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SHORT COMMUNICATION

Evaluation of Gender in the Oral Pharmacokinetics of Clindamycin in Humans

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ABSTRACT: Clindamycin is an antimicrobial agent metabolized by CYP3A4. Gender may influence the pharmacokinetics of drugs metabolized by this pathway, however, no information about differences in the pharmacokinetics of clindamycin in men and women is available. The purpose of this study was to evaluate gender differences in clindamycin oral pharmacokinetics. Twenty-four subjects (11 men and 13 women) received an oral 600 mg dose of clindamycin under fasting conditions and plasma concentrations were obtained at selected times during 12 h. Increased plasma levels were observed in women, but when the dose was normalized by the body weight of individuals, these differences disappeared, indicating that gender does not play an important role in the pharmacokinetics of this drug. Copyright © 2008 John Wiley & Sons, Ltd.

Key words: clindamycin pharmacokinetics; gender differences; CYP3A4

Introduction

Clindamycin is an antibiotic that is employed in the treatment of several infectious diseases produced by anaerobic and gram(+) cocci [1,2]. This drug is metabolized through CYP3A4 and CYP3A5 forming two metabolites, clindamycin sulfoxide and *N*-desmethyl clindamycin [3]. So far, limited information about its pharmacokinetics is available [4,5] and possible gender differences have not been evaluated. Gender variability in the pharmacokinetics of drugs metabolized by different enzymatic pathways has been described [6,7]. Although differences in the activity of CYP3A4 between genders have been reported [8–10], pharmacokinetic differences in drugs metabolized by this enzymatic pathway are not always observed [11–14]. Due to this controversy, it is difficult to establish *a priori* if gender differences in the pharmacokinetics of drugs metabolized by CYP3A4 will be present. Since clindamycin is metabolized by this enzymatic pathway, it is important to establish if there are gender differences in its oral pharmacokinetics.

Subjects, Material and Methods

Subjects

Twenty-four healthy volunteers (13 women and 11 men) were enrolled in this study. Demographic data of the subjects are shown in Table 1.

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Table 1. Demographic data and pharmacokinetic parameters obtained in women and men after administration of a single 600 mg oral dose. Data are expressed as mean ± SEM

Parameter	Women	Men
Age (y)	21.46 ± 0.70	25.45 ± 1.66[a]
Height (cm)	158.85 ± 1.59	170.45 ± 2.36[a]
Weight (kg)	59.31 ± 1.88	68.77 ± 3.41[a]
C_{max} (μg/ml)	5.94 ± 0.42	5.15 ± 0.44[a]
NC_{max} (μg kg/ml mg)	0.59 ± 0.05	0.61 ± 0.05
t_{max} (h)	1.08 ± 0.09	0.93 ± 0.10
$AUC_{12\,h}$ (μg h/ml)	25.04 ± 1.71	21.24 ± 2.13[a]
$NAUC_{12\,h}$ (μg h kg/ml mg)	2.48 ± 0.20	2.56 ± 0.38
AUC_{∞} (μg h/ml)	26.87 ± 1.71	24.63 ± 2.51
$NAUC_{\infty}$ (μg h kg/ml mg)	2.66 ± 0.20	2.88 ± 0.44
$t_{1/2}$ (h)	3.34 ± 0.41	3.57 ± 0.37
Vd/F (l)	120.16 ± 22.70	132.55 ± 15.88
NVd/F (l/kg)	2.04 ± 0.36	2.00 ± 0.24
CL (l/h)	23.48 ± 1.53	26.52 ± 2.48
NCL (l/h kg)	0.40 ± 0.03	0.40 ± 0.04

[a] $p < 0.05$.

All subjects were fit according to medical history, clinical examination and suitable laboratory tests and read the protocol approved by the Institutional Research and Ethics Committees and gave written informed consent for participation.

Experimental design

Clindamycin (Dalacin®) was manufactured by Pharmacia & Upjohn (Mexico City). After an overnight fast, a control blood sample was obtained and subjects received an oral dose of 600 mg of clindamycin. Blood samples were obtained at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h after drug administration. Plasma was obtained by centrifugation of blood and stored frozen at −80°C until analysed by a high-performance liquid chromatographic (HPLC) method.

Determination of clindamycin in plasma

Clindamycin plasma levels were determined by HPLC according to the method described by Liu *et al*. [15] with some modifications. Briefly, plasma samples (0.5 ml) were extracted by protein precipitation with 0.6 ml of a mixture of methanol and 0.1 M sodium acetate pH 5.2 (70:30, v/v) and 40 μl of 70% perchloric acid. Separation of the compound was carried out in a Symmetry C8 of 150 × 3.9 mm of 5 μm particle size column at room temperature eluted with a mixture of 0.05 M sodium dihydrogen phosphate, methanol and acetonitrile (745:70:190, v/v/v) at a flow rate of 1.5 ml/min and detection was performed by absorbance at 204 nm. Under these conditions the retention time for clindamycin was 8 min and the method was linear in the range 0.3–10 μg/ml. Intra- and inter-day accuracy was in the range 97.47%–102.5% and the coefficient of variation was always lower than 6.5%, indicating that this method is suitable for pharmacokinetic studies of clindamycin.

Pharmacokinetic and statistical analysis

Pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{12\,h}$, AUC_{∞}, $t_{1/2}$, *CL/F* and *Vd/F*) were obtained by non-compartmental techniques [16]. Normalized C_{max} and *AUC* (NC_{max} and *NAUC*) were obtained by dividing the parameter by the dose normalized by the subject weight. Normalized clearance (*NCL/F*) and volume of distribution (*NVd/F*) were obtained by dividing the parameter over the subject weight. Pharmacokinetic analysis was carried out using the WinNonlin Professional software Ver. 2.1 (Pharsight, Palo Alto, CA, USA). Pharmacokinetic parameters obtained in the two genders were compared by unpaired Student's t-tests. A value of $p < 0.05$ was considered as significantly different.

Results

Figure 1a depicts the mean ± SEM plasma level-time course of clindamycin obtained after administration of an oral dose of 600 mg to women and men. It can be observed that higher levels were reached in women than in men that disappeared when the data were normalized by the administered dose per kg of weight (Figure 1b). The pharmacokinetic parameters obtained are shown in Table 1. Differences in C_{max} and $AUC_{12\,h}$ were observed. The values obtained for AUC_{∞}, *Vd/F* and *CL/F* were slightly higher in men than in women, however, they did not reach statistical significant difference. This tendency may be due

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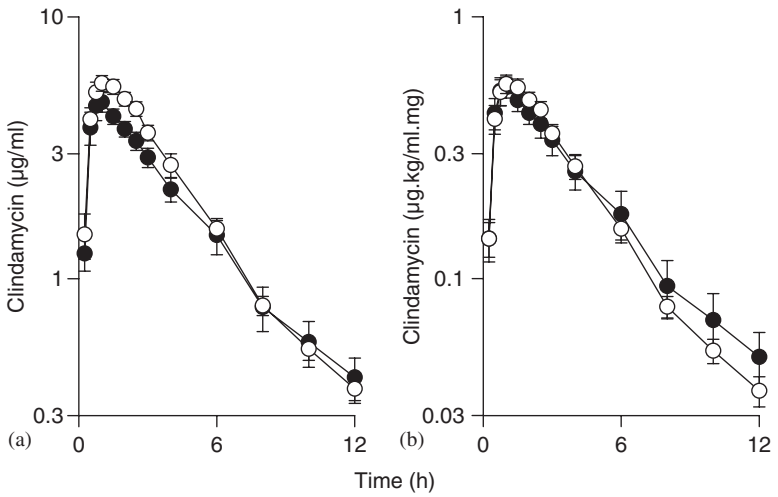

Figure 1. Mean (± SEM) plasma levels against time curves of clindamycin after administration of a 600 mg oral dose to 13 women (white circles) and 11 men (black circles) without normalization (a) or normalized by dose and weight (b)

to the differences in the body weight of the individuals.

Discussion

The oral pharmacokinetics of clindamycin in women and men was compared. It has been reported previously that gender differences in the pharmacokinetics of drugs metabolized by CYP3A4 may occur [8–10]. However, although a higher enzymatic activity of CYP3A4 in women has been described [8,9], sometimes this increased activity is not reflected in changes in the pharmacokinetic parameters [11], therefore, it is necessary to evaluate case by case. Obviously, the clearance of drugs is not the only factor that determines the plasma levels of compounds, since absorption and distribution of drugs play important roles. It has been reported that gender differences may be due to these two factors. Concerning the distribution of drugs, gender differences in the body weight and the total body water have been reported. It has been established that a difference of at least 20% was observed between genders [17] that may lead to pharmacokinetic differences between genders in the distribution of drugs [18]. In the case of clindamycin, it was observed that the higher levels reached in women can be fully explained by the difference in the body weight of individuals and, therefore, no evidence for gender differences in the disposition of clindamycin was observed.

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