Bioavailability of a controlled-release cyclobenzaprine tablet and influence of a high fat meal on bioavailability

M.N. Gai, E. Costa and A. Arancibia

Center for Development in Pharmaceutical Technology, Department of Science and Pharmaceutical Technology, Faculty of Chemical and Pharmaceutical Sciences, University of Chile, Santiago de Chile

Key words
cyclobenzaprine – controlled release – bioavailability – food

Abstract. Objective: To evaluate the systemic bioavailability of a new controlled release cyclobenzaprine tablet, and the influence of a high fat meal on its bioavailability. Subjects, materials and methods: 24 and 12 healthy male subjects were recruited for the bioavailability and influence of diet studies, respectively. Experimental design for both studies was an open randomized, 2-period, single dose, crossover study. In the bioavailability study, each subject received in different occasions, a single oral dose of cyclobenzaprine of immediate (10 mg) or controlled release (20 mg) tablet, followed by a 2-week washout period. In the influence of diet study, the volunteers received the controlled-release tablet concomitantly with a high fat meal or in a state of fasting. Results: In the bioavailability study, plasma cyclobenzaprine profiles were in agreement with a controlled release system. This formulation presented a 92.8% of relative bioavailability (IC 85.5 – 105%) and a significant reduction in C_{max} (IC 58 – 65.5%), when compared with equal dose of the immediate release tablet. The presence of food increased AUC (11.6%) and C_{max} (48%). For both parameters the calculated 90% confidence interval was not in the bioequivalence interval, 97.4 – 125.8% for AUC and 111.7 – 184.2% for C_{max}. Conclusions: The controlled release tablet showed a relative bioavailability comparable with equal dose of the immediate release product and produced a significantly lower C_{max}, as expected in a controlled release formulation. The concomitant administration of the tablet with a high fat meal produced an increase on its bioavailability, mainly in C_{max}, with no evidence of dose-dumping.

Correspondence to
M.N. Gai, PhD
Avda Vicuna Mackenna 20,
Providencia Santiago, Chile
mgai@uchile.cl

Introduction

Cyclobenzaprine hydrochloride is a centrally acting muscle relaxant that has been widely used over 25 years for relief of muscle spasm associated with acute, painful musculoskeletal conditions [Katz and Dube 1988].

Earlier information pointed out that cyclobenzaprine is well absorbed, is widely distributed among body tissues, is subject to enterohepatic circulation [Hucker et al. 1977, 1978]. The drug is extensively metabolized via oxidative and conjugative pathways [Wang at al. 1996]. A more recent investigation informed a bioavailability of 55%, compared with an intravenous solution, a linear pharmacokinetics, and the need of dose reduction in elderly people and patients with liver disease [Winchell et al. 2002].

Cyclobenzaprine is generally prescribed at a regimen of 10 mg 3 times daily, in immediate release dosage forms. However, patients under this dosing schedule inform excessive drowsiness. For this reason, it is a common medical practice among Chilean physicians to prescribe the medicine twice a day. In order to reduce cyclobenzaprine plasma fluctuations in the steady state and to allow a once a day administration, a controlled release tablet, 20 mg dose, using a pH independent hydrophilic matrix as release mechanism, was developed, regarding that no controlled release dosage form was locally available. Two extended-released dosage amounts of AMRIX (15 and 30 mg) were approved in February 2007 by the U.S. Food and Drug Administration for the US market.

The aims of this work were to evaluate the relative bioavailability of this new formulation compared with the immediate release product and to assess the influence of a high fat diet over the bioavailability of the controlled release formulation.

Subjects, materials and methods

Subjects

24 healthy, male, nonsmoking volunteers were recruited for the bioavailability study. Subjects data were mean age 25.9 years ± 4.7, a mean weight of 72,7 kg ± 10.7 and a mean height of 175 cm ± 6. Twelve healthy, male, nonsmoking volunteers were recruited for the influence of the diet study. Subjects data were mean age 26.9 years ± 3.6, a mean weight of 73.2 kg ± 12.6 and a mean height of 176 cm ± 5.

All subjects were informed about course, risks, and aims of both studies. They gave their written informed consent after comprehensing the full nature and purpose of the experiences. Clinical laboratory tests and physical examination were made to all the subjects in order to check their health state. The volunteers were free from any significant cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal and hematological disease, as assessed by general physical examination. The following laboratory tests were performed: hematological analysis, urine analysis, blood glucose, urea, uric acid, creatinine, total and direct bilirubin, albumin and total proteins, GOT, GPT, total alkaline phosphatase. All the subjects were negative for HIV.

Studies protocols were approved by the Ethics Committee of the Clinical Hospital of the University of Chile, where the clinical stages were performed.

Study design

Both studies were an open randomized, 2-period single dose crossover study.

Subjects fasted overnight and were asked not to take drugs, alcohol and methylxanthines beverages at least 10 days prior to the study. The first 24 h of the study the volunteers were submitted into the hospital and were under medical surveillance. The rest of the time they were ambulatory. The wash-out period between doses was 2 weeks.

On each period of the bioavailability study, the volunteers received one 10 mg tablet of the reference product or one 20 mg controlled release tablet, according to the experimental design. The tablet was swallowed with 250 ml of tap water. All volunteers were required to remain fasting until 4 h after dose when a standard breakfast was served. A standard meal was provided at 6, 9, 12 and 24 h after dosing. Liquid consumption was permitted ad libitum 2 h after dose, but methylxantines containing drinks were prohibited.

To evaluate the influence of diet on bioavailability, a high lipid meal consisting of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk (900 kcal, 50% fat) [FDA Guidance 2002] was administered early in the morning to the subjects who were fasting. The subjects received one cyclobenzaprine controlled release tablet (20 mg) with 250 ml of tap water 10 minutes after consuming the breakfast. The other meals of the day (at 6, 9, 12 and 24 h) were the same administered in the bioavailability study. Control situation was administration during fasting.

Formulations

Test formulation was Cyclobenzaprine 20 mg controlled release tablet, developed by Laboratorio Saval, Chile. It is a pH-independent hydrophilic matrix formulation.

Reference product was a cyclobenzaprine 10 mg immediate release tablet from the Chilean market, batch number 1201603.

At the time of the experiments, both formulations were at least 18 months far from their expiration dates.

Collection of blood samples and drug analysis: blood samples from a suitable antecubital vein were collected into heparinized tubes before administration and at 0,5 – 1 – 2 – 3 – 4 – 6 – 9 – 12 – 24 – 48 – 72 – 92 and 120 h for the reference product and at 0,5 – 1 – 2 – 4 – 6 – 9 – 12 – 14 – 24 – 48 – 72 – 92 and 120 h for the controlled release tablet.

The samples were centrifuged (10 min at 3,000 rpm) and the plasma was harvested and stored at –20 °C until assayed for cyclobenzaprine content.

Cyclobenzaprine plasma concentrations were determined by a validated high performance liquid chromatographic method with tandem mass spectrometric detection (LC-MS-MS). Methodology was developed and validated by Cartesius Analytical Unit (Sao

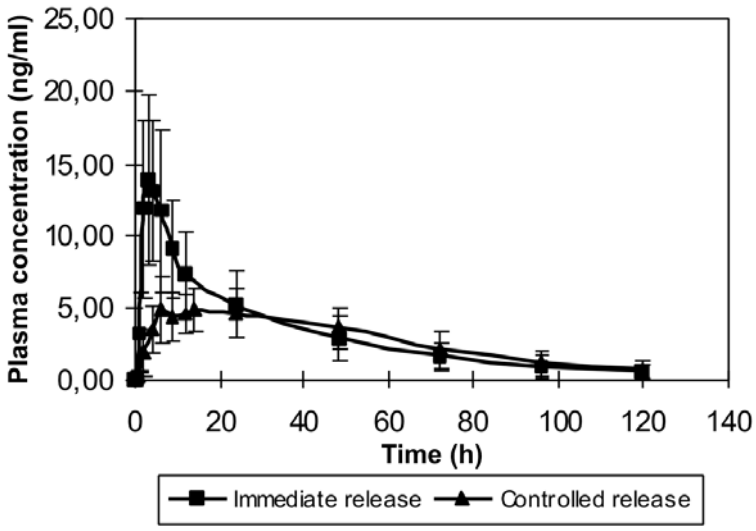

Figure 1. Means ± SD of plasma cyclobenzaprine concentration-time curves obtained after the administration of immediate and controlled release tablets.

Paulo, Brazil). Validation parameters were: selectivity, detection limit, quantitation limit, linearity, precision, accuracy, recovery, stability (standard and working solutions, frozen samples, freeze thaw cycles, and samples in autosampler).

Calibration curves were prepared in the range 1 – 20 ng/ml. Quantitation limit was 1 ng/ml.

Pharmacokinetics and statistical analysis

The area under the curve (AUC) until the last sampling time was obtained from trapezoidal rule. AUC from last sampling time to infinity was obtained through the relationship (C_{last} sampling time/λ_z) where λ_z is the rate constant of the terminal phase. Maximum concentration (C_{max}), the time to obtain C_{max} (t_{max}) and lag time were obtained directly from the curves. Mean residence time (MRT) and half life were also calculated. In the bioavailability study AUC and C_{max} of the reference product were normalized to a dose of 20 mg.

A Student t-test for paired data was used to compare half lives, MRT and lag times. Statistical analysis used in bioequivalence studies was used to compare AUC and C_{max}. The 90% CI of the geometric mean for the individual test/reference ratios for AUC and C_{max} were obtained, with bioequivalence acceptable boundaries of 80 – 125%. Wilcoxon test was applied to nonparametric t_{max}.

Results and discussion

All enrolled subjects completed the two studies. The compound was well tolerated under all the experimental situations. Volunteers reported minor drowsiness as the main side effect. All volunteers were discharged in good health.

Bioavailability study

The mean ± SD plasma cyclobenzaprine concentration-time curves for the test and reference preparations are illustrated in Figure 1. High relative standard deviations were obtained at the first sampling times, over 80% during the first hour and close to 40% for the other sampling times. High intersubject variation has also been reported in previous pharmacokinetic studies [Hucker et al. 1977, Winchell et al. 2002].

The mean plasma concentrations profiles are in accordance with the release mechanism of both formulations. Higher C_{max} at earliest times were obtained for the immediate release tablet. As expected, substantially lower C_{max} were obtained for the controlled release tablet with an important delay in t_{max} (Figure 1).

Table 1 summarizes pharmacokinetic parameters obtained in the bioavailability study. As observed with the plasma profiles, pharmacokinetic parameters also showed a high intersubject variability, especially those related to the absorption process. Disposition parameters exhibited the lowest variability. No particular variability could be attributable to any of the products under study.

Rate constants of the terminal phase (λ_z) and half-lives did not show any statistical difference (Table 1) indicating no changes in disposition process. Under these conditions, AUC can be used as a direct measure of the amount of drug effectively absorbed. Over 85% of AUC was determined by experimental sampling times for all the subjects, with an average higher than 92%.

Table 1. Pharmacokinetic parameters (mean ± SD) of 24 healthy subjects after single dose administration of immediate and controlled release cyclobenzaprine tablets.

Parameter	Immediate release tablet		Controlled release tablet		Statistical analysis
$AUC_{(0-\infty)}$ (ng h/ml)	420 ± 202.7		390 ± 188.5		85.5 – 105.0 %
C_{max} (ng/ml)	15.9 ± 6.3		5.5 ± 1.7		58 – 65.5%
λz (h^{-1})	0.025 ± 0.0007		0.027 ± 0.0077		p = 0.4257
$t_{1/2}$ (h)	30.1 ± 8.6		28.2 ± 8.0		p = 0.4395
MRT (h)	39.5 ± 11.1		51.6 ± 11.6		p = 0.0006
lag time (h)	0.33 ± 0.28		0.58 ± 0.19		p = 0.0004
	Median	Range	Median	Range	
t_{max} (h)	3.0	2 – 6	13	6 – 48	p <0.0001

Table 2. Pharmacokinetic parameters (mean ± SD) of 12 healthy subjects after single dose administration of the controlled release cyclobenzaprine tablet under fasted and fed conditions.

Parameter	Fast		Fed		Statistical analysis
$AUC_{(0-\infty)}$ (ng h/ml)	306.2 ± 123.8		341.6 ± 167.0		97.4 – 125.8 %
C_{max} (ng/ml)	4.9 ± 1.0		7.2 ± 4.3		111.7 – 184.2 %
λz (h^{-1})	0.028 ± 0.009		0.025 ± 0.004		p = 0.1625
$t_{1/2}$ (h)	27.2± 8.7		28.0 ± 4.1		p = 0.1897
MRT (h)	49.4 ± 12.8		46.6 ± 7.0		p = 0.3249
lag time (h)	0.5 ± 0.2		0.5 ± 0.37		p = 0.5558
	Median	Range	Median	Range	
t_{max} (h)	14	6 – 24	9	4 - 24	p = 0.042

As cyclobenzaprine follows a linear pharmacokinetics [Winchell et al. 2002], AUC and C_{max} obtained with the administration of 10 mg immediate release tablet were normalized to a dose of 20 mg. Relative bioavailability of the controlled release tablet was 92.8%. The analysis of AUC for test and reference product, using the parametric 90% confidence intervals of the mean geometric values for the test/reference ratio were within the bioequivalence acceptable boundaries (Table 1). Conversely, the same comparison made for C_{max} was completely out of the 80 – 125% interval, due to the lower rate of absorption produced by the controlled release formulation.

According to a controlled release system, t_{max} and MRT were significantly higher for the new product under study, due to a lower rate of absorption. A statistical difference was obtained in lag times (Table 1). In a hydrophilic matrix, the mechanism and kinetics of drug release are dependent on the solubility of the active moiety and the swelling and erosion properties of the polymer, with water soluble compounds released predominantly by diffusion [Colombo et al. 2000, Hardy el al. 2007, Li et al. 2005]. As cyclobenzaprine hydrochloride is a high soluble water drug [The Unites States Pharmacopeia 30 National Formulary 25. 2007], the delay in the beginning of the absorption could be explained by the time needed to form the gelified layer, through which the drug diffuses from the system to the gastrointestinal fluids.

Influence of diet on bioavailability

Figure 2a shows the mean cyclobenzaprine plasma profiles, after the administration

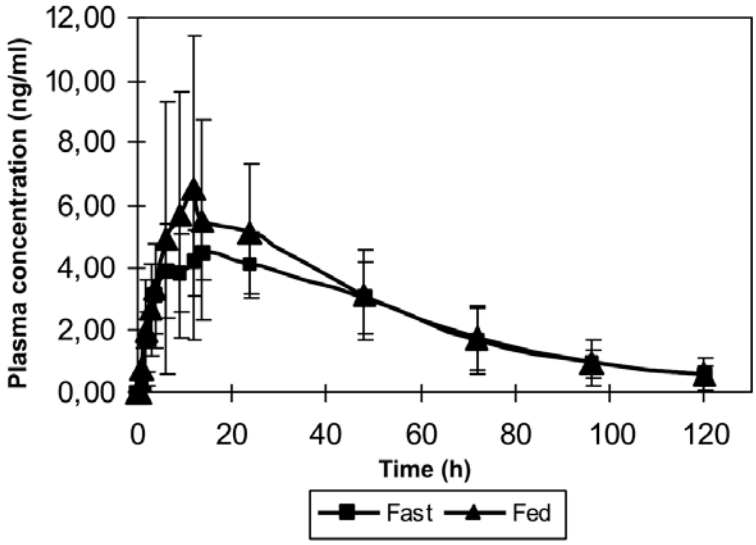

Figure 2a. Means ± SD of plasma cyclobenzaprine concentration-time curves obtained after the administration of the controlled release tablet under fasting and feeding conditions.

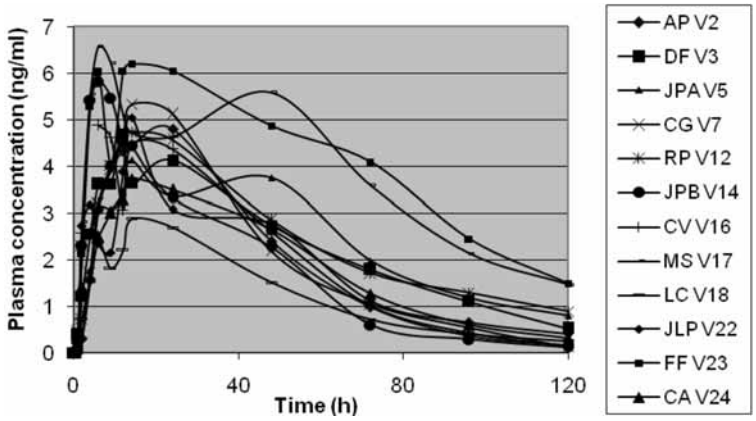

Figure 2b. Individual plasma cyclobenzaprine concentration-time curves obtained in the fasting condition.

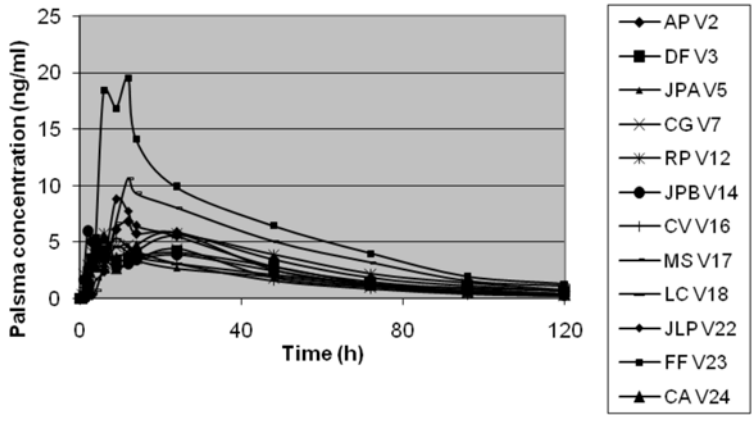

Figure 2c. Individual plasma cyclobenzaprine concentration-time curves obtained in the feeding condition.

of the controlled release tablet under fasting and feeding conditions. As in the bioavailability study, pharmacokinetic parameters related with the absorption process presented higher variation than those related with disposition, but in this study intersubject variability was enhanced by food (Table 2) (Figures 2b,c). No statistical differences were found in disposition parameters λ_z and half-life.

Physiological changes induced by food produced an increase on the bioavailability of the tablet. The values of AUC and C_{max} were significantly greater than those in the fasted condition. Higher variability in C_{max} was found in the feeding condition than in the fasting state (59.4% versus 20.8% RSD). Three volunteers had practically the same C_{max} under fasting and feeding conditions; 2 subjects were in the range 10 – 20% higher under fed administration; 4 volunteers were between 40 and 70% higher and 1 volunteer had a 300% increase in C_{max} under feeding conditions.

The increase of 11% in AUC and 47% in C_{max}, produced 90% CI of 97.4 – 125.8% and 111.7 – 184.2%, respectively, both not in the bioequivalence interval. Wilcoxon test revealed that t_{max} was significantly shorter in the fed state (Table 2).

Solid food in general and products of lipid digestion produce a delay in gastric emptying and among others an increase in the secretion of biliar salts. The first mechanism could explain the high variability in absorption parameters, since this delay is very variable among subjects who had eaten. For many drugs this delay would also be reflected in a delay of the absorption process considering that the stomach is not a good site for absorption [Charman et al.1997, Fleisher et al. 1999, Singh 1999, Toothaker and Welling 1980].

The stimulation of bile flow induced by fat ingestion could explain a higher erosion of the gelified layer of the controlled release matrix, producing an increase in AUC and C_{max}. Undoubtely, C_{max} is the most important change, almost 50% compared with the fasting state. Associated with the significant change in t_{max}, a higher absorption rate produced by the physiological changes induced by meal ingestion could be assumed. Controlled release products can be affected by food ingestion producing a dose-dumping phenomenon,

consisting in a rapid release of the dose contained in the system, which could produce plasma concentrations over the therapeutic window [Hendeles et al. 1985]. The magnitude of the change in C_{max} observed in this study did not apparently classify as dose-dumping, since a 20 mg dose of the immediate release tablet would produce a C_{max} of 15.9 ng/ml (Table 1), much higher than the mean C_{max} obtained in the feeding state, 7.2 ng/ml (Table 2).

Conclusions

The controlled release tablet showed a relative bioavailability of 92.4% and a significantly lower C_{max}, compared with a immediate release tablet. This behavior is consistent with a controlled release pattern. The concomitant administration of the tablet under study with a high fat meal produced an increase on its bioavailability, mainly in C_{max}, but with no evidence of dose-dumping.

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