Eur J Clin Pharmacol (1990) 38: 605–608

European Journal of Clinical Pharmacology

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Albendazole kinetics in patients with echinococcosis: Delayed absorption and impaired elimination in cholestasis

J. Cotting, T. Zeugin, U. Steiger, and J. Reichen

Department of Clinical Pharmacology, University of Berne, Switzerland

Received: October 11, 1989/Accepted in revised form: November 29, 1989

Summary. The pharmacokinetics of albendazole and its main metabolite, albendazole sulphoxide, have been examined after giving a single oral dose of 200 mg albendazole to 19 patients with either *Echinococcus multilocularis* or *E. granulosus,* 5 of whom had significant extrahepatic obstruction due to the underlying disease. The AUC of albendazole sulphoxide was increased in the latter patients (mean 122 $\mu mol \cdot h \cdot l^{-1}$ compared to 17 $\mu mol \cdot h \cdot l^{-1}$ in the non-obstructed group). Obstructed patients had delayed absorption, k_a averaging 0.39 compared to 1.41 h^{-1} in non-obstructed patients. The corresponding elimination rate constant, k_e was also prolonged, averaging 0.041 and 0.13 h^{-1} in the two groups, respectively. Four patients were restudied after complete or partial resolution of the cholestasis. The pharmacokinetic parameters in them had returned towards values comparable to those in the non-obstructed patients.

Key words: albendazole; albendazole sulphoxide, absorption, elimination, benzimidazole, pharmacokinetics, echinococcosis, cholestasis

Albendazole, a benzimidazole derivative with broad spectrum anthelmintic activity, may be superior to mebendazole in the treatment of echinococcosis in man [1, 2]. The postulated reason for this is that its principal metabolite albendazole sulphoxide, which is believed to be the active agent, achieves a much higher level in the cysts, namely about one fifth or more of the serum concentration after prolonged therapy [3]. This is thought to be a consequence of a better absorption of albendazole and of its extensive first pass metabolism to albendazole sulphoxide, which makes it almost impossible to find measurable levels of the parent drug albendazole. Albendazole sulphoxide is parasitostatic as judged by its in vitro effects on the viability of hydatid protoscolices [4].

The metabolism of albendazole in animals is well documented: Gyurik et al. [5] identified 9 metabolites in urine from cattle, sheep, rats and mice. In all species the main metabolite in urine was albendazole sulphoxide, the pattern of other metabolites being species-specific. Bioactivation of albendazole to albendazole sulphoxide has also been demonstrated with human microsomes [6].

Table 1. Details of the 19 patients studied. Group I contained patients with no evidence of cholestasis and Group II refers to patients with obstructive jaundice

Patient (E.g./E.a.)	no.	age (y)	sex	body weight (kg)	*E. granulosus* *E. alveolaris*	Mebendazole Pretreatment	Ethanol consumption[a]	Other drugs[b]
Group I:	1	25	f	62	E.g.	+	–	Amoxicillin, Gentamicin
	2	45	m	57	E.g.	+	+	–
	3	25	m	61	E.g.	–	+	–
	4	31	m	66	E.g.	–	–	–
	5	60	m	83	E.a.	+	+	Amoxicillin, Clavulanic acid
	6	64	m	76	E.a.	–	–	Propranolol
	7	58	f	76	E.a.	+	–	Astemizol
	8	32	m	89	E.g.	–	+	Atenolol
	9	32	m	77	E.g.	+	–	–
	10	40	m	88	E.g.	+		–
	11	54	m	93	E.a.	–	+	–
	12	37	f	76	E.a.	+	–	–
	13	38	m	87	E.a.	–	–	–
	14	48	f	53	E.a.	+	–	–
Group II:	15	48	m	60	E.a.	–	–	Diazepam, Cholestyramine
	16	62	m	74	E.a.	+	–	Ceftriaxone
	17	70	m	82	E.g.	+	–	Ceftriaxon, Gentamicin
	18	35	f	70	E.a.	–	–	Oxatomid
	19	41	f	42	E.a.	+	–	Metronidazole, Ceftriaxone

[a] – = < 30 g/day; + = > 30 g/day

[b] within last 7 days before kinetic study

Table 2. Clinical biochemistry findings in Group I (no cholestasis), Group II (obstructive jaundice) and Group III (patients of Group II after relief of obstruction)

Patient no.		Units normal range	AST (U/l) 0–27	AP (U/l) 30–90	Bilirubin (μmol/l) 3.4–26	Serum albumin (g/l) 32–52	Creatinine (μmol) 59–116
Group I	1		14	46	5	nd	64
	2		21	87	10	36	59
	3		8	no	no	nd	72
	4		14	52	7	37	82
	5		28	94	7	35	89
	6		11	79	12	32	82
	7		12	76	9	31	72
	8		12	101	9	33	113
	9		37	67	14	36	97
	10		14	64	8	37	92
	11		26	79	11	33	97
	12		28	52	15	34	75
	13		14	39	10	40	83
	14		12	59	9	37	88
Group II	15		29	359	201	30	59
	16		184	869	140	19	50
	17		46	189	389	27	82
	18		81	168	151	24	68
	19		67	222	179	29	50
Group III	15		17	52	16	nd	86
	17		22	100	11	33	80
	18		12	108	6	34	56
	19		33	347	71	27	45

In contrast there are few data available on the pharmacokinetics of albendazole in man [7–9]. Its bioavailability is increased when it is administered together with a fatty meal [7, 8], suggesting an absorption mechanism requiring bile. Cholestasis has been shown to increase the plasma level of mebendazole [10]. Therefore, the effect of cholestasis on the pharmacokinetics of albendazole and its main metabolite, albendazole sulphoxide, have now been investigated.

Materials and methods

Patients

Nineteen consecutive patients (6 females and 13 females) with serologically and radiologically confirmed cystic ($n = 7$) or alveolar ($n = 12$) echinococcal disease were included in the study. Their details are given in Tables 1 and 2. Eleven patients had previously undergone treatment with mebendazole (Table 1). That drug had been stopped at least 1 week before the study. Ten of the 19 patients had undergone surgery for the underlying disease. The estimated daily alcohol consumption was less than 30 g/day except in 5 patients (Table 1). All patients had normal renal function at the time of study. The patients were classified into three groups by radiological (CT-scan, sonography and other diagnostic procedures) as well as by laboratory findings:

Group I. 14 patients (mean (SD) 42 (13) y) with no evidence of major obstruction. Radiology revealed no intra- or extrahepatic bile duct dilatation except in Patients 6 (post left hepatic resection) and 7 (post right hemihepatectomy), who had slight intrahepatic dilatation of the small bile ducts, but without biochemical evidence of cholestasis.

Group II. 5 patients (mean age 51 (15) y) with significant extrahepatic obstruction due to *E. multilocularis* or *E. granulosus* documented by different radiological techniques. In Patient 15 an endoscopic cholangiogram (ERCP) and CT-scan had revealed stenosis of the common hepatic duct. Patient 16 had obstruction of the distal common bile duct due to parasitic debris and compression at the hilus, documented by CT scan, sonography and percutaneous cholangiogram (PTC). In Patient 17 compression at the hilum of the liver due to a cyst and obstruction of the common bile duct by parasitic debris was shown by ERCP and CT-scan. Patient 18 had obstruction of the left and stenosis of the right hepatic duct (ERCP, biliary scintigraphy, CT). Patient 19 had stenosis at the hilus (ERCP, CT, biliary scintigraphy) after left hemihepatectomy. The further evolution of the disease in these patients is described in the definition of Group III:

Group III. 4 of the 5 patients in Group II were restudied after complete ($n = 3$) or partial ($n = 1$) resolution of the obstruction. Clearance of the obstruction was seen after albendazole treatment alone in Patients 15 and 18. In Patient 17 resolution of the obstruction was achieved by surgical drainage of the cyst and biliodigestive anastomosis. In Patient 19 partial resolution was obtained by a biliodigestive anastomosis, but with persisting segmental intrahepatic obstruction indicated by laboratory and radiological findings. Patient 16 had died from the underlying disease and could not be restudied. The interval between the first and the second kinetic studies in Patients 15, 17, 18 and 19 was 5.5, 2, 3 and 8.5 months, respectively.

Experimental design

Informed consent was obtained from all patients. The study was approved by the Ethics Comittee of the Faculty of Medicine, University of Berne. In all except one patient the study was performed before the first cycle of anthelmintic treatment with albendazole.

No drugs were taken on the day of the study, except for antibiotics by 5 patients. Drugs administered within the last 7 days before and/or during the study are listed in Table 1. After an overnight fast

Table 3. Pharmacokinetics of albendazole sulphoxide in Group I (non-cholestatic patients), Group II (obstructive jaundice) and Group III patients

Patient	no.	AUC (μmol · h · l^{-1})	$t_{1/2a}$ (h)	$t_{1/2el}$ (h)	C_{max} (μmol · l^{-1})	t_{max} (h)
Group I	1	4	0.9	1.8	0.79	4.0
	2	4	0.6	2.3	0.82	1.5
	3	4	0.6	3.0	0.69	1.5
	4	8	0.8	5.8	1.34	1.0
	5	12	1.1	5.0	1.36	2.5
	6	14	0.7	13.0	1.01	2.5
	7	16	0.5	7.3	1.99	3.5
	8	18	0.2	10.2	1.24	1.7
	9	20	0.1	14.3	1.67	2.5
	10	21	0.9	8.1	1.57	4.0
	11	22	0.6	9.5	1.38	2.0
	12	28	1.6	6.7	2.10	6.0
	13	29	0.5	25.0	0.84	4.0
	14	34	0.9	7.3	3.27	3.5
mean (SD)		17 (10)	0.7 (0.4)	8.5 (6.0)	1.43 (0.69)	2.9 (1.3)
Group II	15	46	2.2	7.0	2.73	10.0
	16	75	5.8	27.7	1.38	18.0
	17	86	1.7	50.1	1.26	5.0
	18	186	1.6	13.0	8.00	7.0
	19	218	1.0	60.9	2.35	10.0
mean (SD)		122 (75)	2.5 (1.9)	31.7 (23.3)	3.14 (2.79)	10.0 (4.9)
Group III	15	12	0.8	7.5	1.06	1.0
	17	18	0.4	12.2	1.03	2.5
	18	36	0.9	8.5	3.28	1.5
	19	37	3.2	7.2	2.66	10.0
mean (SD)		26 (12)	1.3 (1.3)	8.9 (2.3)	2.01 (1.14)	3.8 (4.2)

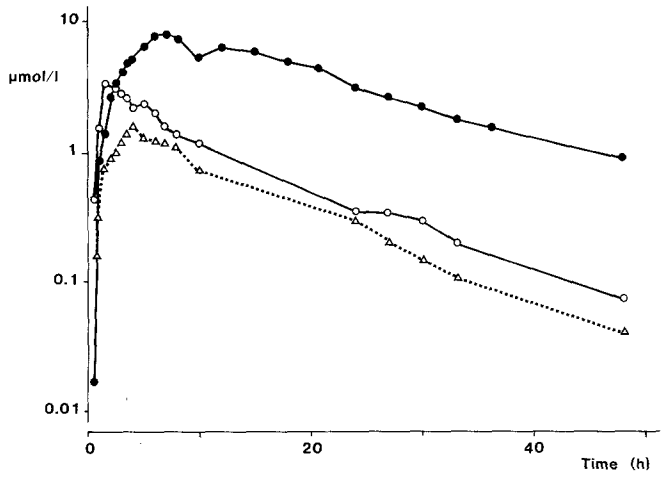

Fig. 1. Albendazole sulphoxide levels in plasma after oral administration of 200 mg albendazole to a non-obstructed patient (No. 1, (Δ) and to Patient 18 during (•) and after resolution (○) of biliary obstruction

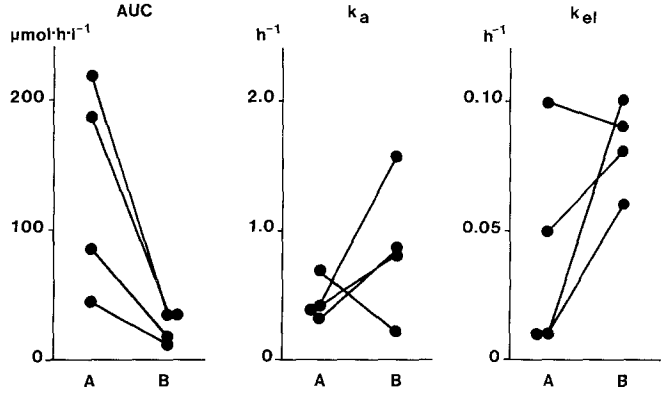

Fig. 2. Effect of obstruction and its relief on AUC, k_a and k_{el} of albendazole sulphoxide. Only the change in AUC reached statistical significance ($P < 0.05$)

an indwelling catheter was placed in a cubital or forearm vein and a blank blood sample was obtained in a heparinized tube. Then, a single oral dose of 200 mg albendazole was administered together with a standard breakfast containing coffee, bread, butter and marmalade, supplemented with fat (50 ml cream) to increase absorption [8]. Consecutive blood samples were collected as far as possible every 30 min up to 4 h, and then at 5, 6, 7, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33 and 48 h. Blood samples were centrifuged and kept frozen at −20 °C until analysed.

Analytical procedures

Analysis was carried out as previously described [11]. Briefly, after three-fold extraction with ethyl acetate and petroleum ether, the samples were dissolved in the mobile phase and injected into a RP-C18 column. The mobile phase consisted of a 75% mixture of 232 µl H_3PO_4 85% in H_2O 1 l and 25% of a mixture or acetonitrile and methanol (560:190). UV detection at 290 nm was employed. Quantitation of albendazole and albendazole sulphoxide was achieved by integration using the ratio of the area of albendazole sulphoxide to the internal standard (ciclobendazole). Interday-reproducibilities were 14.5%, 7.3% and 9.1% at concentrations of albendazole sulphoxide of 0.5, 2.5 and 5.0 µmol·l^{-1}, respectively [11].

Data and statistical analysis

Groups II and III were compared by a paired *t*-test and the means of those groups by Student's *t*-test [12]. k_a, $t_{1/2a}$, k_{el} and $t_{1/2el}$ were tested after logarithmic transformation, since only that gave equal probabilities for $t_{1/2}$ and k. All values are given as mean (SD). The level of significance was set at $P < 0.05$.

The pharmacokinetics of albendazole sulphoxide was calculated using an open one compartment model; the kinetic parameters were estimated using PKCALC [13] on an IBM-AT computer.

Results

An example of a typical study is given in Fig. 1, and the pharmacokinetic parameters are summarized in Table 3. In Group I, the group with no evidence of major obstruction, the total area under the plasma concentration-time curve (AUC) of albendazole sulphoxide averaged 17 [10] µmol·h·l^{-1}; the absorption rate constant, k_a, was 1.41 (1.19) h^{-1}; the elimination constant, k_{el}, averaged 0.13 (0.11) h^{-1}, and the corresponding elimination half-life was 8.52 (6.02) h.

Comparison of the findings in the obstructed patients (Group II) with Group I revealed the following differences: the AUC of albendazole sulphoxide was increased by 618% ($p < 0.0001$); and the absorption rate constant, k_a, was 72% lower than in the controls 0.39 (0.20) h^{-1}, and accordingly t_{max} was prolonged by 70% ($p < 0.0001$). The elimination rate constant averaged 0.041 (0.037) h^{-1}, about one-third of the value in non-obstructed patients. Elimination half-life values varied widely and there was overlap between non-obstructed and obstructed patients (Table 3).

Four patients were examined after resolution of the obstruction (Fig. 2). The total AUC after resolution of the obstruction decreased to 26 (12) µmol·h·l^{-1} ($p < 0.03$), corresponding to 21 (5)% of the AUC whilst obstructed. Three of the 4 patients showed more rapid absorption (k_a: 0.87 (0.56) h^{-1}) and a decrease in the elimination constant to 0.08 (0.02) h^{-1}. These data failed to reach statistical significance.

The parent compound, albendazole, was only measurable in Patient 18 during cholestasis. In no other subject could albendazole be detected, due to its rapid metabolism to albendazole sulphoxide. The metabolite of albendazole sulphoxide, albendazole sulphone, could only be detected in trace amounts.

Discussion

The study has demonstrated that the pharmacokinetics of albendazole sulphoxide, the major and active metabolite of the anthelmintic albendazole, can adequately be described by a one compartment model, with average absorption and elimination half-lives of 0.7 and 8.5 h, respectively. Extrahepatic obstruction significantly prolonged both processes, resulting in doubling of the maximum serum concentration.

Albendazole undergoes high first pass extraction and rapid and apparently complete metabolism to albendazole sulphoxide in man [7, 8]. Consequently, in the present study albendazole could not be detected in plasma, except in one subject with severe obstruction and an extremely high level

of albendazole sulphoxide. Therefore, the absorption of albendazole and its metabolism to the sulphoxide were combined into one parameter, k_a. This seemed justified by the absence of the parent compound and the adequacy of the fit to the one compartment model.

In agreement with the three previous reports [7–9], both k_a and k_{el} of albendazole sulphoxide exhibited marked interindividual variability. Whether this was related to pharmacogenetic polymorphism for sulphoxidation [14] remains unclear; the sulphoxidation of albendazole to its sulphoxide appears to be mediated by a microsomal, non-cytochrome P-450-dependent mechanism [15], while the sulphoxidation polymorphism is thought to be due to a cytosolic enzyme [16].

The significant increase in the AUC of albendazole sulphoxide in patients with biliary obstruction demonstrates that metabolic activation of albendazole to the sulphoxide in obstructed individuals was not markedly impaired. The plasma levels in those patients were considerably higher than in the others. Whereas higher levels of mebendazole have been described in patients with cholestasis [10], this phenomenon does not appear previously to have been reported for albendazole.

Marriner et al. were the first to note that a fatty meal improved the absorption of albendazole [7], and this was formally proven by Lange et al. [8]. The observation here that the absorption half-life was significantly prolonged in patients with extrahepatic cholestasis suggests that bile is required for the rapid absorption of albendazole.

The reason for the prolonged elimination in obstruction remains uncertain. Biliary concentrations of albendazole and its sulphoxide are very low [7], so failure of biliary excretion appears unlikely as the explanation. Extrahepatic obstruction is known to affect drug metabolism in man [17, 18], and is the most likely explanation for the decreased elimination of albendazole sulphoxide in the obstructed patients. The fact that resolution of the obstruction was associated with virtual normalization of the pharmacokinetics of albendazole sulphoxide (Fig. 1) also argues for an obstruction-related impairment in drug metabolism.

Only small amounts of the sulphone could be detected in plasma from the present patients after a single dose. In later treatment cycles, however, the sulphone amounted to as much as 25% of albendazole sulphoxide (data not shown), in agreement with others [2, 3].

In conclusion, the absorption of albendazole appears to depend on an intact enterohepatic circulation. Activation to its main active metabolite, albendazole sulphoxide, occurs rapidly, with marked individual variability, and is not impaired in biliary obstruction. Extrahepatic cholestasis is associated with markedly impaired elimination of albendazole sulphoxide. This, as well as the variability in pharmacokinetics, emphasize the need for careful monitoring to prevent severe side effects of albendazole.

Acknowledgements. We acknowledge the expert technical assistance of Ms. Ch. Talos and R. Stuber and the nursing assistance of Ms. M. Currado and I. Nünlist. We are grateful to Ms. M. Kappeler for the artwork and to Ms. V. Bidar for her secretarial assistance. The work was supported by the Swiss National Foundation, (32-9365.87). JR was the recipient of a RCDA of the SNF (3.731.0.87). Albendazole was generously provided by Dr. R. J. Horton, Director Worldwide Products Groups, Smith, Kline and French Laboratories, Hertfordshire, England.

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Prof. J. Reichen
Department of Clinical Pharmacology
University of Berne
Murtenstraße 35
CH-3010 Berne
Switzerland