The effect of dose form on the bioavailability of mebendazole in man

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Four different dose forms of mebendazole were administered to human volunteers, and urine was collected and assayed for mebendazole and unconjugated metabolites of mebendazole. Oral administration of mebendazole as an oily suspension slightly enhances the bioavailability of the drug, however mebendazole is not absorbed following rectal administration. The major urinary metabolite of mebendazole in humans is 2-amino-5(6)[α -hydroxybenzyl]benzimidazole (IV), not 2-amino-5(6) benzoylbenzimidazole (II), as previously reported.

Keywords mebendazole bioavailability formulation

Introduction

Mebendazole is a very insoluble drug widely used for the treatment of intestinal helminth infections. During the last decade it has been the subject of a considerable amount of research as an agent for the chemotherapy of echinococcosis.

The successful treatment of this disease with mebendazole requires that a sufficient quantity of the administered dose is absorbed to achieve therapeutic plasma concentrations. Such a concentration is estimated to be approximately 100 ng/ml (Witassek *et al.*, 1981; Bryceson *et al.*, 1982).

Although the poor solubility of mebendazole is advantageous in the treatment of intestinal helminth infections, this low solubility means that the drug is poorly bioavailable for the treatment of systemic infections.

We have examined the prodrug approach to drug delivery in an effort to improve the bioavailability of the compound (Dawson & Watson, 1983). In this investigation we examine the physical approach to the problem by calculating the relative bioavailability of four different formulations of mebendazole by analysis of urinary excretion data.

Methods

Mebendazole powder (I, Figure 1), Vermox® (100 mg tablets, and 2% suspension), were supplied by Janssen Pharmaceutica, Australia. The known metabolites of mebendazole, 2-amino-5(6)benzoylbenzimidazole (II, Figure 1), methyl-5 (6) [α -hydroxybenzyl]-2-benzimidazole carbamate (III, Figure 1) and 2-amino-5(6)[α -hydroxybenzyl]benzimidazole (IV, Figure 1) were synthesized as described previously (Dawson & Watson, 1983), with the exception that (IV) was made from alkaline hydrolysis of (III), not reduction of (II) as this procedure gives higher yields of (IV). The ethyl analogue of mebendazole, (V, Figure 1), was used as the internal standard in chromatographic analyses.

Subject selection

This study was carried out using 13 healthy male volunteers. The group had an average age of 24 years. None had a history of renal or hepatic disease, nor were any receiving any medication. All gave their written consent to take part in the study after all objectives and procedures had been fully explained to them.

Figure 1 The structures of mebendazole, (I); 2-amino-5(6)-benzoylbenzimidazole, (II); methyl-5(6) [α -hydroxybenzyl]benzimidazole carbamate, (III); 2-amino-5(6)[α -hydroxybenzyl]benzimidazole, (IV) and methyl 5(6)-benzoylbenzimidazole carbamate (V).

Protocol

At intervals of at least 1 week, each subject was administered five 100 mg Vermox® tablets, 25 ml of a 2% Vermox® suspension, and five gelatin capsules each containing 100 mg of mebendazole dispersed in 0.9 ml of olive oil. Six of the subjects were also dosed with a suppository containing mebendazole (500 mg) in a massupol base. Treatments were randomised and each oral dose was administered with a standard breakfast, as administration with food is reported to enhance the absorption of mebendazole (Münst *et al.*, 1980). Urine was collected from each subject for 36 h.

Urine assay

An aliquot of urine (5 ml) was spiked with 1.5 μ g of (V) as the internal standard, and the pH of the sample was adjusted to 11 with sodium hydroxide solution. The urine was extracted with 2×10 ml portions of ethyl acetate, the combined ethyl acetate layers were evaporated to dryness, and the residue was dissolved in 50 μ l of DMSO. Aliquots (20 μ l) were assayed by h.p.l.c. at each of the wavelengths 254 nm

and 280 nm. H.p.l.c. assays were carried out on an Altex model 322MP gradient elution high performance liquid chromatograph (Altex Scientific, Berkley, California), equipped with an ultraviolet detector (254 nm and 280 nm), a Hewlett-Packard model 3380A integrator/recorder (Hewlett-Packard, Avondale Pennsylvania, USA) and a Waters Intelligent Sample Processor model 710B (Waters Associates, Sydney Australia). Gradient elution analyses were carried out on a 250 mm $\times$ 4.6 mm i.d. chromatographic column packed in this laboratory with LiChrosorb® RP8 10 μ m packing material. The mobile phase consisted of methanol : distilled water 53:47, (pump A), and methanol : ammonium phosphate buffer (0.01 M), (pump B). The flow rate was 1.7 ml/min, which produced a column pressure of 104–107 bar. Analyses were commenced with pump A providing 100% of the mobile phase. After 7 min a curved gradient began which brought pump B up to 100% over a period of 5 min and held these conditions for 7 more min, at which time the column was pumped free of ions by passing 25 column volumes of electrolyte free mobile phase through the system.

Table 1 Mean and s.d. of the mean of urinary excretion data for volunteers dosed with various formulations of mebendazole.

Dose form	Dose excreted in urine (%)	Proportion of each compound expressed as a percentage of the total amount detected in the urine unconjugated			
		(I)	(II)	(III)	(IV)
T	1.43 ± 0.74	0.34 ± 0.37	12.38 ± 3.96	0.22 ± 0.22	87.06 ± 3.91
C	1.85 ± 0.79	0.34 ± 0.36	12.50 ± 4.76	0.22 ± 0.36	86.84 ± 5.13
S	1.33 ± 0.31	0.19 ± 0.17	11.93 ± 3.17	0.30 ± 0.33	87.58 ± 3.57

T = tablets, C = capsules, S = suspension.

Results and discussion

Table 1 shows the mean and s.d. of the mean of the percentage of the dose recovered from the urine as conjugated (I), (II), (III) and (IV). Also shown is the mean and the s.d. of the mean of the proportion of each compound detected in the urine as a percentage of the total amount of the dose excreted as unconjugated (I), (II), (III) and (IV). From Table 1 it can be seen that only a small proportion of the dose (1.33–1.85%) is excreted in the urine after oral administration of mebendazole.

Application of the paired *t*-test to the data relating to the percentage of the dose excreted as unconjugated (I), (II), (III) and (IV) in the urine shows that there is no difference between the amount excreted after administration of Vermox® tablets or suspension, but there is an increase in the amount excreted in the urine when mebendazole was dosed as the powder dispersed in oil, at the 5% level of significance.

The major unconjugated metabolite of mebendazole was (IV), 86%, with a smaller amount of (II), 12.6%, and only small amounts of (I) and (III) were detected. The pattern of metabolite excretion was not altered by administration of the different formulations. Neither mebendazole nor any metabolites of mebendazole were detected in the urine of those volunteers dosed with the suppository. The relative proportions of mebendazole and its metabolites detected in the urine of these volunteers after oral administration of the drug were similar to those found following administration of a tracer dose of mebendazole to another group of volunteers (Dawson *et al.*, 1984).

Administration of mebendazole dispersed in olive oil led to a 30% increase in the percentage of the dose excreted in the urine. This increase in bioavailability of mebendazole was probably due to the ability of the oil to aid dissolution, through solution of the drug in the oil, from which it is partitioned into the aqueous gastrointestinal contents. As the total volume of olive oil administered when mebendazole was dosed in this formulation was less than 5 ml, this small amount of oil probably would not cause a significant effect on the rate of stomach emptying.

As neither mebendazole nor metabolites of mebendazole were detected in the urine following rectal administration, absorption of the drug from this site is either very limited, or does not occur, and therefore is not a suitable site for administration of the drug.

There are two conclusions which may be drawn from this study: Firstly, an increase in bioavailability, and perhaps efficacy of mebendazole in the treatment of extraintestinal infections, may be obtained by investigation of alternative formulations of the drug. Secondly, the major urinary metabolite of mebendazole in humans is (IV) not (II) as previously reported (Van Wijngaarden, 1971; Brugmans *et al.*, 1971; Demoen *et al.*, 1973). That (IV) had not been reported as the major urinary metabolite of mebendazole may be due to the relatively low molar extinction coefficient of (IV) at the wavelengths commonly used for analysis of mebendazole and its metabolites, the similar chromatographic properties of (II) and (IV), and the low affinity of (IV) for the organic solvents commonly used to extract biological fluids.

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