SHORT COMMUNICATION, © Basic & Clinical Pharmacology & Toxicology 2005, **97**, 122–124.
Printed in Denmark . All rights reserved

Pharmacology & Toxicology

ISSN 1742-7835

Short Communication

Influence of a Mexican Diet on the Bioavailability of Albendazole

S. Sergio Mares[1], C. Helgi Jung[1,2], A. Temuchino López[3] and Dinora F. González-Esquivel[1]

[1]Laboratory of Neuropsychopharmacology, National Institute of Neurology and Neurosurgery, [2]Faculty of Chemistry, UNAM, and [3]Division of Neurology, National Institute of Neurology and Neurosurgery, México, D. F., México

(Received February 25, 2005; Accepted March 28, 2005)

With a mexican diet we have found that after a single oral dose of 800 mg of albendazole, maximum plasma levels and the area under the plasma concentration curve increased seven and eight times respectively, however the elimination rate was not altered.

In order to evaluate the influence of a Mexican diet on the bioavailability of albendazole a two-way cross-over comparative study was carried out in healthy volunteers after a single oral dose of 800 mg in fasting and fed state. Sixteen healthy volunteers were included, nine men and seven women. The mean age was 24.7 years (range 18 to 33 years) and the mean weight was 62.9 kg (range 50 to 82 kg). The protocol was approved by the local ethics committee, and informed written consent was obtained from each subject after detailed explanation of the purpose and risks of the study. The volunteers did not take any other medication or alcohol for at least 15 days prior the study .

The volunteers were randomly separated into two groups of 8 each. Albendazole (Eskazole™, 400 mg) was administered in a single oral dose of 800 mg to both groups after an overnight fast. Group I received the drug with 240 ml of water and food was withheld for 4 hr after the drug was taken; then a standard lunch was allowed. Group II received albendazole after a Mexican diet which consisted of two fried eggs with tomato, onion and chili, two slices of bacon, chilaquiles (tortillas (55 g) with tomato, chili and cream (12 g) and a glass of milk (240 ml) (fat 57.1%, protein 16%, carbohydrates 26%, 963.5 kcal).

Blood samples were obtained through an indwelling catheter placed in the antecubital vein at 0, 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, 4, 6 ,8 12, 24 and 48 hr after the drug administration. Samples were centrifuged and the plasma was separated and stored at $-20°$ until analysis. The study was repeated in a cross-over design allowing 1 week of wash-out between treatments.

Albendazole sulfoxide, the main active metabolite, is readly recupered in the plasma of rat, cattle and sheep. In man the first-pass metabolism to albendazole sulfoxide is rapid and apparently complete. It is well known that two distinct microsomal enzymatic pathways are responsible for the sequential sulphoxidation of albendazole. The first, a flavin-containing monooxygenase system is involved in the oxidation of albendazole to albendazole sulfoxide through an nicotin-amide-adenine dinucleotide phosphate (reduced form) (NADPH)-dependent reaction). The other, cytochrome P450 is involved in oxidation of albendazole sulfoxide to albendazole sulphone. Involvement of both systems, flavin-containing monooxygenase system and cytochrome P-450, in albendazole metabolism have been demonstrated in rat, sheep, cattle and pig liver microsomes, as well in differentiated human hepatoma cell line (Jung & González-Esquivel 2002). Then, the active metabolite albendazole sulfoxide was measured in plasma by a high performance liquid chromatographic method previously reported (Hurtado *et al.* 1989). The analytical method consisted of a solid extraction with methanol using Sep-Pak C18 cartridges (Waters Assoc.); after the evaporation of the organic solvent the residue was redissolved and injected for analysis. The method was linear from 0.0625 to 4 μg/ml. The maximum coefficients of variation of the within- and inter-day reproducibility were 7.5% and 6.9% respectively. The recovery ranged from 95 to 98%.

Peak plasma concentrations (C_{max}) and time to reach C_{max} (t_{max}) were obtained directly from the individual plasma concentration profiles. The area under the plasma curve concentration (AUC 0-t and AUC_{0}-$\propto$) was calculated by the linear trapezoidal method. Apparent oral clearance (Cl) and volume of distribution (Vd), each expressed as a function of bioavailability (F) were calculated individually using WinNonLin (v 2.0) software.

Fig. 1 shows the mean plasma concentration-time curves of albendazole sulfoxide obtained after a single oral dose of

Author for correspondence: Dinora F. González Esquivel, Laboratory of Neuropsychopharmacology, National Institute of Neurology and Neurosurgery, Insurgentes Sur 3877, La Fama, 14269 Tlalpan, México (fax +515 5424 0808, e-mail dinofab@hotmail.com).

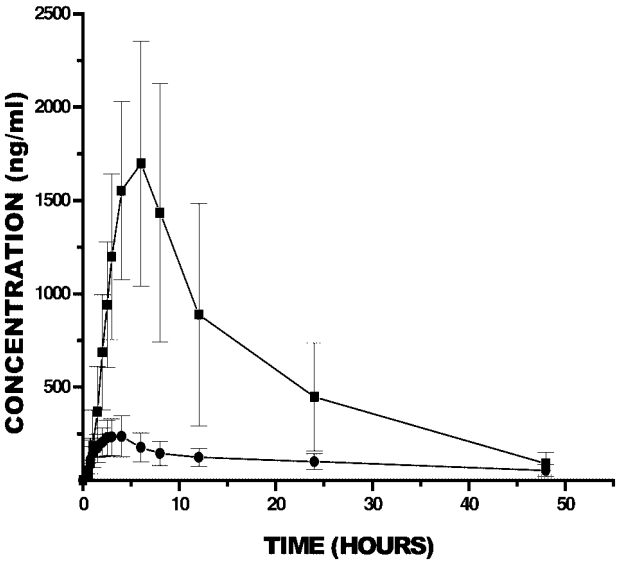

Fig. 1. Mean plasma concentration of albendazole sulfoxide after a single oral dose of 800 mg of albendazole in fasting state (●) and after a fatty meal (■).

800 mg of albendazole under fasting and non-fasting conditions. Pharmacokinetic parameters are shown in table 1. C_{max} values ranged from 145.8 to 366.26 ng/ml under fasting condition and from 1160.1 to 2393.44 ng/ml with the mexican diet. Mean C_{max} value was enhanced 7 times after the administration with the diet. The interindividual variability of C_{max} was great. The coefficients of variation were 42% and 34% in fasting and fed state respectively. After administration of albendazole with the Mexican diet the mean AUC from 0 to 48 hr increased by 814%. As expected, a significant delay in t_{max} was observed, with t_{max} values of 3.16 ± 1.1 hr and 5.13 ± 1.59 hr for fasting and fed condition respectively.

Our results show that bioavailability of albendazole was significantly influenced by food intake. Statistical significant differences were found in C_{max} and AUC, however plasma elimination half-lives were similar to each other and comparable to those obtained previously (Marriner *et al.* 1986; Jung *et al.* 1992a), therefore it appears that food does not affect the elimination rate of the metabolite. Although Vd/F and Cl/F decreased in fed state, the effect is probably associated to an increase in the fraction of dose absorbed (F) which could be related to a major dissolution of albendazole in the gastrointestinal tract due to the surfactant effect of the bile salts which are secreted after the meal. Previous *in vitro* studies have shown that solubility and not absorption was the rate-limiting step in the absorption of albendazole (Jung *et al.* 1998b). In the same way, dissolution studies made with low solubility compounds have shown that the concentration of solubilizing compounds in bile salts or in meals is the prime determinant of solubility of these drugs and hence dissolution behaviour (Galia *et al.* 1996).

The therapeutic response of albendazole in cases of neurocysticercosis is variable and difficult to predict (Jung *et al.* 1992). The poor intestinal absorption of albendazole due to its low aqueous solubility is probably the major determinant of the variable response rate. Our results show that the bioavailability of albendazole was increased when it was combined with the Mexican diet. The increase in plasma levels of albendazole sulfoxide did not decrease the interindividual variability, therefore it can be assumed that the main causes of variability are due to differences in gastric pH or to differences in intestinal metabolism (Schipper *et al.* 2000; Nagy *et al.* 2002).

The Mexican diet of today is a variety of foods and dishes that represent a blend of pre-Columbian, Spanish, French and more recently, American culture. The typical Mexican diet is rich in complex carbohydrates, which are provided mainly by corn and corn products, beans, rice and bread. The diet also contains protein in form of beans, eggs, fish and a variety of meat. Because of extensive use of frying as a cooking method, the diet is also high in fat. Several investigators have evaluated the influence of food on bioavailability of albendazole. Awadzi *et al.* (1994) evaluated the influence of a local Ghanian fatty breakfast (43.1 g) and found that the relative bioavailability increased four times. Nagy *et al.* (2002) administered a fatty meal with 57 g of fat (1399 kcal) and found that AUC was enhanced 9.4 times. In

Table 1.

Mean pharmacokinetic parameters of albendazole sulfoxide after administration of 800 mg of albendazole and after fasting or a high fatty-meal in 16 healthy volunteers.

Parameter	Fasting	95% confidence Interval	High-fat diet	95% Confidence Interval
$ABC_{0\text{-}t}$ (μg · hr/ml)*	4.025 (2.537)	±1.35	27.792 (14.15)	±7.542
$ABC_{0\text{-}\alpha}$ (μg · hr/ml)*	5.062 (2.775)	±1.478	29.356 (14.563)	±7.758
C_{max} (μg/ml)*	0.256 (0.110)	±0.059	1.776 (0.616)	±0.328
T_{max} (hr)*	3.156 (1.106)	±0.589	5.125 (1.586)	±0.845
$t_{1/2}$ (hr)	9.8456 (3.961)	±2.11	9.176 (2.012)	±1.072
Cl/F (ml/hr)*	0.243 (0.213)	±0.013	0.035 (0.022)	±0.011
Vd/F (ml)*	2.947 (1.889)	±1.006	0.447 (0.234)	±0.125

Values are mean (S.D.); * statistical difference at $P<0.05$.
ABC=area under the plasmaconcentration-time curve; C_{max}=maximum plasma concentration; T_{max}=time to reach the C_{max}; $T_{1/2}$=elimination half-life; K_e=elimunation rate constant; Cl/F=apparent oral clearance: Vd/F=Volume of distribution.

another study a soybean oil emulsion was used to enhance albendazole solubility, showing a 1.6 times enhancement of relative bioavailability (Lange *et al.* 1998). The results of the present study show that the relative bioavailability was increased 8 times. Considering that our Mexican diet contained 61.1 g of fat, the increase in plasma levels is more probably due to the fat content of the meal and not to the other dietary components.

It should be noted that the breakfast given to the participants is a typical Mexican breakfast, thus it would be relatively easy to recommend albendazole with this type of diet to patients with neurocysticercosis in order to increase plasma levels.

Acknowledgements

The authors thanks to CONACYT and to Laboratorios Armstrong de México for the financial support to carry out the present study.

Sergio Mares Sámano received a student grant from CONACYT.

The authors have disclosed that they do not have commercial or other associations that might pose a conflict of interest.

References

Awadzi, K., M. Hero, N. Opoku, D. Büttner, P. A. Coventry, M. A. Prime, M. Orme & G. Edwards: The chemotherapy of onchocerciasis XVII. A clinical evaluation of albendazole in patients with onchocerciasis; effects of food and pretreatment ivermectin on drug response and pharmacokinetics. *Trop. Med. Parasitol.* 1994, **45**, 203–208.

Galia, E., E. Nicolaides, C. Reppas & J. B. Dressman: New media discriminate dissolution of poorly soluble drugs. *Pharm. Res.* 1996, **13**, S-262.

Hurtado, M., M. T. Medina, J. Sotelo & H. Jung: Sensitive high-performance liquid chromatographic assay for albendazole and its main metabolite albendazole sulphoxide in plasma and cerebrospinal fluid. *J. Chomatogr.* 1989, **494**, 403–407.

Jung, H., M. Hurtado, M. Sánchez, M. T. Medina & J. Sotelo: Clinical pharmacokinetics of albendazole in patients with brain cysticercosis. *J. Clin. Pharmacol.* 1992a, **32**, 28–31.

Jung, H., L. Medina, I. Fuentes & R. Moreno-Esparza: Absorption studies of albendazole and some physicochemical properties of the drug and its metabolite albendazole sulphoxide. *J. Pharm. Pharmacol.* 1998b, **50**, 43–48.

Jung, H. & D. F. González Esquivel: Pharmacology of anticysticercal therapy. In: *Taenia solium cisticercosis from basic to clinical science*. Eds.: G. Singh and S. Prabhakar. CABI Publ. UK 2002, 363–374.

Lange, H., R. Eggers & J. Bircher: Increased systemic availability of albendazole when taken with a fatty meal. *Eur. J. Clin. Pharmacol.* 1988, **34**, 315–317.

Marriner, S. E., D. L. Morris, B. Dickson & J. A. Bogan: Pharmacokinetics of albendazole in man. *Eur. J. Clin. Pharmacol.* 1986, **30**, 705–708.

Nagy, J., H. G. Schipper, R. P. Koopmans, J. J. Butter, C. J. Van Boxtel & P. A. Kager: Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability. *Amer. J. Med. Hyg.* 2002, **66**, 260–263.

Schipper, H. G., R. P. Koopmans, J.Nagy, J. J. Butter, P. A. Kager & C. J. Van Boxtel: Effect of dose increase or cimetidine co-administration on albendazol bioavailability. *Amer. J. Trop. Med. Hyg.* 2000, **63**, 270–273.