IMPROVING BIOAVAILABILITY AND ANTHELMINTIC ACTIVITY OF ALBENDAZOLE BY PREPARING ALBENDAZOLE-CYCLODEXTRIN COMPLEXES

GARCÍA-RODRIGUEZ J.J.*, TORRADO J.** & BOLÁS F.*

Summary :

The bioavailability and anthelmintic activity of albendazole-cyclodextrin complexes (ABZ-CDC) compared to albendazole suspensions in carboxymethylcellulose (ABZ-CMC) was assessed in a mouse model for *Trichinella* infections. Swiss CD-1 mice experimentally infected with *T.spiralis* were treated with both formulations against enteral (adult worms) and parenteral (migrating and encysted larvae). Oral bioavailability was assessed in age matched mice treated with 50 mg/kg of both formulations. The anthelmintic effects and plasma concentration of the active metabolite albendazole-sulphoxide (ABZSO) enantiomer (–) were significantly increased following administration of ABZ-CDC in relation to ABZ-CMC.

KEY WORDS : albendazole, bioavailability, *Trichinella*, cyclodextrins.

Albendazole (ABZ) is a broad spectrum antiparasitic drug acting against protozoa and helminth parasites. Following oral administration ABZ is quickly biotransformed in its active intermediate metabolite albendazole-sulphoxide (ABZSO) which subsequently is oxidized to the inactive form of sulphone (ABZSO2) (Gyurik *et al.*, 1981). ABZSO exhibits chirality with two enantioneric forms present in plasma (Delatour *et al.*, 1990). As other benzimidazole-carbamates ABZ is poorly soluble in water and therefore its absorption by the oral tract is reduced (Villaverde *et al.*, 1992). In the present paper the oral bioavailability and anthelmintic activity of ABZ formulated as solid complexes in hydroxypropyl-ß-cyclodextrin (ABZ-CDC) was evaluated in a mouse model for experimental trichinellosis.

MATERIAL AND METHODS

PARASITE

The MFEL/ES/S2 GM-1-ISS48 isolate of *T. spiralis* was used. The methods for infection and worm collection were those described by Denhan & Martínez (1970).

Departmento de Parasitología* y Departamento de Farmacia y Tecnología Farmaceutica**. Facultad de Farmacia, Universidad Complutense, Spain.
Tel.: 34-91- 394 18 18 – Fax: 34-91-394 18 15
E-mail: bolas@eucmax.sim.ucm.es

DRUGS AND FORMULATIONS

ABZ was suplied by Chemo Iberica Co (Spain). ABZ suspension was prepared in 0.5 % sodium-carboxymethylcellulose (ABZ-CMC). ABZ-CDC were prepared by the co-precipitation and freeze-drying methods (Castillo *et al.*, 1999)

INFECTIONS AND TREATMENTS

Swiss CD-1 mice aged eight weeks were purchased from Charles River, France. For anthelmintic assays animals were each infected with 300 larvae of *T. spiralis* and then orally treated with albendazole against three different stages of the life cycle as summarised in table I.

Stage	Dose (mg/kg)	Treatment (Days p.i.)	Worm counting (Days p.i.)
Adult	5, 10	1	6
Migrating larvae	50, 100	13, 14, 15	30
Encysted larvae	50, 100	35, 36, 37	45

Table I. – Treatment schedule.

ORAL BIOAVAILABILITY

Age matched animals to those used for infection were treated with 50 mg/kg of ABZ-CMC or ABZ-CDC. Thereafter, five mice per each sample point were anaesthetised with 15 % urethan solution and their blood collected from the heart by cardiac puncture at points 0.25, 0.5, 0.75, 1.5, 3, 6, 24, 48 and 72 hours post-treatment and the corresponding sera individually tested for ABZ, ABZSO (+, –) and ABZSO2 metabolites by HPLC (García J.J. *et al.*, 1999).

RESULTS

The pharmacokinetic profiles of ABZSO following administration of ABZ-CMC and ABZ-CDC is shown in Fig. 1. Absorption was quicker when

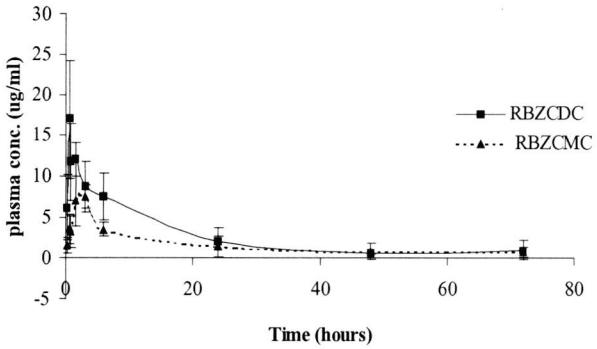

Fig. 1. – Plasma concentrations of ABZSO in plasma of mice following oral administration of 50 mg/kg of ABZ-CMC or ABZ-CDC. Each point represent the Mean ± standard deviation of five samples.

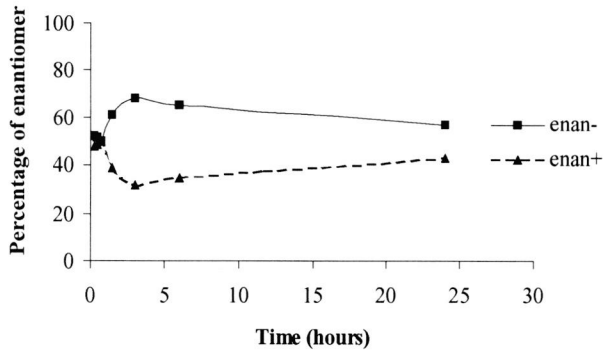

Fig. 2. – Enantiomeric separation of ABZSO in plasma of mice following oral administration of 50 mg/kg of ABZ-CMC. Each point represent the mean of five samples.

ABZ was included in CDC than when suspended in CMC (ABZSO Tmax = 0.5 h and 3 h respectively). ABZSO plasma concentrations achieved were significantly higher following administration of ABZ-CDC than ABZ-CMC (Cmax = 16.96 µg/ml and 7.53 µg/ml, AUC = 78.185 µg.h/ml and 34.296 µg.h/ml, respectively). Plasma concentrations of ABZ and ABZSO2 were at the base level (data not shown). Administration of ABZ-CDC significantly increases the proportion of the more abundant enantiomer ABZSO (Figs 2 and 3). Comparison of anthelmintic effects of both formulations is summarised in Fig. 4.

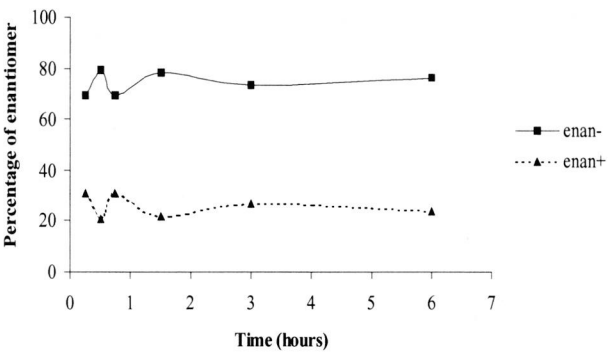

Fig. 3. – Enantiomeric separation of ABZSO in plasma of mice following oral administration of 50 mg/kg of ABZ-CDC. Each point represent the mean of five samples.

DISCUSSION

Results from this work show that cyclodextrins are good drug formulating devises as significant higher bioavailability of ABZSO is achieved when ABZ is administered included in cyclodextrin in relation to conventional suspension in CMC. The higher plasma concentrations for ABZSO following treatment with ABZ-CDC could result in the increased anthelmintic effects against all stages of *Trichinella* life cycle, specially those against intestinal and muscular stages. This improvement in pharmacokinetics as well as in anthelmintic effects of ABZ-CDC against intestinal stages is comparable to that obtained with ABZ formulated in solid dispersion in PVP (Lopez *et al.*, 1997) however ABZ-CDC complexes are easier to prepare and of higher chemical stability. The enantiomeric profiles of ABZSO are similar to those previouly reported in mice (García *et al.*, 1999) and in rats (Delatour *et al.*, 1990). The proportion of the supposed more abundant enantioner (–) is significantly increased following administration of ABZ-CDC with respect to ABZ-CMC. This could indicate that this form is the main responsible for anthelmintic activity.

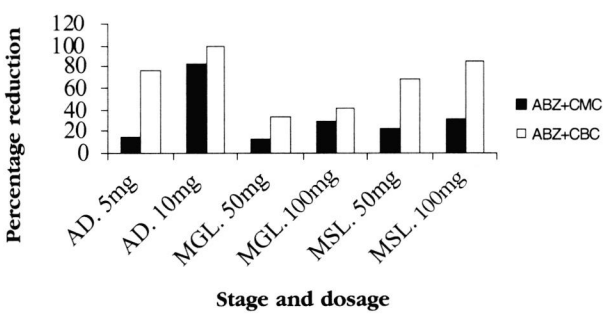

Fig. 4. – Anthelmintic activities of ABZ-CMC and ABZ-CDC against different stages of *T. spiralis* in mice (AD: Adult worms, MGL: Migrating larvae; MSL: Encysted muscle larvae).

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