

# Human pharmacokinetics of the muscle relaxant, eperisone hydrochloride by liquid chromatography–electrospray tandem mass spectrometry

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**Abstract** Eperisone hydrochloride (4'-ethyl-2-methyl-3-piperidinopropiophenone hydrochloride) is a muscle relaxant agent, widely used in the treatment of patients with muscular contractures, low back pain or spasticity. Because of its mechanism of action (inhibition of gamma-efferent firing and local vasodilatation activity), side effects on central nervous system are rarely observed. A sensitive liquid chromatography–electrospray ionization-mass spectrometry method for determination of eperisone in human plasma has been developed, with a lower limit of quantification of 0.01 ng/mL. The method was applied to a pharmacokinetic study in 12 healthy volunteers given eperisone 100 mg as single dose on day 1 and three times daily on days 2 to 4. Eperisone was rapidly absorbed after oral administration ( $T_{\max} = 1.6$  h) as it was expected by its

fast-onset relaxant activity. Moreover, eperisone underwent a rapid elimination from the body (biological half-life 1.87 h), which was not modified during the repeated dosing as suggested by the  $C_{\max}$  cumulation observed, not different from that expected for a  $t_{1/2}$  of 1.87 h as suggested by the similar and negligible plasma concentration values (0.063 and 0.067 ng/mL) measured on day 4 before the morning dose and 12 h after evening dose, thus ruling out any potential risk for drug accumulation. Thus, the pharmacokinetic characteristics of eperisone provide further justification for its tolerability in patients with low back pain or spastic palsy, in which the drug is given for periods ranging from few days to several months, respectively.

**Keywords** Eperisone · Pharmacokinetics · Tandem mass spectrometry · Human plasma

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## Abbreviations

LBP	Low back pain
CNS	Central nervous system
EPS	Eperisone
PK	Pharmacokinetic
GI	Gastrointestinal
$T_{\max}$	Time of maximum concentration
$C_{\max}$	Maximum plasma concentration
ng	Nanogram
mL	Millilitre
mg	Milligram
LLOQ	Lower limits of quantification
LC–MS/MS	Liquid chromatography–mass spectrometry triple quadrupole mass spectrometry
UCMC	University of Catania Medical Center
GCP	Good clinical practice
ECG	Electrocardiogram
HBV	Hepatitis B virus

HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
$t_{1/2}$	Plasma concentration half-life
SPC	Summary of product characteristics
rpm	Revolutions per minute
min	minute
HPLC	High performance liquid chromatography
ESI	Electrospray ionization
TOL	Tolperisone
$\mu\text{l}$	Microliter
mM	Millimole
v/v	Volume to volume
$m/z$	Mass to charge
$\text{AUC}_{0-t}$	Area under the plasma concentration curve administration to last observed concentration at time t
$\lambda_z$	Terminal elimination rate constant
$\text{AUC}_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinity time
$C_{\text{last}}$	Last quantified concentration
ANOVA	Analysis of variance
AUC	Area under the plasma concentration curve
CV	Coefficient of variation
SD	Standard deviation
h	Hour

## 1 Introduction

Low back pain (LBP) is generally thought to result from a self-perpetuating cycle of pain and muscle spasm, which is triggered by a pathological lesion in the lumbosacral region (e.g. facet joints, discs, muscles, or ligaments). The spastic palsy is also a clinical condition characterized by a velocity-dependent increase of muscle tone due to “parapyramidal” disturbance of the inhibitory afferents to the second motor neuron.

In both conditions, central muscle relaxant agents are widely used by physicians, although their use has been questioned by the occurrence of clinically relevant side effects mostly affecting the central nervous system (CNS), such as sedation, drowsiness, headache, blurred vision, nausea, and vomiting. Potential for drug abuse and dependency have been also reported (Elder 1991). In spite of this concern, however, many clinical guidelines still recommend the use of muscle relaxants, either alone or in combination with anti-inflammatory drugs for the management of LBP, and numerous physicians report the use of muscle relaxants although they are conditionally discouraged by their well known side effects (Di Iorio et al. 2000).

Eperisone hydrochloride (4'-ethyl-2-methyl-3-piperidinopropiophenone hydrochloride) is used clinically in the treatment of patients with LBP (Beltrame et al. 2008; Cabitza and Randelli 2008; Sartini 2008; Viladot Pericé et al. 2008) or spastic palsy (Bresolin et al. 2009a, b). Its peculiar mechanism of action is believed to blockade both sodium and calcium voltage-gated channels (Kocsis et al. 2005), exerting its activity mainly on the spinal cord structures by reducing the gamma-efferent firing and inhibiting the spinal cord activities (Ito et al. 1985; Morikawa et al. 1987). Furthermore, eperisone (EPS) have also shown some vasodilator activity with a consequent increase in muscle blood perfusion (Iwase et al. 1992; Sakai et al. 2008), and it exerts an antinociceptive effect by antagonistic activity on P substance (Fujioka and Kuriyama 1985). Because of its mechanisms of action, EPS is almost devoid of the side effects on CNS that are often reported with other centrally acting muscle relaxants.

Published pharmacokinetic (PK) investigations have shown that oral EPS is rapidly absorbed from the gastrointestinal (GI) tract with time to peak plasma concentrations ( $T_{\text{max}}$ ) of 1.1 h (Li et al. 2004), 1.28 h (Min Kyo et al. 2007) and 1.5 h (Takamatsu et al. 1992). This is a valuable characteristic of eperisone, since an essential request by general physicians for all muscle relaxants is their rapid onset of action, especially in LBP patients.

In contrast, the peak plasma concentrations ( $C_{\text{max}}$ ) have been reported to range within a wider interval, from 1.25 (Min Kyo et al. 2007) to 3.08 ng/mL (Li et al. 2004), after oral administration of a single 100 mg tablet of eperisone. The discrepancies observed in the  $C_{\text{max}}$  of EPS may result from the different assay methods employed in the PK studies, which have shown variable lower limits of quantification (LLOQ) ranging between 0.2 and 1 ng/mL in the most recent studies (Li et al. 2004; Min Kyo et al. 2007). These LLOQ are not sensitive enough for PK research because the  $C_{\text{max}}$  of EPS in some patients can be only approximately 0.5 ng/mL, and often the plasma concentrations observed in the terminal elimination phase are below 0.2 ng/mL.

We have therefore developed a liquid chromatography–mass spectrometry triple quadrupole mass spectrometry (LC–MS/MS) assay method for a rapid and sensitive determination of EPS, with the target LLOQ of 0.01 ng/mL in human plasma. Our aim was also to reduce the amount of human plasma and the time of sample processing needed for the assay of EPS. We have also taken the opportunity of this sensitive assay method to further investigate the PK of EPS when administered as single dose or as repeated dose three times a day after meals according to the regimen suggested for therapy; in particular, we wanted to gather more information on its potential for drug accumulation.

## 2 Materials and methods

### 2.1 Subjects

This study was carried out on 12 male healthy non-smoking volunteers aged 18–50 years. Subjects were called to participate in the study after detailed appropriate information on the nature and characteristics of the drug, as well as on the intention and executive formalities of the trial. The study was conducted at the University of Catania Medical Center (UCMC), in accordance with the protocol, GCP requirements and the principles of the Declaration of Helsinki, and the applicable regulatory requirements. The study protocol was reviewed and approved by the UCMC Ethical Committee. Informed written consent was obtained from all volunteers. The aim of the investigation was fully explained to all the subjects and informed consent was obtained in each case. Before treatments, and at the end of the study, all study subjects undertook a complete physical examination including systolic and diastolic blood pressure, heart rate (in sitting condition), electrocardiogram (ECG) and routine clinical laboratory analyses. The laboratory analyses included haematology, blood chemistry (urea, glucose, creatinine, bilirubin total, glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, cholesterol, and triglycerides), virology (HBV, HCV and HIV), urine analysis and screening for drugs abuse (methadone, benzodiazepines, cocaine, amphetamine/methamphetamine, opiates, barbiturates, tetrahydrocannabinol, and tricyclic antidepressants).

### 2.2 Study design

Aim of the study was to assess the pharmacokinetic profile of EPS after single (on day 1) and repeated (t.i.d. on days 2 to 4) oral administration of eperisone hydrochloride 100 mg tablets. Since the  $t_{1/2}$  reported in the SPC and obtained in the present study was less than 2 h, the wash out period applied between the two phases of the study was considered adequate.

Twelve male healthy subjects, 18–50 years old, were enrolled. Each subject was given 100 mg tablets of eperisone hydrochloride after meal, in a single dose on day 1 and at the dose of three tablets daily for the next 3 days. In detail, EPS was administered at 8.00 a.m. on day 1, and at 8.00 a.m., 2.00 p.m. and 8.00 p.m. on days 2 to 4.

Blood samples were collected (Fig. 1):

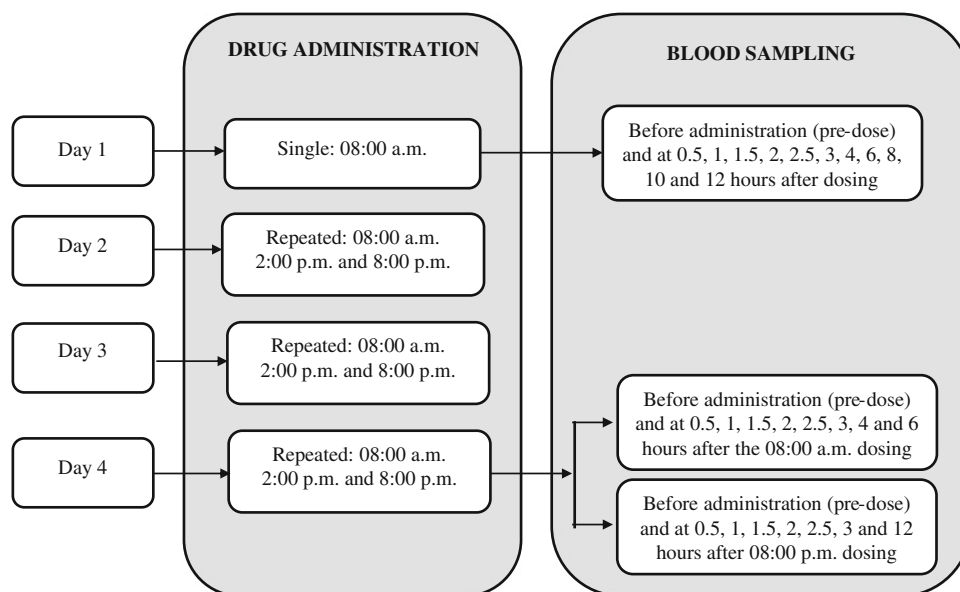
- On day 1: before administration (pre-dose) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h after dosing;
- on day 4: before the 1st dosing at time 0 (pre-dose), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 h after dosing and before the 3rd dosing at time 0 (pre-dose) and at 0.5, 1, 1.5, 2, 2.5, 3, 12 h after dosing.

Each blood sample was immediately centrifuged at 4,100 rpm for 5 min and each plasma sample was separated and stored at  $-20^{\circ}$  C until analyzed.

### 2.3 Analytical method

EPS plasma concentrations were determined using a LC–MS/MS equipped (Agilent 1100 series HPLC and an

**Fig. 1** Flow-chart of the PK study



Agilent 6410 series Triple Quad.) with an electrospray ionization (ESI) source (Agilent Technologies, USA) and tolperisone (TOL) as internal standard (Min Kyo et al. 2007). The chromatographic separation was achieved on a Gemini-NX C<sub>18</sub> (50 × 2.0 mm, 3 μm) column. All data were acquired employing Agilent 6410 Quantitative Analysis version B.01.03 analyst data processing software. The investigator who analyzed plasma samples was blind to treatment. EPS was extracted from plasma according to the following procedure. 500 μl of plasma in glass tubes were added with 10 μl (250 ng/mL) TOL, the mixture was vortex-mixed for approximately 1 min and added with 500 μl of saturated sodium bicarbonate solution, the plasma samples were extracted with 3.5 ml of ethyl acetate in single glass tubes. This was then mixed on a shaker for 10 min and centrifuged for 10 min at 4,100 rpm. A 3 ml portion of the organic phase was transferred to glass tubes and evaporated at 50°C for 60 min with a vacuum system. The residue was reconstituted with 100 μl of 10 mM ammonium acetate buffer solution pH 4.1:methanol (50:50, v/v) as mobile phase and an aliquot of 5 μl was injected into the HPLC column. EPS was ionized under positive ionization conditions. The product ion mass spectra of EPS and the TOL are shown in Fig. 2. The predominant peaks in the primary ESI spectra of EPS and TOL correspond to the [M–H]<sup>+</sup> ions at *m/z* 260.3 and 246.3, respectively. Both product ions for EPS and TOL had a *m/z* of 98.2. Chromatograms were integrated and the calibration curves were plotted as the peak area of EPS corrected for variation in amounts of internal standard observed, versus EPS concentration.

## 2.4 Pharmacokinetic parameters

The following PK parameters were determined using non-compartmental analysis:

maximum plasma concentration (*C*<sub>max</sub>) and time of maximum concentration (*T*<sub>max</sub>) were determined observationally, area under plasma concentration–time curve was calculated by numerical integration using the linear trapezoidal rule as follows:

$$\text{AUC}_{0-t} = \sum_{i=2}^n 0.5(C_i + C_{i-1})(t_i - t_{i-1})$$

Estimates of the terminal half-life *t*<sub>1/2</sub> were calculated using the following equation:

$t_{1/2} = 0.693/\lambda_z$ , where  $\lambda_z$  is the terminal elimination rate constant calculated by regression analysis on the natural log of plasma values versus time, between a time point where log linear  $\lambda_z$  elimination phase begins and the time at which the last concentration above the LLOQ occurred.

$\lambda_z$  was calculated as the slope multiplied by (–1).

The area under concentration–time curve from time zero to infinity was calculated according to the following equation:

$$\text{AUC}_{0-\infty} = \text{AUC}_{0-t} + C_{\text{last}}/\lambda_z$$

Plasma concentrations that were below the LLOQ were treated as zero.

## 2.5 Statistical analysis

A descriptive statistical analysis was carried out on the above mentioned parameters. Analysis of variance (ANOVA) was performed in order to verify the effect of repeated t.i.d. administration on the parameters AUC and *C*<sub>max</sub> relative to single dose after logarithmic transformation, using the “general linear model” procedure. The parameter *T*<sub>max</sub> was evaluated by a non-parametric procedure, the Wilcoxon matched-pair ranks test. A *P* value of 0.05 or less was considered as indicative of a significant difference.

## 3 Results

### 3.1 Method of assay

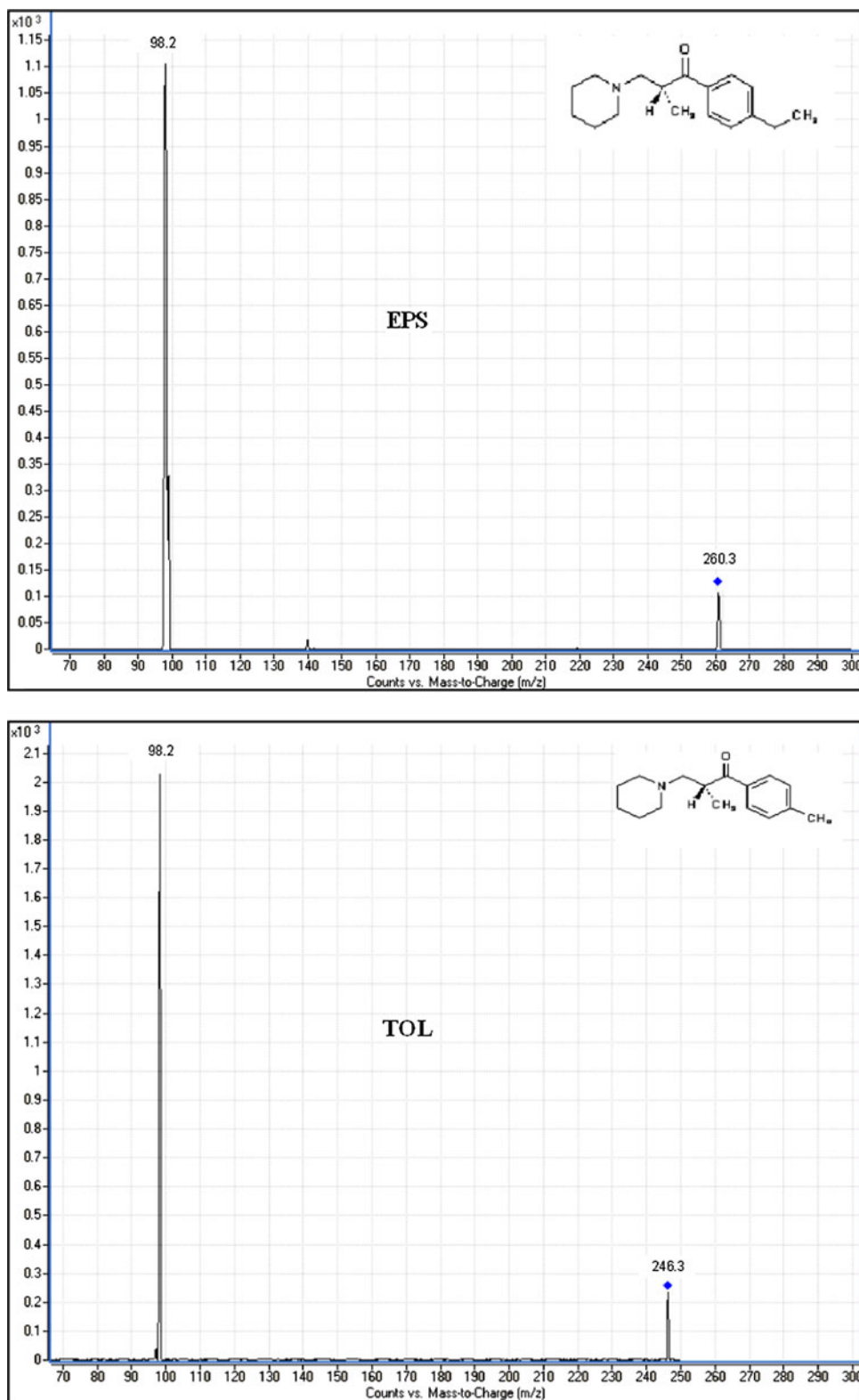
The validation results indicate that the assay has an adequate selectivity, specificity and sensitivity.

The assay was linear over a range of 0.01–10 ng/mL for EPS. The results for the intra- and inter-assay precision (calculated using over 3 analytical runs at 4 concentration levels, *n* = 6) ranged from 1.94 to 9.79% and from 1.86 to 10.04%, respectively. The inter-assay accuracy ranged from –1.41 to 4.18%. The coefficients of variation (CV) were less than 15% for both drugs. The lower limit of quantification was 0.010 ng/mL. Recoveries of the analysis were determined at two different EPS concentrations. The matrix effect for the measurement of EPS and TOL were not significant.

### 3.2 Pharmacokinetic analysis

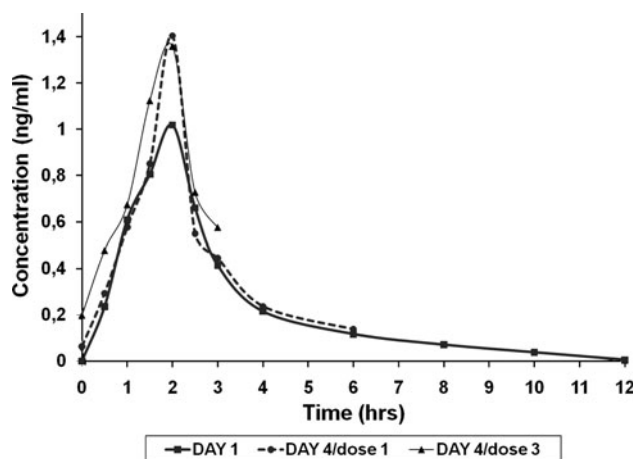
The mean values of EPS plasma concentrations at each sampling time point after administration of 100 mg tablets of eperisone hydrochloride are outlined in Fig. 3. The mean values of EPS log plasma concentrations versus time are outlined in Fig. 4. PK parameters represent mean values of the data of each subject analyzed separately. When a single dose of 100 mg tablet was given orally immediately after meal, the *T*<sub>max</sub> averaged 1.67 ± 0.49 (SD) h (range 1–2.5). The *C*<sub>max</sub> was 1.61 ng/mL ± 1.17 (range 0.40–3.77), the terminal elimination half-life (*t*<sub>1/2</sub>) was 1.87 ± 0.73 h (range 0.95–3.53), and the AUC<sub>0-∞</sub> was 2.79 ± 2.12 ng/ml/h

**Fig. 2** The product ion mass spectra of eperisone (EPS) and tolperisone (TOL)

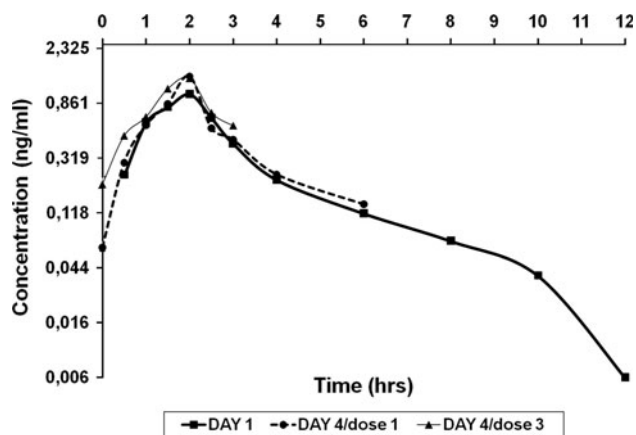


(range 0.68–7.14) (Table 1). The drug plasma concentration measured immediately before the first dose of day 4 was on average  $0.063 \pm 0.048$  ng/mL; this suggests that the drug

accumulation during a t.i.d. administration is negligible. Moreover, the plasma concentrations 12 h after the third dose of day 4 averaged  $0.067 \pm 0.048$  ng/mL, thus



**Fig. 3** Mean plasma concentration–time profile of eperisone after oral administration at 100 mg tablets to the human volunteers



**Fig. 4** Mean eperisone log plasma concentrations versus time

suggesting that a steady-state condition is achieved, as expected from the  $t_{1/2}$  of eperisone.

The comparison of the  $AUC_{0-6}$  after the first administration of day 4 versus the  $AUC_{0-\infty}$  of the single dose administration (day 1) does not show any increase in drug exposure (2.674 vs. 2.798 ng/mL/h) (Table 1). In order to check the intra-day drug accumulation after a t.i.d. administration, a comparison of  $C_{max}$  after the first and third dose has been performed on day 4. The mean  $C_{max}$  values were  $1.636 \pm 1.299$  and  $1.715 \pm 1.469$  ng/mL, respectively, being the difference not statistically significant. The mean  $C_{max}$  after the single dose of day 1 was  $1.611 \pm 1.166$  ng/mL; also in this case there was no statistically significant difference between the  $C_{max}$  values at day 1 and day 4 (Table 1). No serious adverse event was reported, and no deviation from normal values was observed in the lab exams. Only three subjects claimed of minor headache and epigastric pain that were considered possibly related to the drug administration.

**Table 1** Pharmacokinetic parameters of eperisone in human volunteers after single and multiple doses

Parameter (unit)	Day 1	Day 4/dose 1	Day 4/dose 3
<b><math>AUC_{0-t}</math> (ng/mL/h)</b>			
Mean	2.740		
SD	2.128		
CV%	77.654		
<b><math>AUC_{0-6}</math> (ng/mL/h)</b>			
Mean	2.414	2.674	
SD	1.825	2.074	
CV%	75.634	77.552	
<b><math>AUC_{0-\infty}</math> (ng/mL/h)</b>			
Mean	2.798		
SD	2.118		
CV%	75.709		
<b><math>C_{max}</math> (ng/mL)</b>			
Mean	1.611	1.636	1.715
SD	1.166	1.299	1.469
CV%	72.393	79.399	85.664
<b><math>T_{max}</math> (h)</b>			
Mean	1.667	1.750	1.667
SD	0.492	0.452	0.389
CV%	29.542	25.844	23.355
<b><math>t_{1/2}</math> (h)</b>			
Mean	1.873		
SD	0.725		
CV%	38.702		
<b><math>\lambda_z</math></b>			
Mean	0.422		
SD	0.161		
CV%	38.075		

## 4 Discussion

Eperisone hydrochloride, a central muscle relaxant, is widely used for the treatment of spasticity and muscle contracture and it is administered orally at a dose of 100 mg, usually at 300 mg/day (Beltrame et al. 2008; Cabitza and Randelli 2008; Sartini 2008; Viladot Pericé et al. 2008; Bresolin et al. 2009a, b). The aim of the study was to assess the pharmacokinetic profile of EPS at the dose of 100 mg tablet of eperisone hydrochloride administered in single and multiple doses.

A rapid and sensitive liquid chromatography–electrospray ionization–mass spectrometry method for the determination of EPS in human plasma was set up. The LLOQ was 0.01 ng/mL.

The results of the PK analysis in human volunteers confirm that EPS is rapidly absorbed after oral administration with meals; the  $T_{max}$  occurs at about 100 min, suggesting that at least part of the drug absorption could

have taken place in the stomach. A short  $T_{\max}$  after oral administration is an essential request by general physicians for all these compounds, especially in the treatment of LBP patients which ask for a fast-onset muscle relaxant and analgesic activity. For such a reason, parenteral formulations are usually preferred should the drug not guarantee a fast absorption from the GI tract after oral administration.

In our study, the  $T_{\max}$  value of EPS was comparable to those observed in other previous investigations (Li et al. 2004; Min Kyo et al. 2007; Takamatsu et al. 1992), and it was similar to the  $T_{\max}$  reported for other oral fast-acting muscle relaxants, such as tizanidine (1 h in fasting subjects and 2–3 h after a meal) (RxList, the Internet Drug Index 2010), baclofen (1.9 h) (Wuis et al. 1990) or thiocolchicoside (1 h) (Trellu et al. 2004). However, EPS seems to show some advantages over other muscle relaxant agents in terms of systemic tolerability. Since central muscle relaxants are used in repeated administration in LBP patients and chronically in the therapy of spastic palsy, the tolerability profile represents a central issue in the choice of the optimal treatment strategy.

EPS has been recently associated with a lower incidence of adverse events than thiocolchicoside, diazepam and baclofen (Cabitza and Randelli 2008; Viladot Pericé et al. 2008; Marchettini and Pecori 2009), confirming the good tolerability profile for eperisone, while over time many patients do not tolerate the side effects of other muscle relaxant agents (Tariq et al. 2005). Reasons for the better safety/risk ratio of EPS are probably related to its mechanism of action (inhibition of gamma-efferent firing on the spinal cord structure and local vasodilator activity with no CNS involvement) and, according to our observations, to its PK behavior as well. In fact, EPS is characterized by a biological half-life of 1.87 h in our study and similar values are reported in previous studies (Li et al. 2004; Min Kyo et al. 2007). Furthermore, it has been verified that by administration of EPS t.i.d. with meals no accumulation different from that expected for a drug with a half-life of less than 2 h was observed. All together, the PK characteristics of EPS can provide further justification, in addition to its mechanism of action, for its profile of tolerability in patients with LBP or spastic palsy, in which the drug is given for periods of time ranging from few days to several months, respectively.

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