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Effect of clotrimazole on microsomal metabolism and pharmacokinetics of albendazole

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Abstract

Albendazole is a broad spectrum anthelmintic drug widely used in human and veterinary medicine. Intestinal and hepatic albendazole metabolism leads to albendazole sulfoxide (active metabolite) and albendazole sulfone (inactive metabolite) formation. Microsomal sulfonase activity can be abolished by in-vitro interaction with clotrimazole and pharmacokinetic studies confirm this interaction. After albendazole incubation, albendazole sulfone formation was completely inhibited by 50 μM clotrimazole in intestinal incubations and a 50% inhibition was observed in hepatic incubations. The lower inhibition constant (K_i) value observed in the intestinal incubations ($9.4 \pm 1.0\ \mu$M) compared with the hepatic counterparts ($23.3 \pm 15.8\ \mu$M) pointed to a greater affinity of the enzymatic systems in the intestine. Regarding the formation of albendazole sulfoxide, an inhibition close to 50% was observed in liver and intestine at 10 μM clotrimazole. The pharmacokinetic parameters obtained following the oral co-administration of albendazole sulfoxide and clotrimazole corroborated the in-vitro inhibition of albendazole sulfone formation, since the ratio of the area under the plasma concentration–time curves for the sulfoxide/sulfone (AUC_{ABZSO}/AUC_{ABZSO2}) was significantly higher (38.1%). In addition, the AUC and C_{max} for albendazole sulfone were significantly lower. The effect of clotrimazole was also studied after prolonged treatment. Hepatic microsomal metabolism of albendazole was induced after 10 days of clotrimazole administration, with significant increases in formation of albendazole sulfoxide (40%) and sulfone (27%). These results offer further insight into the metabolism of benzimidazole drugs and highlight the difficulty involved in human therapy with these anthelmintics, since after prolonged treatment the drug interactions are affected differentially.

Introduction

Albendazole, a benzimidazole carbamate (methyl 5 propylthio-1 *H*-benzimidazole-2-yl carbamate), is a broad-spectrum anthelmintic compound used against a large variety of parasitoses such as hydatidosis (Gil-Grande et al 1993), intestinal nematodosis (Bennett & Guyatt 2000), neurocysticercosis (Sotelo 1997) and lymphatic filariasis (Cox 2000). It is also used to treat microsporidial and cryptosporidial infections, both emerging diseases with human immunodeficiency virus (Costa & Weiss 2000; Zulu et al 2002). In addition, its possible use in the treatment of hepatic carcinomas has been reported (Pourgholami et al 2001).

Hydatid disease due to *Echinococcus granulosus* is endemic in many countries. Treatment with albendazole has been shown to be a useful advance in the treatment of abdominal hydatid disease, both when used as a single agent for treatment and as an adjunct to surgical therapy (Gil-Grande et al 1993), otherwise such treatment requires prolonged administration over several weeks (Horton 1997).

After oral administration, albendazole is biotransformed into two main metabolites: albendazole sulfoxide and albendazole sulfone. The sulfoxide is considered to be the active metabolite since the parent compound is undetectable in plasma (Redondo et al 1998). Two microsomal enzymatic systems have been suggested to be responsible for the sequential sulfoxidation of albendazole: the cytochrome P450 system (CYP450) and the flavin monooxygenase system (FMO). Both systems have been suggested to be

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responsible for the sulfoxidation of albendazole (Rawden et al 2000), while CYP450 is the main determinant of sulfonation (Souhaili-El Amri et al 1988). The involvement of the two pathways in albendazole metabolism has been observed in man (Rolin et al 1989) and rats (Moroni et al 1995; Villaverde et al 1995), as well as in other domestic species. Moreover, recent data suggest that CYP3A4 may be the key contributor of albendazole metabolism in liver (Rawden et al 2000) and intestine (Nagy et al 2002). Albendazole sulfoxide has two antipodes, enantiomers (−) and (+), produced from albendazole, which can be separated by HPLC; (+)-albendazole sulfoxide is associated with the activity of FMO, whereas CYP450 participates in the production of (−)-albendazole sulfoxide (Delatour et al 1991).

The liver has been considered the main organ involved in albendazole metabolism (Souhaili-El Amri et al 1988), although microsomal intestinal sulfoxidation has also been implicated (Villaverde et al 1995) and the albendazole sulfoxide thus formed can be effluxed to the intestinal lumen (Redondo et al 1999). The role of the intestine in drug disposition is not only related to absorption and the importance and impact of intestinal drug metabolism has increased considerably in recent decades.

Albendazole therapy is difficult; its low water solubility and its poor absorption from the gastrointestinal tract result in low bioavailability and reduced efficacy. New approaches for chemotherapy need to focus on the modulation of albendazole metabolism. One potentially useful approach is the combination of albendazole with other drugs, such as the structural analogue fenbendazole (Galtier et al 1986; Merino et al 1999) or metabolic inhibitors such as methimazole (Lanusse et al 1993) and cimetidine (Wen et al 1996).

Regarding clotrimazole, an N-substituted imidazole drug, this compound has been shown to act as an inhibitor of CYP3A (Thummel & Wilkinson 1998) and sulfonase (Dupuy et al 1997). It has been shown to prevent the formation of DNA adducts in-vitro and has been associated with a reduction in skin tumours in neonatal rats through a CYP450 inhibitory mechanism.

The oral bioavailability of CYP3A4 substrates can be profoundly altered by modulators of enzyme catalytic activity. The effect of a co-administered modulator of CYP3A function might be expected to be more pronounced at the level of the intestine, compared with the liver, based on presumed local concentration differences during the period of modulator absorption (Thummel & Wilkinson 1998).

The purpose of this study was to assess the effect of clotrimazole on the formation of albendazole sulfone at intestinal and hepatic levels based on microsomal and pharmacokinetic studies. In addition, the differential interaction of clotrimazole with albendazole metabolism after chronic administration of clotrimazole was assessed. The experimental design included chiral analyses of the samples to quantify the relative importance of the FMO and CYP450 enzymatic systems in the effect of clotrimazole.

Material and Methods

Chemicals

The albendazole, albendazole sulfoxide and albendazole sulfone used to carry out the study and to prepare standard solutions were kindly supplied by Smith-Kline & Beecham S. A. (Madrid, Spain). Mebendazole, used as internal standard, and clotrimazole were purchased from Sigma Chemical Co. (St Louis, MO).

Animals

Male Wistar rats (250 ± 40 g), purchased from IFFA CREDO (Barcelona, Spain), were housed three per cage in a temperature-controlled room (21–23 °C) with 40–60% humidity and a 12-h light–dark cycle. Rats were acclimatised to these conditions for at least one week before the experimental studies were conducted. Standard rodent diet (Panlab SA, Barcelona, Spain) and water were freely available. Before all experiments, the rats were fasted overnight but had free access to water. The rats were handled according to the Principles of Council Directive 86/609/ECC regarding the Protection of Animals used for Experimental and other Scientific Purposes.

In-vitro intestinal and hepatic biotransformation

The bioconversion of albendazole was calculated by measuring albendazole sulfoxide and albendazole sulfone formation through the amount of sulfoxide and sulfone produced by microsomes. The method used to obtain enterocytes was that described by Weiser (1973) and optimized by Whitt & Savage (1988) and Villaverde et al (1995). Cells from the upper and midvillus regions were used as a source of intestinal material. The method used to isolate the enterocytes included eversion of the gut and incubation in chelating medium with EDTA 5 mM and dithiothreitol (DTT) 0.5 mM, substances which removed the enterocytes from the gut. Microsomes from enterocytes were essentially prepared using methods developed for liver microsomes. In brief, microsomes were prepared through ultracentrifugation. Liver tissue or enterocyte suspensions were homogenized with 0.25 M sucrose and then the microsomes were isolated by differential centrifugation using an ordinary method. Microsomal pellets were resuspended in 0.1 M potassium phosphate buffer containing EDTA 1 mM and 20% glycerol and stored at −80 °C until use. The amount of microsomal protein was estimated by the method of Lowry et al (1951). Albendazole sulfoxide and albendazole sulfone formation was achieved in incubations with 25 μM albendazole and 25 μM albendazole sulfoxide in a volume of 1 mL containing the microsomal fraction (1 mg of microsomal protein). In the inhibition incubations, clotrimazole was added to the incubation mixture at different concentrations. Albendazole, albendazole sulfoxide and clotrimazole were dissolved in methanol (10 μL). Incubations were performed under aerobic conditions at 37 °C in a shaking

bath, with a pre-incubation of 2 min in the presence of an NADPH-regenerating system, according to the technique described by Galtier et al (1986). Vials with neither protein nor the NADPH-generating system were used as controls. The time set to carry out the assays was 8 min, this being related to the linear phase of product formation.

To calculate the inhibition constant (K_i) value of albendazole sulfone formation, intestinal and hepatic microsomes from rats not undergoing treatment were used and the concentrations of clotrimazole were 25, 50 and 100 μM. In the case of the K_i value of albendazole sulfoxide formation, five concentrations of clotrimazole were used (10, 20, 30, 50 and 100 μM).

Dixon plots of reciprocals of reaction velocity vs inhibitor concentration were used to calculate K_i according to the SIMFIT v.5.0 computer programme (Bardsley, W. G., University of Manchester, UK). The parameters used to study the inhibition of metabolite formation (V_o, formation velocity without inhibitor; V_i, formation velocity in presence of inhibitor, nmol min^{-1} mg^{-1}) were determined according to Gibbs et al (1999).

Chronic dosing with clotrimazole

To study the effect of chronic dosing with clotrimazole on microsomal albendazole metabolism, the drug (10.6 mg kg^{-1}) was administered to rats for ten consecutive days. The control group comprised rats receiving physiological saline. After weighing the rats, the dose was administered through oral cannula in the morning (08:00 h). Six rats were used for each experimental group. Hepatic and intestinal microsomes were obtained with the same procedures reported previously. Albendazole sulfoxide and sulfone (nmol min^{-1} (mg of protein)$^{-1}$) formation was accomplished with incubations with 25 μM albendazole. The time set to carry out the assays was 8 min.

Pharmacokinetic study of the sulfone formation

Fifteen rats were used in the pharmacokinetic study. A one-week washout period was allowed between the administration of each treatment studied: oral doses of a control suspension of albendazole sulfoxide (Ricobendazol 2.5%; Pfizer, Madrid, Spain) (7.5 mg kg^{-1}) and 7.5 mg kg^{-1} albendazole sulfoxide plus clotrimazole (10 mg kg^{-1}).

All treatments were administered by gastric intubation (1 mL per rat) at 08:00 h. Blood samples (0.4 mL) were drawn by retro-orbital venous plexus puncture after anaesthetising the rats with ethyl ether. The samples were collected at 30 min and 1, 2, 4, 8, 10, 12, 15 and 18 h after dosing, with an average collection time of about 2 min. Three groups of five rats were set up at random and sampled with a minimum interval time of 3 h. Blood samples were transferred into heparinized Eppendorf tubes to prevent clotting and immediately centrifuged (3000 *g* for 15 min) to obtain the plasma, which was stored at $-20\,^{\circ}C$ until analysis.

Pharmacokinetic parameters were obtained by non-compartmental (model-independent) methods, using the Pk Solutions 2.0 computer program (SUMMIT Research Services, Ashland, USA). The elimination half-life ($t_{\frac{1}{2}}$) was calculated as $\ln 2\beta^{-1}$. The peak plasma concentration (C_{max}) and the time to peak concentration (T_{max}) were read from the concentration–time curves plotted. The area under the concentration–time curves (AUC) was calculated using the trapezoidal rule and further extrapolation to infinity ($AUC_{0-\infty}$). Statistical moment theory was applied to calculate the mean residence time (MRT), which was determined as the ratio of the area under the first moment of the concentration–time curve (AUMC) and the AUC (Gibaldi 1991).

Analytical methodology

Samples from in-vitro experiments were extracted by the addition of 3 mL of dichloromethane to the incubation mixture (0.2 μg mebendazole was added as internal standard), shaking with a vortex device and evaporating the organic phase to dryness under a nitrogen atmosphere. The residue was then dissolved in 100 μL of methanol and analysed by HPLC.

In the pharmacokinetic study, samples of the plasma collected (100 μL) were added to 1 mL ethyl acetate containing 0.2 μg mebendazole in a propylene tube. The samples were vortexed for 30 s and the organic phase was evaporated to dryness under a nitrogen stream. The dry residue was dissolved in 100 μL of methanol and then analysed by HPLC. The HPLC parameters and the quantification method used for the analysis had been described by Redondo et al (1998).

To establish the relative importance of the FMO and CYP450 enzymatic systems in microsomal studies, chiral analyses of the samples were performed. For the enantiomeric analysis, during the HPLC analysis, the albendazole sulfoxide fraction was collected and evaporated under a nitrogen stream. The dissolved residue was then chromatographed on a chiral column in which the stationary phase was an α1-glycoprotein immobilized on silica (Chiral AGP, ChromTech AB, Sweden) in accordance with the conditions previously described by Delatour et al (1991). This step provided the relative proportions of both (−)- and (+)-albendazole sulfoxide enantiomers.

Data analysis

Data are presented as means and standard deviations. All statistical calculations were performed using Student's test (unpaired). Differences between two sets of data (albendazole sulfoxide versus albendazole sulfoxide–clotrimazole treatment, $n = 6$; saline versus clotrimazole, $n = 6$) were considered statistically different if $P < 0.05$.

Results

Inhibition of albendazole sulfone formation

Microsomal study

The use of increasing concentrations of clotrimazole with a fixed concentration (25 μM) of albendazole allowed us to

study the effect of clotrimazole on intestinal and hepatic microsomal activity. Analysis of these results revealed a strong inhibition of albendazole sulfone formation in intestine and liver by clotrimazole. In fact, the sulfone formation was completely inhibited by clotrimazole at 50 μM in intestinal incubations and close to 60% inhibition was observed in hepatic incubations (Figure 1A). Since the inhibition of albendazole sulfone formation was so important, intestinal and hepatic incubations with albendazole sulfoxide were performed to study the effect of clotrimazole on this metabolic step in greater depth (Figure 1B). The K_i values pointed to a greater affinity of the enzyme in the case of intestinal incubations ($K_i = 9.4 \pm 1.0\ \mu$M) as compared with hepatic ones ($K_i = 23.3 \pm 15.8\ \mu$M).

Pharmacokinetic study

Regarding the pharmacokinetic parameters obtained for albendazole sulfone after co-administration of albendazole sulfoxide and clotrimazole (Table 1), the area under the curve (AUC) and C_{max} were significantly lower (24.9% and 38.4%, respectively) after the co-administration of clotrimazole. In addition, the AUC_{ABZSO}/AUC_{ABZSO2} ratio was significantly higher (38.1%). The pharmacokinetic parameters for albendazole sulfoxide were not significantly modified (data not shown).

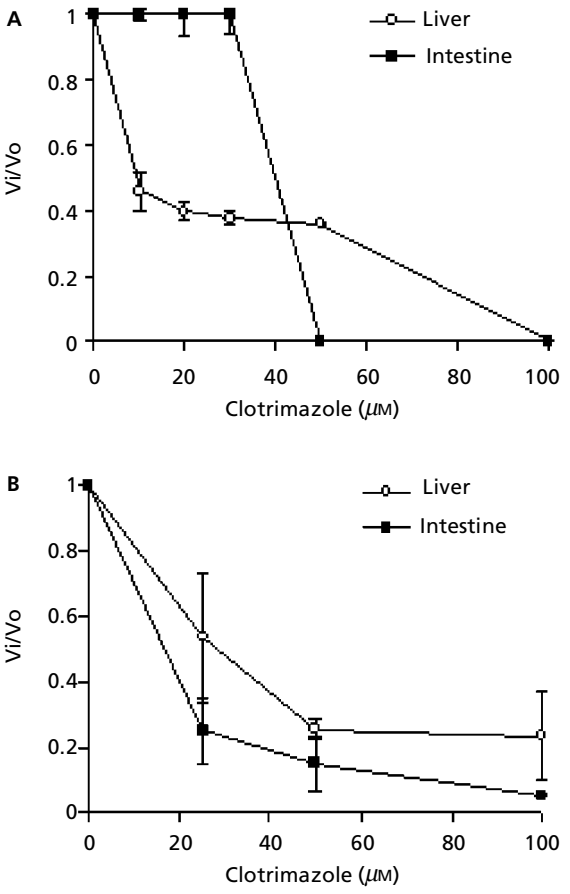

Figure 1 Inhibition of albendazole sulfone formation achieved with the incubation of 25 μM albendazole (A) and 25 μM albendazole sulfoxide (B) and increasing concentrations of clotrimazole with rat intestinal and hepatic microsomes. Vo, formation velocity without inhibitor; Vi, formation velocity in presence of inhibitor. Data are mean ± s.d. from triplicate incubations.

Inhibition of albendazole sulfoxide formation

Albendazole sulfoxide formation was inhibited in the presence of clotrimazole in microsomal incubations of albendazole (Figure 2). The inhibition of sulfoxide formation was close to 50% at 10 μM clotrimazole when compared with the activity seen without inhibitor (0.07 ± 0.01 vs 0.15 ± 0.03 nmol min^{-1} (mg of protein)$^{-1}$ in intestine and 0.34 ± 0.06 vs 0.59 ± 0.08 nmol min^{-1} (mg of protein)$^{-1}$ in liver). The degree of inhibition of albendazole sulfoxide formation by clotrimazole was similar in intestine ($K_i = 7.2 \pm 3.3\ \mu$M) and liver ($K_i = 4.8 \pm 1.7\ \mu$M).

The enantiomeric analysis of the samples after the incubations in the presence of clotrimazole revealed a clear decrease in the percentage of (−)-albendazole sulfoxide, the enantiomeric form produced by the CYP450 system. The results were similar regardless of

Table 1 Pharmacokinetic parameters for albendazole sulfone obtained after the oral administration of albendazole sulfoxide either alone or co-administered with clotrimazole to rats.

Pharmacokinetic parameter	Oral administration	
	Albendazole sulfoxide	Albendazole sulfoxide + clotrimazole
$AUC_{(0-t)}$ (μg·h mL^{-1})	7.90 ± 0.72	6.00 ± 0.52*
MRT (h)	6.73 ± 0.46	6.37 ± 0.31
$t_{\frac{1}{2}}$ (h)	2.57 ± 0.48	3.93 ± 0.51*
T_{max} (h)	6.50 ± 2.52	4.66 ± 1.15
C_{max} (μg mL^{-1})	0.86 ± 0.02	0.53 ± 0.03*
AUC_{ABZSO}/AUC_{ABZSO2}	2.65 ± 0.30	3.66 ± 0.32*

Data are means ± s.d. *$P \leq 0.05$, compared with control group.

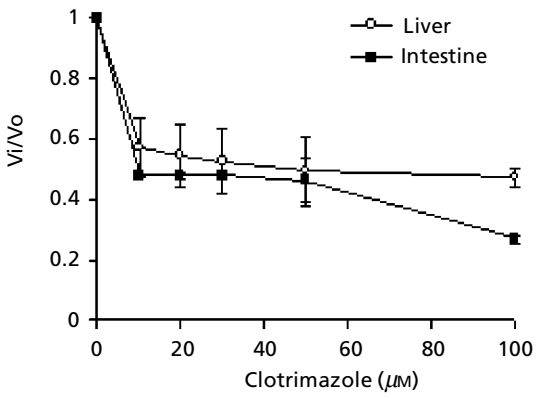

Figure 2 Inhibition of albendazole sulfoxide formation achieved with the incubation of 25 μM albendazole and increasing concentrations of clotrimazole with rat intestinal and hepatic microsomes. Vo, formation velocity without inhibitor; Vi, formation velocity in presence of inhibitor. Data are mean ± s.d. from triplicate incubations.

the concentration of clotrimazole used. On average, the decrease was 35.0% in the intestine and 31.9% in the liver.

Effect of long-term administration of clotrimazole on albendazole sulfoxide and sulfone formations

Table 2 shows the formation of albendazole sulfoxide and sulfone and the enantiomeric percentages obtained after incubation of albendazole with intestinal and hepatic microsomes. Microsomes were obtained from 10-day clotrimazole-treated rats. The degree of involvement of each enzymatic system was obtained from the enantiomeric percentages.

There was a significant induction of sulfoxide and sulfone formation due to continuous administration of clotrimazole (0.824 ± 0.042 vs 0.588 ± 0.031 nmol min^{-1} mg^{-1} for albendazole sulfoxide formation and 0.127 ± 0.017 vs 0.100 ± 0.008 nmol min^{-1} mg^{-1} for sulfone formation), in contrast to the results obtained without long-term administration (Figures 1 and 2). In the case of incubation with intestinal microsomes, a significant inhibition of albendazole sulfoxide formation was observed, as was seen without long-term administration, although in this case the effect was not statistically different. The degree of albendazole sulfone formation observed with intestinal microsomes was very low and the effect of clotrimazole was not significant.

The degree of involvement of CYP450 in the process was greater at the hepatic level. The results shown in Table 2 suggest that the inducing effect of clotrimazole at this level could possibly occur through the CYP450 system (67.74% of CYP450 involvement in clotrimazole group vs 65.16% in control group, although this difference is not statistically different). At the intestinal level, there was no change in the enantiomeric percentages.

Discussion

Inhibition of albendazole sulfone formation

The use of metabolic inhibitors is a widely used strategy to increase drug bioavailability. Several mechanisms may be involved in the enhancement of albendazole and albendazole sulfoxide bioavailability, increasing their systemic exposure and efficacy: inhibition of sulfoxidation by CYP450 using cimetidine (Wen et al 1996), inhibition of sulfoxidation by FMO using methimazole (Lanusse et al 1993; Villaverde et al 1995) and inhibition of sulfonation using clotrimazole, as demonstrated in this study.

The results pointed to a clear inhibition of albendazole sulfone formation after incubation of albendazole with clotrimazole (100% with intestinal and hepatic microsomes at 100 μM, Figure 1A). Since clotrimazole is a CYP3A inhibitor (Thummel & Wilkinson 1998), the main enzyme in rat intestine, the differences in the inhibition constant observed in the incubations with albendazole sulfoxide between intestinal ($K_i = 9.4 \pm 1.0$ μM) and hepatic microsomes ($K_i = 23.3 \pm 15.8$) can be attributed to differences in CYP3A concentration and activity in each tissue. Clotrimazole has previously been reported to act as an inhibitor of sulfonase activity in the case of fipronil

Table 2 Albendazole sulfoxide and albendazole sulfone formation and the degree of involvement of each enzymatic system obtained from the enantiomeric percentages after albendazole incubations with intestinal and hepatic microsomes from rats treated for 10 days with clotrimazole or saline.

	Albendazole sulfoxide (nmol min^{-1} mg^{-1})	CYP450 (% involvement)	FMO (% involvement)	Albendazole sulfone (nmol min^{-1} mg^{-1})
Liver				
Saline	0.588 ± 0.031	65.16	34.84	0.100 ± 0.008
Clotrimazole	0.824 ± 0.042*	67.74	32.26	0.127 ± 0.017*
Intestine				
Saline	0.197 ± 0.012	50.25	49.75	0.011 ± 0.002
Clotrimazole	0.116 ± 0.049	50.37	49.63	0.018 ± 0.006

Data are means ± s.d. *$P \leq 0.05$, compared with control group (saline).

(Dupuy et al 1997). In addition, the inhibition of CYP3A produced by clotrimazole has been reported in-vitro using human and rat hepatic microsomes and human hepatocyte cultures (Maurice et al 1992; Tassaneeyakul et al 1998; Suzuki et al 2000).

Since it seems that albendazole sulfone formation is very sensitive to the presence of clotrimazole in the incubation medium (inhibition of nearly 80% in liver and 100% in intestine observed at clotrimazole 100 μM, Figure 1B), a pharmacokinetic study of the interaction of the sulfoxide and clotrimazole in the rat was performed.

The pharmacokinetic parameters for albendazole sulfone after oral co-administration of clotrimazole and albendazole sulfoxide (Table 1) showed a clear in-vivo inhibition of sulfoxide metabolism; specifically, there was a significant increase of the AUC_{ABZSO}/AUC_{ABZSO2} ratio observed with the clotrimazole treatment. Study of this ratio has previously been used to compare differences in sulfonation capacity among pharmacokinetic groups (McKellar et al 1993). In addition, the decrease in AUC and C_{max} and the increase in $t_{\frac{1}{2}}$ are clear indicators of the inhibition of albendazole sulfone formation.

Regarding albendazole sulfone formation, the percentage of inhibition (about 50%) observed in the albendazole incubations and intestinal and hepatic microsomes from non-treated rats (Figure 2) was the same as that reported by Moroni et al (1995) with hepatic microsomes. In addition, the decrease in the percentage of (−)-albendazole sulfoxide, observed by those authors with hepatic microsomes in the presence of clotrimazole (36.3%), is very similar to ours (31.9%).

Effect of long-term administration of clotrimazole

Unlike the inhibitory effect produced by clotrimazole on albendazole metabolism without long-term administration, the results obtained in rats administered with clotrimazole over 10 days (Table 2) revealed a clear inductive effect of clotrimazole on hepatic albendazole metabolism (40% of sulfoxide and 27% of sulfone formation). However, an inhibition of the intestinal metabolism was observed (41% of albendazole sulfoxide formation), as was seen without long-term administration although the effect was not statistically different.

In general, the phenomenon of enzymatic induction is more apparent after prolonged exposure to the inductor agent. Since the percentage of (−)-albendazole sulfoxide was slightly increased with clotrimazole treatment, a possible induction of CYP450 at the hepatic level might have been caused by clotrimazole. The induction of CYP450 isoenzymes by clotrimazole has been widely reported in the literature when treatment was continuous. Suzuki at al (2000) reported an in-vitro induction of CYP3A human and rat microsomes after 24 h of treatment with clotrimazole. Hostetler et al (1989) described an induction of the CYP450 system with values five-fold higher than controls when clotrimazole was administered to rats for 3 days.

The main CYP450 induction reported involves a transcriptional activation of CYP450 genes. This kind of induction by clotrimazole in the case of CYP3A4 has been reported in human hepatocyte cultures (Maurice et al 1992). Post-transcriptional regulation, increasing the protein levels of CYP3A by stabilization, has been also reported in-vitro for clotrimazole (Eliasson et al 1994).

Regarding the non-significant effect of clotrimazole on albendazole sulfoxide formation observed in the intestine in rats treated for 10 days, it should be stressed that the ability of a compound to induce CYP450 in the liver is not correlated with its ability to induce it in extrahepatic tissues (Harmsworth & Franklin 1990; Lin et al 1999). Harmsworth & Franklin (1990) stated that clotrimazole, the strongest hepatic inductor in their study, had little inducing effect in other organs, such as the intestine. In addition, hepatic CYP3A4 activity is not correlated with intestinal CYP3A4 levels, indicating that intestinal and hepatic CYP450s are not co-regulated (Lown et al 1994). Moreover, based on catalytic activity, NADPH-P450 reductase levels and cytochrome b5 content in each organ, intestinal and hepatic CYP3A could have different characteristics (Emoto et al 2001). Emoto et al (2001) also consider that the interaction patterns of the substrates with CYP3A depend on the tissue involved.

The inhibition of intestinal CYP3A is especially important in drugs with a high first-pass metabolism after oral administration. Sometimes, inhibition may even affect only intestinal CYP3A, as occurs with the ingestion of grapefruit juice (Bailey et al 1998).

Conclusions

According to the microsomal and pharmacokinetic studies carried out here, clotrimazole is an inhibitor of albendazole metabolism — mainly of albendazole sulfone formation. However, after long-term administration of clotrimazole, an induction of the hepatic metabolism of albendazole was observed. The induction observed here is very relevant if it is taken into account that the clinical interactions reported for clotrimazole are always as an inhibitor (Thummel & Wilkinson 1998). The role of CYP450 and FMO isoenzymes responsible for the intestinal inhibition of albendazole metabolism should be addressed in future research.

Taken together, our results further contribute to the understanding of the metabolism of benzimidazole drugs and the implications of the potential practical interactions of clotrimazole in the efficacy of anthelminthics in human and veterinary medicine.

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