

Bioequivalence Study of 2 Orodispersible Formulations of Ondansetron 8 mg in Healthy Volunteers

Authors

M. Cánovas¹, J. Ríos², G. Domenech², J. Cebrecos³, P. Pelagio³, M. Canals^{1*}, F. Polonio¹, F. Cabré¹

Affiliations

¹Laboratorios Lesvi, S. L.- Invent Farma Group, Sant Joan Despí, Barcelona, Spain

²Laboratory of Biostatistics and Epidemiology (Universitat Autònoma de Barcelona), Bellaterra, Barcelona, Spain

³Laboratorio de análisis Dr. Echevarne, Barcelona, Spain

Key words

- antiemetic
- bioequivalence
- CAS 99614-02-5
- ondansetron
- pharmacokinetics

Abstract

This study was designed to compare the rate and extent of absorption of 2 oral formulations of ondansetron (CAS 99614-02-5) 8 mg orodispersible tablets in healthy volunteers. 22 subjects were administered ondansetron orodispersible tablets of test and reference formulation in a single-dose, 2-period, 2-sequence, fasting, open-label, crossover and randomised study. Plasma concentrations were determined by LC/MS/MS.

Log-transformed AUCs and C_{\max} values were tested for bioequivalence based on the ratios of the geometric means (test/reference). T_{\max} was analysed nonparametrically. The 90% confidence intervals of the geometric mean values for the test/reference ratios for AUC_{0-t} and C_{\max} were within the bioequivalence acceptance range of 80–125%. According to the European Guideline [1] it may be therefore concluded that test formulation of ondansetron 8mg orodispersible tablet is bioequivalent to the reference formulation.

Introduction

Ondansetron (CAS 99614-02-5) is an effective and well-tolerated antiemetic that has been used extensively for the prevention of emesis and nausea associated with a wide variety of chemotherapy and radiotherapy regimens [2].

Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT₃ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5-HT₃ receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting [3].

In normal volunteers, single intravenous doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations [4].

Ondansetron is completely and rapidly absorbed from the gastrointestinal tract after oral administration, and does not accumulate with repeated oral administration. Owing to hepatic first-pass metabolism, its bioavailability is only about 60% compared with ondansetron administered by infusion over 15 min. Bioavailability is slightly increased when administered after a standard meal, and is not influenced by coadministration of antacids; a slightly enhanced bioavailability has been observed in patients with cancer. Since the time to reach peak concentration is 0.5–2 h after oral ingestion, the drug should be administered at least 30 min before chemotherapy. Ondansetron is widely distributed (volume of distribution approximately 160 L) and binds moderately (70–76%) to plasma proteins; the elimination half-life averages approximately 3.8 ± 1 h. Clearance occurs by hepatic metabolism (95%) rather than renal excretion. Metabolites do

received 19.09.2011

accepted 28.10.2011

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DOI <http://dx.doi.org/10.1055/s-0031-1295488>
 Arzneimittelforschung 2012; 62: 59–62
 © Georg Thieme Verlag KG
 Stuttgart · New York
 ISSN 0004-4172

Correspondence

M. Cánovas

Academic degree: Degree in Pharmacy, Doctor of Pharmacy
 Laboratorios Lesvi
 S.L.
 Avenida Barcelona 69
 08970 Sant Joan Despí
 Barcelona
 Spain
 Tel.: +34/93/602 2417
 Fax: +34/93/373 8751
 mcanovas@lesvi.com

* working at the institution at the time of the trial

not play a role in the activity of the drug, and there is no evidence of genetic polymorphic metabolism [5].

According to the European Guideline [1] 2 products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. The aim of the study here reported was to compare the rate and extent of absorption of 2 oral formulations of ondansetron orodispersible tablets 8 mg (test and reference) in a single-dose, 2 period, 2-sequence, crossover randomised study in healthy volunteers. As secondary objective the safety of both formulations was assessed.

Subjects and Methods

The study was carried out in Laboratorio de análisis Dr. F. Echevarne Phase I Unit, Hospital Dos de Maig, Barcelona, Spain. The study was registered in the EudraCT database (EudraCT number: 2008-000734-51). Prior to the study, the volunteers were informed about the nature, purpose, risks and discomforts that could arise from their participation; and about their right to withdraw at any time. Subjects documented their willingness to participate by signing the informed consent form. Study protocol and information given to study subjects were approved by the AEMPS and by an independent ethics committee; the "Hospital de L'Hospitalet – Consorci Sanitari Integral" (Barcelona, Spain). The study was performed in accordance to the Helsinki Declaration (revised version of Edinburgh 2000) and the provisions of Good Clinical Practice [6].

Study subjects

Subjects included in the study were healthy female and male volunteers ranged from 18 to 41 years (mean \pm SD; 30.32 ± 6.67), weighed 49–94 kg (67.59 ± 10.49), with a height between 155–189 cm (169.8 ± 10.28) and a Body Mass Index (BMI) between 19–26.88 kg/m² (23.43 ± 2.61).

All subjects were in good health conditions confirmed by a normal medical history, physical and clinical laboratory examinations, vital signs measurement, a 12-lead electrocardiogram assessment and serology and drug of abuse tests. Subjects were excluded if they took an investigational product in another clinical trial or donated blood in the previous 3 months, those with intake of excessive alcohol (greater than 30 g/day), with intake of foods or beverages containing xanthines (more than 5 units of coffee, tea or cola drinks per day), smokers (5 or more than 5 cigarettes/day), with regular intake of any medication in the previous 30 days before starting the study, were pregnant, breastfeeding or taking oral contraceptives.

Drug products

The following formulations were used: Ondansetron 8 mg orodispersible tablets manufactured by Laboratorios Lesvi, S.L., Sant Joan Despí, Spain (batch number GAL08048C, expiry date 11/2008) as the test product and Ondansetron 8 mg orodispersible tablets manufactured by Glaxo Wellcome GmbH & Co., Bad Oldesloe, Germany (batch number 7E001, expiry date 05/2010) as the reference product.

Study design

The study was conducted in a single-dose, 2-period, 2-sequence, fasting, open-label, crossover randomised design, comparing the bioavailability of a new generic formulation (test) and a trade name formulation (reference) of ondansetron 8 mg orodispersible tablets.

During each period, the volunteers were admitted to Phase I Unit and after an overnight fasting period of at least 10h, they received one 8 mg ondansetron orodispersible tablet test or reference formulation according to the randomisation scheme. Due to the summary of products characteristics [7] recommended to take the medication without liquids, each tablet was placed on the top of each volunteer's tongue without any liquid and was dispersed within seconds, and then swallowed with the saliva. During the hospitalization (until +24h post-dose) caloric and liquid intake were controlled by the investigator's team. Following drug administration, study subjects continued in fasting conditions for a minimum of 4 h and standard meals were served at scheduled times (+4h, +6h, +10h, and +12h after drug administration). Volunteers were free to drink additional beverages provided free of alcohol, CO₂, caffeine and grapefruit from 4 h after drug administration.

In the second period, the volunteers received the alternate product (test or reference) after a wash-out period of 1 week.

Serial blood samples (8 mL) were collected in glass tubes containing lithium heparin at pre-dose and at 0.33, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.50, 3, 3.50, 4, 5, 6, 8, 10, 12, 18 and 24 h post-dosing in each period. Following centrifugation (3000 r.p.m, 4 °C, 10 min), the plasma supernatant was aliquoted into 2 polypropylene tubes (approximately 2 mL) and stored frozen at -20 ± 5 °C until assayed.

Analysis of plasma samples

Concentrations of ondansetron in plasma samples were analysed using a validated method involving HPLC with MS/MS detection (LC/MS/MS) in Laboratorio de análisis Dr. Echevarne, Barcelona, Spain. Calibration curves were linear in the range of 2–50 ng/mL with coefficients of correlations ≥ 0.9921 . The validated stability period of the samples covered extensively the period between the blood draws and completion of the analytical determination. The study was conducted in compliance with the Principles of Good Laboratory Practice.

Pharmacokinetic analysis

The pharmacokinetic parameters were estimated according to a non-compartmental method and were calculated individually for each subject from ondansetron levels in plasma using WinNonlin Professional software [8]. The actual times of blood sampling were taken for these calculations and concentrations values below the limit of quantification were set to zero for the analysis.

For the purpose of bioequivalence analysis, the primary pharmacokinetic parameters were AUC_{0-t} (area under the plasma concentration-time curve from zero to the last measurable concentration) calculated by means of the mixed linear log-trapezoidal method and C_{max} (maximum plasma concentration) observed directly from the plasma concentration-time curve. Other evaluated pharmacokinetic parameters were AUC_{0-∞} (area under the plasma concentration-time curve from zero to infinity) estimated by extrapolating to infinity AUC_{0-t}, C_{max}/AUC_{0-∞}, t_{max} (time of the peak concentration), extrapolated area (%), t_{1/2} (terminal half life time), λ_z (terminal rate constant of

elimination), F (relative bioavailability between test and reference), Cl/F (apparent total plasma clearance), V_z/F (apparent volume of distribution) and MRT (mean residence time).

Statistical analysis

The sample size was determined by taking into account data from previous studies that showed a coefficient of variation of a maximum of 18% approximately, derived from the residual variability obtained in the analysis of variance (ANOVA) after log-transformation. According to Zhang's approach [9] a total of 22 volunteers was considered sufficient to achieve a power of 90% with an alpha level protection of 0.05, assuming the *a priori* maximum difference of 5% between formulations.

The bioequivalence assessment was done using a parametric approximation for AUC_{0-t} , $AUC_{0-\infty}$, C_{max} and $C_{max}/AUC_{0-\infty}$ after logarithmic transformation. For each parameter, a 90% parametric confidence interval was defined for the ratio test/reference using the residual variability obtained from the ANOVA. Additionally, the parametric Schuirmann's approach [10] by means of a 2 one-sided *t*-test was also calculated. t_{max} was analysed nonparametrically by means of Hauschke method [11] using BIOEQV 6.2 [12]. The statistical significance was established at $p \leq 0.05$ for all statistical tests.

Bioequivalence assessment was based on a predefined acceptance criterion of 80–125% for the ratio test/reference and its 90% confidence interval for the log-transformed data of AUC_{0-t} , $AUC_{0-\infty}$, C_{max} and $C_{max}/AUC_{0-\infty}$. Acceptance range for un-transformed t_{max} was 70–130%.

An analysis of variance (ANOVA) was performed for the parameters AUC_{0-t} , C_{max} , $AUC_{0-\infty}$, $C_{max}/AUC_{0-\infty}$ and t_{max} in order to evaluate formulation, sequence, sex, sex*formulation, subject within sequence and period effects.

Results

Study population

42 subjects were screened and 23 (11 males and 12 females) subjects were randomized into this clinical trial. One subject dropped out before taking period 1 study medication, hence 22 subjects (11 males and 11 females) completed the study as scheduled and were included in the safety and pharmacokinetic analysis.

Safety

There were no unusual changes from baseline in vital signs, electrocardiogram parameters or physical examination changes. A total of 10 adverse events (AEs), 8 treatment emergent and 2 no-treatment emergent, occurred during the study. 2 AEs occurred in 2 subjects after one single dose of reference formulation and 6 AEs in 6 subjects after 1 single dose of test formulation.

The most frequently reported AE was headache (4 cases), followed by constipation (2 cases). Most of the AEs (9/10) were of mild intensity and no withdrawal occurred due to AEs. 6 of 8 treatment emergent AEs were assessed as being related to the study drug and were mild (5) and moderate (1) intensity.

No serious AEs occurred during the study. The safety profile of both formulations was consistent with the summary of products characteristics [7].

Table 1 Un-transformed descriptive data of pharmacokinetic parameters of test and reference formulations of ondansetron 8 mg orodispersible tablets.

Parameter*	Ondansetron orodispersible tablets	
	Test N=22	Reference N=22
AUC_{0-t} (h*ng/ml)	210.941 (105.491)	219.102 (106.580)
C_{max} (ng/ml)	34.723 (12.304)	36.113 (14.730)
$AUC_{0-\infty}$ (h*ng/ml)	233.212 (114.684)	244.496 (113.481)
$C_{max}/AUC_{0-\infty}$ (h ⁻¹)	0.166 (0.051)	0.159 (0.043)
t_{max} (h)	1.75 (0.75–3.50)	1.75 (1.00–3.00)

*Pharmacokinetic parameters are given as mean (SD). Median and range for t_{max}

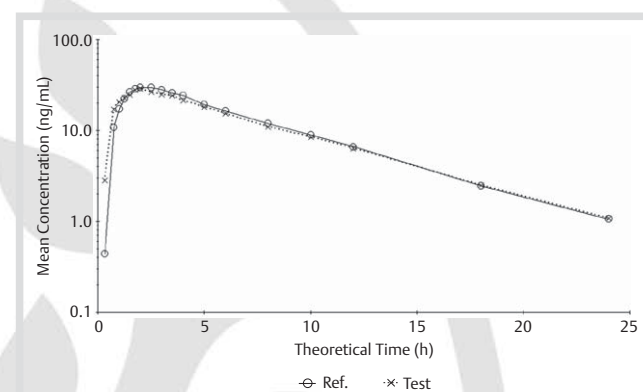


Fig. 1 Semi-log profile of the mean concentration vs. time curve of ondansetron 8 mg orodispersible tablets after oral administration of single dose of test and reference formulation to 22 healthy volunteers.

Drug concentrations

Table 1 presents the mean values and standard deviations for AUC_{0-t} , $AUC_{0-\infty}$, C_{max} and $C_{max}/AUC_{0-\infty}$; t_{max} is presented with the median and the range. The parameters AUC_{0-t} and $AUC_{0-\infty}$ indicate the extent of absorption of the drug, while t_{max} , C_{max} and $C_{max}/AUC_{0-\infty}$ are influenced by the rate of absorption. The mean AUC_{0-t} value of test formulation was 210.941 h*ng/mL (SD 105.491 h*ng/mL), mean AUC_{0-t} of the reference formulation was 219.102 h*ng/mL (SD 106.580 h*ng/mL). C_{max} was 34.723 ± 12.304 ng/mL (mean \pm SD) for test formulation and 36.113 ± 14.730 ng/mL for the reference one.

Mean plasma concentrations of ondansetron (test and reference formulations) over the 24-h sampling period after administration are shown in Fig. 1 (semi-log scale). Plasma profiles were very similar for test and reference formulations.

The percentage AUC extrapolated was less than 20% except for 2 volunteers (20.66% and 23.52% in both cases only for reference formulation). However, plasma concentration levels for both subjects at the last sampling time (24 h after dosing) were under the quantification limit, therefore the sampling schedule covered all the elimination phase and these extrapolations upper than 20% can be explained due to a lack of precision in the estimation of the elimination rate constant.

Bioequivalence evaluation

The 90% confidence interval for the ratio of the logarithmically transformed values of primary variables (AUC_{0-t} and C_{max}) laid between the predefined range of 80–125%. $AUC_{0-\infty}$, $C_{max}/AUC_{0-\infty}$ and t_{max} were also within the acceptance bioequivalence limits (80–125% for $AUC_{0-\infty}$ and $C_{max}/AUC_{0-\infty}$, and 70–130% for t_{max}). Results are presented in Table 2.

Table 2 Bioequivalence assessment summary.

Parameter	Ondansetron orodispersible tablets	
	T/R Ratio (%)	90% CI (%)
AUC _{0-t} (h*ng/ml)*	96.51	90.25–103.21
C _{max} (ng/ml)*	97.37	90.48–104.78
AUC _{0-∞} (h*ng/ml)*	95.13	88.96–101.72
C _{max} /AUC _{0-∞} (h ⁻¹)*	102.35	94.86–110.44
t _{max} (h) [§]	91.3	80.0–109.5

*Log-transformed data

§Hauschke's non-parametric ratio and 90% confidence interval

No period, sex, formulation or sequence effects were found in the ANOVA for the main and secondary pharmacokinetic parameters. The formulation by sex interaction term was statistically significant for AUC_{0-t} and C_{max}, however considering that neither the formulation nor the sex effect were significant and that both formulations were perfectly bioequivalent, this difference had no impact on the assessment of the bioequivalence and must be considered as a random finding.

Discussion

Based upon 90% confidence interval for the ratio of geometric means (test/reference) of logarithmically transformed AUC_{0-t} and C_{max}, the conclusion of bioequivalence can be arisen for the 2 ondansetron 8 mg orodispersible tablet formulations (test and reference). The 90% confidence intervals for the ratio of AUC_{0-∞}, C_{max}/AUC_{0-∞} and t_{max} were also within the bioequivalence limits. Based on the study data, it can be confirmed that drug exposure between reference and test formulation is comparable. Both formulations were well tolerated and no relevant differences in safety profiles between them were found. Considering that the observed plasma concentration of test and reference formulations are essentially similar and the safety data observed in this study, the generic formulation developed by Laboratorios Lesvi, S.L. is considered bioequivalent to the reference formulation and is expected to produce the same therapeutic response.

Conflict of Interest

All authors of the article declare no conflict of interests in relation to this study.

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