The pharmacokinetics and bioavailability of a tracer dose of [³H]-mebendazole in man

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1 Five volunteers, whose ages ranged between 37 and 64 years, took part in a cross-over study to determine the pharmacokinetics and bioavailability of mebendazole in man following intravenous and oral administration of a tracer dose of [³H]-mebendazole.

2 Following intravenous administration, the average distribution half-life, elimination half-life and rate of clearance were 0.20 h, 1.12 h, and 1.063 min respectively.

3 After oral administration of the solution, the average elimination half-life was 0.93 h, the apparent rate of clearance was 0.846 l/min, the average time to peak plasma concentration was 0.42 h, and the bioavailability of mebendazole was 22%.

4 Comparison of metabolite area under the plasma concentration vs time data from each route of administration indicates that absorption of mebendazole from the gastrointestinal tract at this dose level is almost complete. The low bioavailability observed following oral administration at this dose level is postulated to be due to high first pass elimination.

5 Approximately half of the administered dose of radioactivity following intravenous and oral administration was detected in the urine, and the major unconjugated metabolite of mebendazole was found to be 2-amino-5(6) [α -hydroxybenzyl]benzimidazole (IV), not 2-amino-5(6)benzoylbenzimidazole (II), as previously reported.

Keywords mebendazole pharmacokinetics bioavailability

Introduction

Mebendazole was developed as an agent effective against luminal cestodes of the gastrointestinal tract of animals and man. Following the report of a toxic effect on the larval stage of *Hydatigera taeniaeformis* (Thienpont *et al.*, 1974), the drug was tested against the metacystode of *Echinococcus* species in laboratory animals and found to have a deleterious effect on those parasites (Heath & Chevis, 1974; Krotov *et al.*, 1974; Campbell *et al.*, 1974). Despite the poor solubility of the drug in aqueous solutions, it has subsequently been utilized for the medical treatment of alveolar and cystic hydatid disease (Schantz *et al.*, 1982).

More recently the efficacy of mebendazole in the treatment of onchocerciasis (Rivas Alcalá *et al.*, 1982), and eosinophilic meningoencephalitis (Ambu *et al.*, 1982) has been reported.

Investigations of the efficacy of mebendazole for larval echinococcal infections in the laboratory and clinical settings have been recently reviewed (Schantz *et al.*, 1982), and noted to be variable, one major problem being the limited knowledge of the clinical pharmacokinetics of the drug.

The principal publications reporting the clinical pharmacokinetics of the drug in patients treated for echinococcal infection have been

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limited in extent because no formulation of an intravenous injection has been available (Braithwaite *et al.*, 1982; Witassek *et al.*, 1981).

We have now formulated a solution of radiolabelled mebendazole and have utilized this solution to further define the pharmacokinetics of the drug in terms of bioavailability, half-life and extent of first pass effect following intravenous and oral administration, initially by a pilot study in a single volunteer (Dawson *et al.*, 1982) and now to a group of volunteers in separate studies 5 days apart.

Methods

Selection of subjects

Five subjects, all previously treated with mebendazole for cystic hydatid disease, volunteered to take part in the study. Informed consent was obtained from each subject and the study was approved by the Australian Department of Health and the Ethics Committee of the Department of Surgery, University of Tasmania. There were two males and three females whose ages ranged from 37 to 64 years. One patient was receiving chronic therapy for hypertension, but the other four received no drugs in the 7 days prior to or during the study.

Materials

[³H]-mebendazole (specific activity 6.24 Ci/mmol), [¹⁴C]-mebendazole (specific activity 2.57 mCi/mmol) and unlabelled mebendazole (Figure 1), were supplied by Janssen Pharma-

ceutica, Belgium. The known metabolites of mebendazole, 2-amino-5-(6)-benzoylbenzimidazole (II, Figure 1), methyl-5(6) [(α -hydroxybenzyl) benzimidazole carbamate (III, Figure 1) and 2-amino-5(6) [(α -hydroxybenzyl)benzimidazole (IV, Figure 1) were synthesized as described previously (Dawson & Watson, 1983).

Sterile mebendazole injection

[³H]-mebendazole was dissolved in an aliquot of DMSO, diluted with sterile normal saline to give a final concentration of 0.25% DMSO in the injection and passed through a 0.22 μ m sterile filter mounted in a sterile filtration apparatus. The resulting solution was mixed and again passed through the same filtration system (to ensure that the mixture was homogeneous, as mebendazole was found to bind to the filter), and dispensed into 10 ml ampoules which were sealed by fusion. Each ampoule contained 1.18 μ g of mebendazole (0.025 mCi). The above procedure was carried out in a laminar flow hood. Sterility testing of the injections was carried out according to guidelines laid down by the Australian Department of Health.

Plasma collection and assay

A 10 ml aliquot of the sterile solution was administered intravenously and blood samples were collected from the contralateral arm over an 8 h period. Five days later each patient was given a further 10 ml aliquot of the mebendazole solution orally in 250 ml of orange juice, and blood samples were again collected over an

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).

8 h period. Blood samples were stored on ice until they were centrifuged and the plasma transferred to another tube and stored at -20°C until assayed.

An aliquot of plasma was spiked with a known amount (approximately 800 d/min of [^{14}C]-mebendazole, as the internal standard, and 2 μg of each of mebendazole and its three metabolites so that the effluent corresponding to each compound could be visualized. The spiked plasma was then passed through a Sep Pak C18 which was washed with 20 ml of water. The drug and its metabolites were eluted by passing 5 ml of methanol through the cartridge. The methanol was evaporated to dryness and the residue was dissolved in 35 μl of DMSO, which was assayed as described previously (Dawson & Watson, 1983). The effluent corresponding to each of the eluted compounds was assayed for radioactivity by liquid scintillation counting.

Urine assay

An aliquot of urine (5 ml) was spiked with a mixture containing 5 μg of mebendazole and its three metabolites, 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, and the combined ethyl acetate layers were evaporated to dryness, and the residue dissolved in 50 μl of DMSO. A 20 μl aliquot was assayed by h.p.l.c., and the effluent corresponding to each of the eluted compounds was then assayed for radioactivity by liquid scintillation counting. The recovery of each compound in each sample was calculated from peak-height ratio standard curves. Quantitation of the amount of radioactivity in each urine sample associated with each compound was obtained by calculation of the recovery of each compound, and using the figure so generated to correct the d/min figure obtained from the liquid scintillation counter.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated using the appropriate formulae (Rowland & Tozer 1980) and statistical analyses were carried out using Student's *t*-test.

Results

The pharmacokinetic data obtained for mebendazole following an intravenous and oral tracer dose of the drug are presented in Table 1.

Table 1 Pharmacokinetic data for mebendazole obtained after intravenous and oral administration of the same dose of [^3H]-mebendazole.

	Patient code and mass (kg)					Mean $\pm$ s.d.
	DW (53)	LB (74)	LB (65)	JA (60)	JT (108)	
AUC _{i.v.} (pg ml ⁻¹ h)	30.14	18.93	30.12	23.49	10.27	22.68 $\pm$ 8.18
<i>t</i> _{1/2α i.v.} (h)	0.23	0.25	0.20	0.18	0.13	0.20 $\pm$ 0.05
<i>t</i> _{1/2β i.v.} (h)	1.07	0.83	1.35	0.98	1.36	1.12 $\pm$ 0.24
<i>V</i> _{i.v.} (l/kg)	1.142	0.998	1.176	1.186	1.998	1.230 $\pm$ 0.40
CL (l/min)	0.654	1.040	0.645	0.831	1.831	1.063 $\pm$ 0.45
AUC _{po} (pg ml ⁻¹ h)	3.75	2.64	6.69	6.37	3.73	4.63 $\pm$ 1.79
<i>t</i> _{1/2,α po} (h)	0.88	0.65	1.22	0.73	1.14	0.93 $\pm$ 0.25
<i>t</i> _{max po} (h)	0.50	0.52	0.52	0.28	0.30	0.42 $\pm$ 0.12
CL _{po} (l/min)	0.533	0.833	0.548	0.706	1.563	0.846 $\pm$ 0.424
<i>F</i>	0.12	0.14	0.22	0.27	0.35	0.22 $\pm$ 0.09

Following intravenous administration, mebendazole was rapidly distributed and rapidly eliminated (Figure 2). The average distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$) and rate of clearance (CL) were 0.2 h, 1.12 h and 1.063 l/min respectively.

Figure 2 The variation of plasma concentration vs time of mebendazole (I, ●), and its metabolites (II, ○), (III, ◆) and (IV, □), following i.v. administration of a tracer dose of [^3H]-mebendazole to a volunteer (LB). (100 d/min = 1.43 pg of mebendazole).

After oral administration mebendazole was rapidly absorbed and rapidly eliminated (Figure 3). The average time to peak plasma concentration and average elimination half-life ($t_{1/2\text{zpo}}$) were 0.42 h and 0.94 h respectively. The average bioavailability of mebendazole from the solution was 22%, and the average oral rate of clearance (CL_{po}) was 0.846 l/min.

Table 2 shows the AUC and the elimination half-lives of (II) and (III) following both routes of administration. Also shown is the ratio $\text{AUC}_{\text{po}}/\text{AUC}_{\text{i.v.}}$, the average value for this ratio for both metabolites was approximately unity. $\text{AUC}(0, t)$ for (IV) is also recorded.

Tables 3 and 4 present urinary excretion data. Approximately 50% of the dose was eliminated in the urine during the 24 h following intravenous and oral dosage. The major unconjugated metabolite of mebendazole detected in the urine was (IV), with smaller

Figure 3 The variation of plasma concentration vs time of mebendazole (I, ●), and its metabolites (II, ○), (III, ◆) and (IV, □), following oral administration of a tracer dose of [^3H]-mebendazole to a volunteer (LB). (100 d/min = 1.43 pg of mebendazole).

amounts of (II) and very small amounts of mebendazole and (III).

Discussion

The results of this tracer dose study in patients with a history of cystic hydatid disease compare favourably with those obtained from a pilot study (Dawson *et al.*, 1982), in a young healthy volunteer.

No absorption phase was noted following oral administration in the pilot study, however sampling was commenced earlier in this investigation, and an absorption phase was noted in all subjects. These data suggest that mebendazole at this dose level is rapidly absorbed and rapidly eliminated. Other studies (Münst *et al.*, 1980; Witassek *et al.*, 1981; Braithwaite *et al.*, 1982) in which longer half-life values (2–8 h) were observed, used large oral doses of mebendazole (*ca.* 0.5 g), and probably measured the absorption half-life rather than the elimination half-life.

It is impossible to estimate the extent of absorption from the pharmacokinetic data of a drug if it is subject to a first pass effect.

Table 2 Metabolite data obtained after intravenous and oral administration of the same dose of [^3H]-mebendazole.

	Patient code					Mean $\pm$ s.d.
	DW	LW	LB	JA	JT	
AUC _{i.v.} (pg ml ⁻¹ h)	29.11	26.12	22.06	37.97	18.58	26.77 $\pm$ 7.43
$t_{1/2,z}(\text{II})$ (h)	2.24	2.00	2.93	4.22	3.14	2.91 $\pm$ 0.87
AUC _{po(II)} (pg ml ⁻¹ h)	33.59	20.19	25.65	39.03	18.07	27.31 $\pm$ 8.88
$t_{1/2,zpo}(\text{II})$ (h)	2.19	2.66	2.28	2.97	3.08	2.64 $\pm$ 0.40
$\frac{\text{AUC}_{po(\text{II})}}{\text{AUC}_{i.v.(\text{II})}}$	1.15	0.77	1.16	1.03	0.97	1.02 $\pm$ 0.16
AUC _{i.v.(III)} (pg ml ⁻¹ h)	35.56	24.45	41.79	23.65	21.38	29.37 $\pm$ 8.85
$t_{1/2,z}(\text{III})$ (h)	2.48	1.95	2.65	3.36	2.85	2.66 $\pm$ 0.52
AUC _{po(III)} (pg ml ⁻¹ h)	26.78	25.45	32.33	25.71	24.57	26.97 $\pm$ 3.10
$t_{1/2,zpo}(\text{III})$ (h)	2.23	2.29	1.83	2.73	3.01	2.42 $\pm$ 0.46
$\frac{\text{AUC}_{po(\text{III})}}{\text{AUC}_{i.v.(\text{III})}}$	0.75	1.04	0.77	1.09	1.16	0.96 $\pm$ 0.19
AUC _{i.v.(IV)} (pg ml ⁻¹ h)	ND*	5.94	5.04	ND	3.47	4.82 $\pm$ 1.25
AUC _{po(V)} (pg ml ⁻¹ h)	ND	3.21	3.33	ND	3.83	3.46 $\pm$ 0.33

*ND = not determined

However, a measure of the amount absorbed may be obtained from metabolite data, because if the whole of the dose is absorbed, and if no metabolites formed as a result of metabolism of the oral dose form in the gastrointestinal tract enter the systemic circulation, the metabolite AUC following both oral and intravenous administration should be equal Alvan *et al.*, 1977).

Development of the analytical technique allowed quantitative estimates of the concentration of (II) and (III) in the plasma of each subject in this study to be determined. These two metabolites were also detected in the plasma following administration of therapeutic doses of mebendazole. Compound (IV) was detected in the plasma of the subjects in this study, but the levels were low, and it was not possible to determine the elimination half-life; only AUC(0,t) data, where determined, are presented.

From Table 2 it is apparent that there is no significant difference between the plasma AUC

following intravenous and oral administration, for the metabolites (II) and (III). This provides evidence that the whole of the dose was absorbed, and that the low levels of mebendazole observed following oral administration at this dose level are probably due to the drug being metabolized before it reaches the systemic circulation. Witassek *et al.* (1983) reported that impaired liver function can result in higher plasma mebendazole levels in patients treated with the drug.

The calculated bioavailability of 22% has a range of 12–35%. This large variation may be attributed to variability of the activity of microsomal enzymes between subjects, as Witassek & Bircher (1983) concluded that 'the microsomal function of the liver and/or cholestasis may be important determinants for mebendazole plasma levels'.

Comparison of urinary excretion data supports the hypothesis that the whole of the dose of mebendazole (at this dose level) is absorbed. The amounts of radioactivity excreted in the

Table 3 Urinary excretion data following intravenous and oral administration of [³H]-mebendazole.

Intravenous administration	Patient code					Mean ± s.d.
	DW	LW	LB	JA	JT	
(I) %	0.06	0.09	0.11	0.13	0.08	0.09 ± 0.03
(II) %	1.29	0.83	1.38	0.70	2.12	1.26 ± 0.56
(III) %	0.11	0.10	0.18	0.30	0.14	0.17 ± 0.08
(IV) %	9.03	8.81	7.94	5.76	5.62	7.43 ± 1.64
Total (I)–(IV) %	10.49	9.83	9.61	6.89	7.96	8.96 ± 1.48
Unidentified %	39.07	38.68	46.56	34.41	37.95	39.33 ± 4.44
Total dose in urine %	49.56	48.51	56.17	41.30	45.91	48.29 ± 5.44
<i>Oral administration</i>						
(I) %	0.10	0.10	0.09	0.07	0.07	0.09 ± 0.01
(II) %	1.43	0.93	2.64	0.71	2.32	1.61 ± 0.85
(III) %	0.22	0.16	0.14	0.11	0.11	0.15 ± 0.05
(IV) %	9.70	9.62	8.94	5.92	5.68	7.97 ± 2.00
Total (I)–(IV) %	11.45	10.81	11.81	6.81	8.18	9.81 ± 2.20
Unidentified %	40.46	43.08	38.90	31.36	40.54	38.87 ± 4.46
Total dose in urine %	51.91	53.89	50.71	38.17	48.72	48.68 ± 6.17

urine, and the unconjugated metabolite excretion patterns were similar following intravenous and oral dosage (Tables 3 and 4). The relative proportions of (I), (II), (III) and (IV) excreted in the urine are also similar to those observed following therapeutic doses of the drug (Dawson & Watson, 1985).

The low concentrations of (IV) detected in the plasma compared with the relatively large amount observed in the urine, suggest that this compound is either rapidly cleared by the kidney, or is a product of renal metabolism.

It was possible to account for only 20% of the radioactivity in the urine as unconjugated mebendazole and metabolites, and further attempts to recover more unconjugated metabolites by enzymatic hydrolysis were unsuccessful.

The availability of intravenous plasma concentration vs time data for mebendazole allows an estimate of the bioavailability of mebendazole at therapeutic doses to be calculated. Braithwaite *et al.* (1982) administered mebendazole to patients at the dose level of 10 mg/kg,

and using the predictive equations of Ritschel & Hammer (1980), estimated mebendazole to have a bioavailability of about 0.6%, following an initial oral dose.

By substituting the average AUC and dose data for mebendazole reported by these authors, and the intravenous AUC and dose data from the tracer dose study into Equation 1

$$F = \frac{AUC_{po}}{AUC_{i.v.}} \cdot \frac{Dose_{i.v.}}{Dose_{po}} \quad \text{Equation (1)}$$

a figure of 2.1% is obtained for the relative bioavailability of mebendazole at therapeutic dose levels. Although this value is higher than that reported by the above mentioned authors, it reflects the widely held view that mebendazole has a very low bioavailability.

Three of the subjects participating in this tracer dose study, also participated in that portion of the investigation of Braithwaite *et al.* (1982) which involved the collection of plasma concentration vs time data of (I), (II) and (III) for a single dose interval from patients

Table 4 The average (± s.d.) amounts of compounds (I)–(IV) excreted unchanged in urine expressed as a percentage of the total amount excreted unchanged following an intravenous and oral dose of [³H]-mebendazole.

Route of administration	(I)	(II)	(III)	(IV)
Intravenous	1.09 ± 0.46	14.37 ± 7.20	2.04 ± 1.34	82.90 ± 7.18
Oral	0.88 ± 0.09	16.09 ± 8.70	1.49 ± 0.28	81.54 ± 8.28

Table 5 The ratios of metabolite and mebendazole AUC data at therapeutic and tracer dose levels.

	LW	Patient code LB	JA
$AUC(0,t)$ (I)*	0.23	0.22	0.28
$AUC(0,t)$ (II)			
$AUC(0,t)$ (I)†	0.13	0.26	0.16
$AUC(0,t)$ (II)			
$AUC(0,t)$ (I)*	0.09	0.14	0.27
$AUC(0,t)$ (III)			
$AUC(0,t)$ (I)†	0.10	0.27	0.28
$AUC(0,t)$ (III)			

*Data from Braithwaite *et al.* (1982)

†Data from Table 2

on chronic mebendazole therapy. Using these data and the tracer dose data obtained from the three volunteers LW, LB and JA, the bioavailability of mebendazole at therapeutic dose levels in each patient was calculated to be 2.9%, 3.6% and 4.4% respectively. These estimates compare well with the estimate of the bioavailability of 2.1% calculated from the average plasma concentration *vs* time data presented by Braithwaite *et al.* (1982) for patients receiving an initial oral dose of mebendazole of 10 mg/kg discussed above.

It is interesting to note that the highest calculated bioavailability was observed in the subject who received the lowest dose (JA; mass 63 kg). This may be coincidental or it may be a reflection of the fact that the patients in the 1982 study were dosed on a mg/kg basis, and such a trend would be expected if the fraction of the dose absorbed decreased as the amount of drug administered was increased.

A comparison of the ratio $AUC(0,t)$ for the metabolites (II) and (III) to the $AUC(0,t)$ for mebendazole at therapeutic dose levels, with the equivalent ratios at tracer dose levels is presented in Table 5.

Although it is difficult to draw any firm conclusions from the data in Table 5, it appears that there are no gross differences between the ratios of mebendazole to each metabolite at the two dose levels examined. This may be interpreted as meaning that the metabolic profile of mebendazole is similar at therapeutic and tracer dose levels; that is a change in dose level of over six orders of magnitude.

A second measure of both the metabolic fate of mebendazole at therapeutic dose levels, and an estimate of the bioavailability of mebendazole may be obtained by consideration of the urinary excretion data presented by Dawson & Watson (1985). Following oral administration

of a single dose of mebendazole (five 100 mg Vermox® tablets), an average of 1.4% of the dose was excreted unconjugated in the urine. Of this amount, 0.4 was excreted as mebendazole, 12.4% as (II), 0.2% as (III) and 87.0% as (IV). Comparison of these data with that in Table 2 shows that the relative amounts of mebendazole and its metabolites excreted in the urine following trace and therapeutic doses are similar.

An interpretation of this data is that, increasing the dose of mebendazole from the tracer dose level to the therapeutic dose level does not lead to alteration in the metabolic fate of mebendazole. If this assumption is valid, it can be seen (Table 3) that an average bioavailability of 22% results in 9.8% of the dose being excreted unchanged in the urine. By direct proportions, if 1.4% of the dose is excreted unconjugated in the urine, the relative bioavailability of mebendazole at therapeutic dose levels is calculated to be 3.3%.

This figure compares favourably with the estimate of 2.1% for bioavailability of mebendazole at therapeutic dose levels using the plasma data of Braithwaite *et al.* (1982) and the tracer dose plasma data. A slightly higher value was expected on theoretical considerations, since the average dose administered in the urinary excretion study (Dawson & Watson, 1985) was 6.7 mg/kg, compared with 10 mg/kg administered by Braithwaite and co-workers, as the relative bioavailability of mebendazole, like all insoluble drugs, would be expected to decrease with increasing dose.

The results of this study indicate that the poor bioavailability of mebendazole observed at therapeutic dose levels, is due to a combination of high first pass elimination and the very low solubility of the compound.

Modification of the dose form rather than administration of large doses of the drug may be a more rational method of increasing plasma levels, as the absorption of the drug from the gastrointestinal tract is probably dissolution-rate limited.

Further research work in this area is necessary, as is the development of procedures whereby the efficacy of mebendazole in the treatment of extra-intestinal infections can be related to plasma, tissue and parasite concentrations of the drug.

We are most grateful to Mr Warren Olsen of the Department of Pharmacy, University of Sydney, for valuable discussion, and to the Ramaciotti Foundation for financial support for this study.

The clinical portion of this study was carried out in the Department of Surgery, University of Tasmania.

We thank Janssen Pharmaceutica, Belgium, for the radiochemicals used in this study.

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(Received July 10, 1984,
accepted September 23, 1984)