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Short Communication

Effect of surfactants on Albendazole absorption*

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Introduction

Albendazole (ALB) is a wide-spectrum anthelminthic often used against gastrointestinal parasites. Its action is related to the inhibition of the development in different larvary stages of parasites [1]. ALB (Metil[5-(propiltio)-*H*-benzimidazol-2 yl]carbamate) [2, 3] belongs to the benzimidazole group and, as such, it is insoluble or only slightly soluble in water [2] and its limited absorption from the gut is probably related to the poor water solubility of this drug.

Since the efficacy of ALB in the control of hidatidosis was first demonstrated this use has become generalized. The aim of this work was to improve the intestinal absorption of ALB by increasing solubility by the addition of surfactants, polysorbate 80 (Tween) and sodium taurocholate (STC).

The amphiphilic properties of surfactants allow for stable dispersions of lipophilic substances to be formed, as well as to increase the permeability of biological membranes [4, 5]. These factors contribute to increase the gastrointestinal absorption of drugs.

Experimental

Animals

Male Wistar rats, ranging between 250 and 300 g, were used throughout this study. The animals had been fasted for 18–20 h before surgery.

Reagents

The sample of albendazole supplied by SmithKline Beecham, SAE (Madrid, Spain) (Fig. 1).

Taurcholic acid sodium salt (98%) and Tween 80 (Polyoxyethylensorbiton monooleate) were obtained from Sigma Chemical Company (Madrid, Spain). All other chemicals were of analytical-grade purity (Scharlau).

Method

The intestinal absorption of ALB was studied using two different surfactants (Tween and STC) in a phosphate buffer adjusted to a value of pH 6.7.

In situ rat gut preparation was made by means of the technique described by Doluisio [6] and modified by Plá-Delfina [7]. Briefly, the animal was anaesthetized with urethane (1.3 g kg^{-1} ip), the small intestine was then exposed and input and output cannulae were placed from the pylorus 30 cm downward in a duodeno-jejunal segment. After flushing with saline (in order to clean the internal surface of the gut) 5 ml of the test solution, at 37°C, was introduced into the cannulated segment. At fixed time intervals after dosing the segment was completely emptied. Samples of 0.1 ml

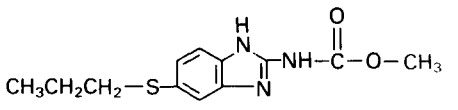

Figure 1
Chemical structure of Albendazole.

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were removed for drug assay and the solution reintroduced in the gut. The sampling intervals were 5 min for a total of 30 min. The initial concentrations of ALB used were 0.025 and 0.0025 mg ml^{-1} in Tween 80 or Taurocholate solutions.

Drug analysis

The concentrations of ALB were determined by reversed-phase LC, with slight modifications [8, 9]. The stationary phase was ODS-C18 and the mobile phase was acetonitrile–triethylamine–water (30:1.5:68.5, v/v/v; pH = 3 using phosphoric acid). The flow rate was set to 1 ml min^{-1} and a variable wavelength detector adjusted at 292 nm.

The absorption rate constant, K_a was calculated by linear regression from

$$\ln C = \ln C_0 - K_a t, \qquad (1)$$

where C and C_0 are the concentrations at time t and the initial concentration, respectively.

Statistical analyses

All results were statistically analysed by analysis of variance. Levels less than 0.05 were not considered significant.

Results and Discussion

Studies of the effect of surfactant on the absorption of Albendazole were made using Tween 80, sodium taurocholate and both separately and together. In preliminary studies the saturated solubility of ALB in 10% Tween, was 0.1 mg ml^{-1}. Therefore, the decision was made to work with a lower concentration (0.05 mg ml^{-1}) in order to obviate possible problems of subsequent precipitation of the product. Because 10% Tween can damage the intestinal membranes, it was diluted to 5%, which is safe [10], so the final perfusion concentration used was 0.025 mg ml^{-1} of Tween at 5%. Other studies were conducted with 0.0025 mg ml^{-1} ALB in 5% Tween.

Figure 2 shows the K_a values obtained for each perfusion concentration of ALB. There being no statistically significant differences between the two concentrations, it was concluded that the transport of ALB through the small intestine of the rat was a *passive* process, as this is the first time data have been obtained on the kinetic mechanism of ALB with the product in solution rather than in suspension.

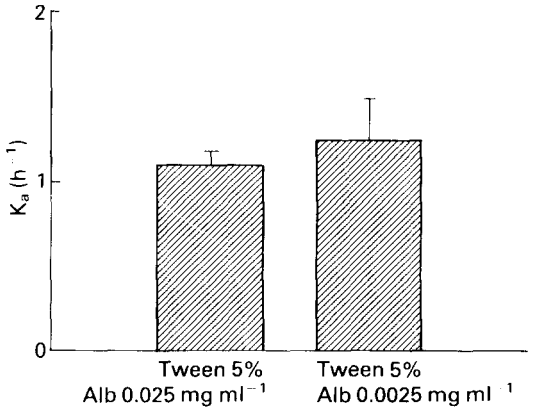

Figure 2
First-order constant absorption (K_a) obtained following intestinal perfusion of Albendazole 0.025 mg ml^{-1} and 0.0025 mg ml^{-1} in Tween (5%).

The surfactant STC was then used in order to compare its effect on the absorption of Albendazole with that of Tween 80. A 76 mM (approximately 4%) solution of STC was determined to be equivalent to a 10% solution of Tween 80, in which conditions the saturation concentration of ALB was 10 times lower (0.01 mg ml^{-1}), i.e. the capacity of Tween to solubilize Albendazole is 10 times greater than that of STC owing to its greater power of micellization. In an analogous method to the first tests, we used a perfusion solution of 0.0025 mg ml^{-1} of Albendazole in taurocholate 38 mM, the results being shown in Table 1.

The absorption constants (K_a) obtained in identical conditions of Albendazole concentration (0.0025 mg ml^{-1}) were 1.250 ± 0.240 ($r > 0.980$) for Tween at 5%, and 2.810 ± 0.116 ($r > 0.99$) for taurocholate at 38 mM, which was significantly higher ($P < 0.05$). The obvious conclusion is that STC, despite having a lower solubilizing capacity, causes the absorption constant of ALB to rise to more than double with regard to Tween at 5%, which represents a great step forward in the studies on the improvement of the absorption of ALB.

Lastly, it was decided to direct our studies towards the determination of the possible synergistic effect of the two surfactants, for which the same concentrations for Albendazole (0.0025 mg ml^{-1}) and of Tween (5%) were maintained while changing those of STC from the CMC (5 mM) to 57 mM.

The data obtained in these experiments are shown in Table 2, where apparent absorption constants analogous to those obtained with

Table 1
Per cent Albendazole concentrations relative to initial (0.0025 mg ml^{-1} in sodium taurocholate 38 mM), remaining in the intestinal lumen

Time (min)	Experimental animal 1	2	3	4	5	Mean ± SD
5	63.10	58.91	57.20	61.86	58.33	59.88 ± 2.23
10	52.22	46.65	45.88	50.44	38.35	46.71 ± 4.79
15	41.60	34.56	34.87	39.45	30.4	36.19 ± 3.93
20	34.35	29.58	29.88	30.40	26.08	30.06 ± 2.63
25	26.05	23.50	22.27	23.73	21.74	23.46 ± 1.49
30	21.07	18.02	17.50	17.54	17.39	18.30 ± 1.40
$K_a(h^{-1})$	2.710	2.840	2.778	3.020	2.700	2.810 ± 0.116
A_0	82.59	73.98	72.21	82.28	62.25	74.66 ± 7.50
$r >$	0.998	0.993	0.996	0.998	0.984	0.994 ± 0.005

K_a, apparent first-order constant; A_0, intercept slope.

Table 2
Mean values (±SD) of first-order rate constant and correlation coefficients ($n = 5$) found after intestinal perfusion of Albendazole (0.0025 mg ml^{-1}) in different solutions of Tween 5% and sodium taurocholate (5, 19, 38 and 57 mM)

Formulation	K_a (h^{-1}) (Mean ± SD)	r (Mean ± SD)
Tween 5% + taurocholate 5 mM	1.239 ± 0.077	0.986 ± 0.005
Tween 5% + taurocholate 19 mM	1.401 ± 0.120	0.975 ± 0.005
Tween 5% + taurocholate 38 mM	1.412 ± 0.030	0.985 ± 0.004
Tween 5% + taurocholate 57 mM	1.392 ± 0.190	0.995 ± 0.002

Tween at 5% are to be observed, there being no statistically significant differences, which clearly demonstrates that when Tween and STC are used together, Tween has the predominant effect, probably because of its greater micellization power.

All these results may be seen more clearly in Fig. 3, which shows that the use of taurocholate at 38 mM alone causes the absorption constant of ALB to rise significantly.

It is known that below the CMC, surfactants increase the absorption of insoluble drugs, but if the drug is included in the micelles the absorption could be decreased [11]. However, using bile salts above CMC, increased absorption constants have been observed [12].

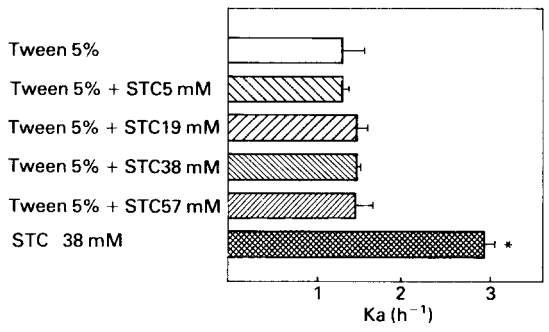

Figure 3
Albendazole absorption constants: summary of results (*, $P < 0.05$).

These studies were conducted at a concentration (38 mM) of bile salt which was the lowest concentration required to solubilize the Albendazol at the studied concentration. This concentration of STC (38 mM) was considerably greater than the CMC. Nevertheless, STC increases the absorption rate constant (K_a) of ALB in rat small intestine significantly when compared to Tween 5%.

These results can be explained in terms of the STC increasing the permeability of the membrane due to its interaction with the membrane phospholipids, which is known to affect drug absorption from the rat small intestine due to the local accumulation of drug on the absorptive surface. These high concentrations of taurocholate have been reported by other authors [12].

The effect that Tween shows is more pronounced on solubilization than STC (at the same conditions). When both surfactants were used, the prevailing effect was that due to Tween.

In summary, a better bioavailability of the ALB can be expected with STC, as well as a

possible decrease in dose and thence a possible reduction of secondary effects [13]. Further studies will be conducted in order to assess whether higher doses of taurocholate could improve the absorption of ALB.

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