma concentration is reached in 0.17–1.5 h following the intramuscular administration [5], in 0.5–1.7 h after the oral administration of drops [2], in 1–3 h after the oral administration of capsules [1] and in 2–6 h after the rectal administration of suppositories [3].The biotransformation of tramadol has been investigated in diverse kind of animals and humans [5]. The principal metabolic pathways, O-and N-desmethylation, involve cytochrome P-450 isoenzymes 2D6 (pivotal), 2B6 and 3A4 [6]. Approximately 10–30% of the parent drug is excreted unmetabolised in the urine [7] Tramadol plasma protein binding is shown to be 4–20% [6]. The mean terminal half-lives of tramadol and O-desmethyltramadol are about 5–7 hours [1-6]. Immediate-release tramadol have a short duration of therapeutic effect and are generally less effective for pain control than other opioid derivatives. Common criticisms of tramadol also include the patient's tendency to develop dependence on the drug itself. The newer extended-release tramadol formulation was designed to increase efficacy, duration of therapeutic effect, tolerance, compliance, and facilitate discontinuation. The aim of this study was to investigate the pharmacokinetic profile of long release formulation of tramadol 100 mg in Mexicans with special reference in comparing these PK parameters with other populations.

Methods

Twelve healthy volunteers (six females), aged between 18 and 55 years were included based on their medical history, clinical examination results, and routine laboratory tests. Subjects with HIV or hepatitis B or C virus were excluded. All healthy volunteers were selected based on information from a database of the Centro de Estudios Científicos y Clínicos Pharma S. A. de C. V. (CECYC Pharma Clinical Unit), Mexico City, Mexico. All eligible subjects provided written informed consent for participation in the study. Subjects were compensated for participation.

Subjects

Twelve healthy volunteers (six females), aged between 18 and 55 years were included based on their medical history, clinical examination results, and routine laboratory tests. Subjects with HIV or hepatitis B or C virus were excluded. All healthy volunteers were selected based on information from a database of the Centro de Estudios Científicos y Clínicos Pharma S. A. de C. V. (CECYC Pharma Clinical Unit), Mexico City, Mexico. All eligible subjects provided written informed consent for participation in the study. Subjects were compensated for participation.

Study design

The study was approved by the ethics and research committees of the Centro de Estudios Científicos y Clínicos Pharma S. A. de C. V. The study was carried out in accordance with the principles of the Declaration of Helsinki and its amendments and the International

Demographic Characteristics	Mean	Standard Deviation	C. V.%	Min-Max
Age (years)	23.25	2.90	12.46	21.00 –30.00
Weight (Kg)	63.80	7.81	12.24	52.60 –76.00
Height (m)	1.65	0.08	4.75	1.50 –1.76
BMI	23.49	1.85	7.88	20.29–25.51
Gender	**Proportion**			
Male	50.0%			
Female	50.0%			

Table 1: Descriptive statistics of demographic characteristics of the volunteers (n=12).

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Conference of Harmonisation Guidelines for Good Clinical Practice. A single, open-label design was used. The subjects arrived at the clinical Unit the day before the beginning of the study. After that, subjects were fasted for 12 hours overnight before drug administration. Blood was drawn for baseline plasma measurements in the following manner: a 20-G catheter (Jelco®, Plus, Medex Medical Ltd. Ascot, United Kingdom) was placed in a suitable forearm vein and a 6-mL blood sample was drawn into a heparinized vacuum tube (Vacutainer®, Becton-dickinson and Company, Franklin Lakes, New Jersey). Subjects received a single long release capsule of tramadol 100 mg (Prontofort®), manufactured by Productos Medix, S. A. de C. V, given with 250 mL of water, and additional blood samples were drawn at 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0 hours after study drug administration. Plasma levels obtained bay centrifugation (2000 g for 10 minutes at room temperature) and stored frozen at -70°C until analyzed using high-performance liquid chromatography (HPLC) with a MS-MS detector.

Determination of plasma tramadol concentrations

Tramadol plasma levels were determined using HPLC with MS_MS detector as adapted by personnel of CECYC Pharma Analytical Unit, in which venlafaxine was used as internal standard, based on the methods of Nobilis and colleagues [4]. Briefly, 0.2 mL of plasma and 0.1 mL of internal standard (venlafaxine), were mixed by shaking in a test tube for 1 minute. The supernatant was filtered through a regenerated cellulose syringe filter (pore size, 0.45 micron) and injected into the chromatographic system. The chromatographic conditions were: column (Zorbax XDB C18, 2.1×50 mm, 5 µm), ammonium formiate solution at 0.025%: Acetonitrile (60:40 v/v) used as mobile phase. The injection volume was 5 µL, the flow rate was maintained constant at 0.3 mL/min, the column temperature was of 30°C and the retention times were between 0.4-0.8 minutes for tramadol and between 0.4-0.8 minutes for venlafaxine. The concentration ranges were from 5.0 a 300.0 ng/mL. The extraction method consisted in a liquid-liquid extraction, with a mixure of methyl-terbutil-ether. The MS-MS detector conditions were source temperature of 120°C, desolvation temperature of 400°C, multiplier of 650.0 V and Capilar of 3 kV.

Tolerability

Tolerability was assessed by monitoring vital signs (blood pressure, heart rate, and body temperature) at baseline, 4.5, 11.5 and 23.5 hours, and subject interviews regarding the potential of adverse events (AEs) during the whole study.

Pharmacokinetics and statistical analysis

Individual plasma concentration-time curves were constructed; C_{max} and t_{max} were directly obtained from the curve. AUC from time 0 (baseline) to 24 hours (AUC_{0-24}) was calculated using the trapezoidal rule. From the terminal log-decay phase, elimination rate constant (ke) was estimated using linear regression, and t1/2 was estimated using the following equation:

$$t_{1/2} = \ln 2/ke$$

Where ln was defined as the natural log; and extrapolation of AUC from baseline to infinity (AUC0-∞) was calculated as follows:

$$AUC_{0-\infty} = AUC_{0-24} + (C24/ke)$$

Where, C72 was defined as concentration at 24 hours.

Results

A total of 12 subjects were enrolled in the study. Subjects had the following characteristics: age range 18 to 49 years (mean ± SD of 23.2 ± 2.9 years), mean weight of 63.8 ± 7.8 kg, and mean height of 1.65 ± 0.08 m (Table 1).

Pharmacokinetic parameters

Individual values of C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$, Cl (clearance) and Vd (apparent volume of distribution) are shown in table 2. Pharmacokinetic mean and SD values were C_{max} of 245.60 ± 54.26 ng/mL, t_{max} of 3.79 ± 0.50 h, AUC_{0-t} of 2,621.39 ± 780.21 hr.ng/mL, $AUC_{0-\infty}$ of 2,917.16 ± 980.29 hr.ng/mL, $t_{1/2}$ of 6.24 ± 1.12 h, Cl of 38.18 ± 13.14 L/h and Vd of 328.71 ± 74.44 L (Table 3). Figure 1 shows the mean (SD) plasma tramadol concentrations after drug administration.

Safety

Some adverse effects occurred in the volunteers during the study after tramadol administration of a 100 mg long release capsules as follows: three volunteers had mild dizziness, and occurred into 4 hours post-dose and disappeared spontaneously without drug medication. These adverse events were classified with probable association with the study drug. Two volunteers had nausea of mild intensity and vomits in between 7 and 10 hours post-dosing. These adverse events were classified with probable association with the study drug and they were

No. Volunteer	C_{max} (ng/mL)	t_{max} (h)	ABC_{0-24} h (h.ng/mL)	$ABC_{0-\infty}$ (h.ng/mL)	$T_{½}$ (h)	Vd (L)	Cl (L/h)
1	293.79	4.00	3,806.61	4,584.59	8.47	266.48	21.81
2	190.70	4.00	1,751.88	1,854.07	5.14	400.03	53.94
3	282.42	4.00	3,370.51	3,994.15	8.12	293.13	25.04
4	280.40	4.00	2,811.33	3,046.44	5.86	277.49	32.83
5	171.80	4.00	1,673.56	1,781.99	5.33	431.61	56.12
6	272.98	4.00	2,521.53	2,691.64	5.43	291.08	37.15
7	338.13	4.00	3,718.78	4,167.99	6.87	237.65	23.99
8	173.18	2.50	1,589.37	1,676.37	5.26	452.32	59.65
9	254.34	4.00	2,925.88	3,160.67	5.64	257.63	31.64
10	247.32	3.00	2,354.22	2,541.60	5.80	329.04	39.35
11	181.12	4.00	1,942.97	2,126.39	6.04	409.69	47.03
12	261.00	4.00	2,990.04	3,380.08	6.99	298.36	29.59
Mean	245.60	3.79	2,621.39	2,917.17	6.24	328.71	38.18
Standard deviation	54.26	0.50	780.21	980.29	1.12	74.44	13.14
CV%	22.09	13.14	29.76	33.60	17.96	22.65	34.42

Table 2: Individual tramadol pharmacokinetic parameters after 100 mg administration in Mexican healthy volunteers.

PK parameter	Tramadol 100 mg		
	Mean	Standard deviation	CV%
C_{max} (ng/mL)	245.60	54.26	22.09
AUC_{0-t} (h.ng/mL)	2,621.39	780.21	29.76
AUC_{0-Inf} (h.ng/mL)	2,917.16	980.29	33.60
T_{max} (h)	3.79	0.50	13.14
$t_{1/2}$ (h)	6.24	1.12	17.96
Vd (L)	328.71	74.44	22.65
Cl (L/h)	38.18	13.14	34.42

Table 3: Descriptive statistics of tramadol 100 mg long acting capsules PK parameters.

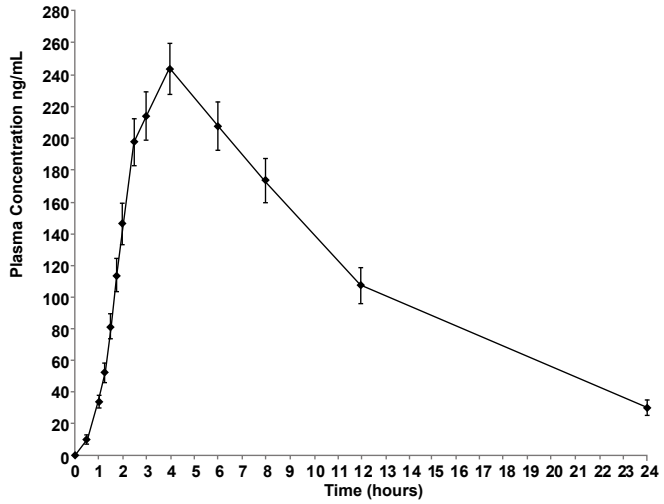

Figure 1: Main plasma profile of tramadol 100 mg long acting capsules.

controlled with ranitidine 50 mg/10 mL, methoclopramide 10 mg/2 mL and a saline solution 1000 mL by intravenous route.

Discussion

Lintz et al. [9] determined the absolute bioavailability of tramadol hydrochloride 200 mg in healthy volunteers by oral and intravenous routes. The absolute bioavailability of tramadol in capsules was 68 ± 13% with a range of 41-84%. Peak serum concentrations of 280 ± 49 ng/ml were reached 2 hours after oral administration of two capsules of tramadol. The terminal phase of the biological half-lives of tramadol was 5.1 ± 0.8 h (oral) and 5.2 ± 0.8 h (intravenous). Karhu conducted a three-way crossover study in healthy volunteers in order to characterize the pharmacokinetics and to assess the dose proportionality of 100 mg, 200 mg and 300 mg strengths of a novel once-a-day tramadol controlled-release tablet. PK results were similar with respect the PK data from Mexican volunteers of our study.

Hernandez-Lopez and colleagues compared the pharmacokinetic profile and oral bioavailability of two tramadol 200 mg tablets with following single-dose administration in 26 healthy volunteers from Spain. Results also were similar than Mexican results. Racial and ethnic differences in drug-metabolizing ability associated with genetic or cultural/environmental factors are not only well recognized but also important in understanding interindividual variability in drug responsiveness. Subrahmanyam demonstrated that cis-tramadol can be metabolized to tramadol metabolites by CYP2B6 and CYP3A4 isoforms. There are information about the pharmacokinetics of drugs metabolized by the CYP 3A4 in Mexican population, where there is interethnic evidence of differences in the PK results of nifedipine [9] midazolam [10], cyclosporine [11] and sildenafil [12]. Although Poland and colleagues [13] reported that CYP 3A activities do not differ between Mexicans [14] and European Americans [15]. In the case of tramadol, we also did not see ethnic differences with respect to Caucasian volunteers [16].

Further clinical studies with the long acting formulation had to be done in patients in order to evaluate the pharmacodynamic activity of the tramadol formulation used in our study.

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