# Albendazole treatment of echinococcosis in humans: Effects on microsomal metabolism and drug tolerance

**We prospectively studied the effect of albendazole on microsomal reserve and on first-pass activation to albendazole sulfoxide in patients with hydatid disease. An aminopyrine breath test was performed in 12 patients while they were receiving albendazole treatment and while they were not. Excretion of $^{14}CO_2$ in breath averaged 0.70% · kg · mmol$^{-1}$ ± 0.20% · kg · mmol$^{-1}$ without treatment and 0.54% · kg · mmol$^{-1}$ ± 0.14% · kg · mmol$^{-1}$ with treatment ($p < 0.005$). Plasma levels of albendazole sulfoxide were measured 4 hours after the morning dose during the first and second half of the 4-week treatment cycles. In nine of the 12 patients albendazole sulfoxide levels decreased during the second half of the cycle by an average of 0.84 ± 0.76 μmol/L ($p < 0.02$). Transaminase levels increased in 10 of the 12 patients during long-term albendazole treatment, and major side effects, including hepatotoxicity, neutropenia, and alopecia, were observed in three patients. We conclude that albendazole partially inhibits microsomal enzyme function but induces its own metabolism. Hepatotoxicity and other possible severe side effects necessitate close therapeutic monitoring of patients who are given albendazole. (CLIN PHARMACOL THER 1990;47:347-53.)**

**Ursula Steiger, MD, Jacques Cotting, MD, and Jürg Reichen, MD**[a] *Berne, Switzerland*

The therapy of choice for human hydatid disease remains radical surgery when feasible.[1] For inoperable patients or for recurrent disease there is no satisfying therapy established as yet. Mebendazole has been used with variable success.[2-4] Because of the poor and often erratic bioavailability of mebendazole, it is currently being replaced by the better bioavailable albendazole. Albendazole is a benzimidazole derivative with promising scolicidal activity in cystic and alveolar echinococcosis.[5-7] Dosage regimens are not standardized as yet and therapeutic plasma levels and the duration of chemotherapy remain to be established. Albendazole has been shown to have more side effects, such as hepatotoxicity and bone marrow depression, than mebendazole.[2,5-9] Therefore, treatment in cycles has been advocated.[6] In *Echinococcus granulosus,* treatment in cycles is at least as effective as continuous mebendazole therapy.[2]

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Reprint requests: Jürg Reichen, MD, Department of Clinical Pharmacology, University of Berne, Murtenstrasse 35, CH-3010 Berne, Switzerland.
[a]Recipient of a Research Career Development Award of the Swiss National Foundation for Scientific Research (3.731.0.87).
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Recently, enhanced metabolism of albendazole sulfoxide to the inactive albendazole sulfone has been described in rat liver microsomes pretreated with albendazole.[10] To better define the rationale for albendazole dosage schedules, we prospectively studied the effect of long-term albendazole therapy on microsomal reserve, on first-pass activation and disposition of the major active metabolite albendazole sulfoxide, and on liver enzymes in patients with echinococcosis. Major side effects were also evaluated.

## MATERIAL AND METHODS

***Patients.*** Informed consent was obtained from all patients. The study had been approved by the Ethics Committee of the Faculty of Medicine, University of Berne, Berne, Switzerland. Twenty patients with cystic or alveolar echinococcosis were studied. Their characteristics are given in Table I; they were treated with 200 mg albendazole three times a day (corresponding to three doses of 755 μmol) given in cycles of 4 weeks interrupted by 2-week drug-free intervals. Two patients (patients 4 and 10) received a reduced divided dose of 200 mg two times a day (two doses of 755 μmol).

The first 12 consecutive patients (patients 1 through 12 in Table I) were characterized with an aminopyrine breath test and conventional liver function tests during an albendazole-free interval and during a cycle of albendazole treatment at a mean interval of 9 weeks

**Table I.** Patient characteristics

| *Patient* | *Age (yr)* | *Sex* | *Body weight (kg)* | *E. granulosus or E. multilocularis* | *Organs involved* | *Other drugs* | *Ethanol consumption (mg/day)** |
|---|---|---|---|---|---|---|---|
| 1 | 49 | M | 63 | Em | Liver | — | <30 |
| 2 | 70 | M | 84 | Eg | Liver | — | <30 |
| 3 | 33 | M | 88 | Eg | Liver | Enalapril | 30-50 |
| 4 | 33 | M | 74 | Eg | Liver | — | <30 |
| 5 | 25 | F | 60 | Eg | Liver | — | <30 |
| 6 | 46 | M | 56 | Eg | Multiorgan† | — | 30-50 |
| 7 | 25 | M | 61 | Eg | Lungs | — | 30-50 |
| 8 | 35 | F | 77 | Em | Liver | — | <30 |
| 9 | 55 | M | 98 | Em | Liver, lungs | Flunitrazepam | >50 |
| 10 | 38 | M | 77 | Em | Liver | — | <30 |
| 11 | 48 | F | 53 | Em | Liver | — | <30 |
| 12 | 43 | F | 50 | Em | Liver | Spironolactone | <30 |
| 13 | 31 | M | 66 | Eg | Liver | — | <30 |
| 14 | 33 | F | 64 | Eg | Liver | — | <30 |
| 15 | 59 | F | 74 | Em | Liver, abdominal wall | — | <30 |
| 16 | 64 | M | 78 | Em | Liver | Propranolol | <30 |
| 17 | 37 | F | 57 | Em | Liver | — | <30 |
| 18 | 60 | M | 83 | Em | Liver | Clevulanic acid | 30-50 |
| 19 | 38 | F | 76 | Em | Liver | — | <30 |
| 20 | 40 | M | 88 | Eg | Liver, lungs | — | <30 |

Em, *Echinococcus multilocularis;* Eg, *Echinococcus granulosus.*
*Estimated values.
†Liver, lungs, mediastinum, and retroperitoneum.

(range, 4 to 20 weeks). At the time of the albendazole treatment the mean cumulative dose of the respective cycle was 11.3 gm albendazole (range, 4.2 to 17.4 gm). None of the patients was jaundiced at the time of the study, but three patients had mild biochemic cholestasis (alkaline phosphatase less than 2 times the upper limit of normal). There were no signs of portal hypertension, and renal function (serum creatinine) was normal. The study subjects took no drugs except for one patient who took spironolactone, one who took enalapril, and one who took flunitrazepam. Ethanol consumption habits are summarized in Table I. One patient (patient 20) is included for evaluation of side effects only because albendazole treatment had to be stopped after 14 days.

Autoinduction was assessed by prospective monitoring of albendazole sulfoxide plasma levels in another 12 consecutive patients (Table I; patients 8 through 19) who fulfilled the following criteria: compliance, availability of plasma albendazole sulfoxide levels 4 hours after the morning dose obtained during both the first and second half of albendazole cycles, and no concomitant regular drug intake known to interact with drug metabolism.

***Analytic techniques.*** The aminopyrine breath test (ABT) was performed in recumbent patients after an overnight fast as previously described in a report from this institution.[11] At the same time, blood for routine liver function tests were obtained. The 30-minute breath sample of the aminopyrine breath test will be reported as percentage of dose times kilograms of body weight times millimoles $CO_2^{-1}$.[11]

Plasma levels of albendazole sulfoxide were determined by a sensitive and specific reversed-phase HPLC method as described elsewhere.[12] Blood samples were collected by venipuncture into tubes containing heparin 4 hours after the morning dose of albendazole. Albendazole was administered together with the usual breakfast. Samples were centrifuged and the plasma was kept frozen at −20° C until analysis.

Conventional liver tests (AST, ALT, alkaline phosphatase) and serum creatinine were determined by standard autoanalyzer methods in the Department of Clinical Chemistry of the University Hospital.

***Statistical analysis.*** The results of the aminopyrine breath test and conventional liver tests (performed in patients while they were receiving albendazole treatment and while they were not) were compared statistically by the Wilcoxons matched pair test.[13] The absolute increase in transaminase activity was correlated

**Table II.** Conventional liver function tests (IU/L) without (off) and with (on) albendazole treatment

| | *AST* | | *ALT* | | *AP* | |
|---|---|---|---|---|---|---|
| *Patient* | *Off* | *On* | *Off* | *On* | *Off* | *On* |
| 1 | 10 | 16 | 20 | 28 | 64 | 56 |
| 2 | 19 | 26 | 21 | 37 | 78 | 73 |
| 3 | 14 | 20 | 21 | 35 | 47 | 41 |
| 4 | 11 | — | 10 | 13 | 56 | — |
| 5 | 13 | 24 | 11 | 36 | 55 | 64 |
| 6 | 19 | 19 | 19 | 21 | 86 | 96 |
| 7 | 17 | — | 19 | — | 88 | — |
| 8 | 17 | 49 | 9 | 19 | 73 | 92 |
| 9 | 16 | 16 | 17 | 17 | 72 | 63 |
| 10 | 19 | 64 | 37 | 238 | 44 | 38 |
| 11 | 11 | 18 | 10 | 12 | 55 | 36 |
| 12 | 21 | 38 | 36 | 74 | 115 | 104 |
| Mean ± SD | 15.6 ± 3.5 | 24.2 ± 17.8 | 19.2 ± 8.9 | 44.2 ± 61.1 | 69.4 ± 20.4 | 66.3 ± 24.7 |
| Wilcoxon matched pair test *(p)* | | 0.0053 | | 0.0037 | | NS |

AST, Serum aspartate transaminase activity (normal, 0 to 27); ALT, serum alanine transaminase activity (normal, 0 to 27); AP, serum alkaline phosphatase activity (normal, 30 to 90); NS, not significant.

with the decrease of aminopyrine breath test results by the method of least-squares analysis.[14] Mean albendazole sulfoxide levels in micromoles per liter matching the criteria given above were calculated for each patient during the first and the second part of cycles, and the results were compared by means of the Wilcoxon matched pair test[13]; $p < 0.05$ was considered statistically significant. Mean ± 1 SD will be reported.

## RESULTS

The effect of albendazole treatment on the aminopyrine breath test is shown in Fig. 1. Excretion of $^{14}CO_2$ at 30 minutes averaged 0.70% · kg · mmol$^{-1}$ ± 0.20% · kg · mmol$^{-1}$ without albendazole treatment and 0.54% · kg · mmol$^{-1}$ ± 0.14% · kg · mmol$^{-1}$ with albendazole treatment (normal range, 0.60% · kg · mmol$^{-1}$ to 1.00% · kg · mmol$^{-1}$). It decreased in 11 of 12 patients during albendazole therapy ($p < 0.005$), with the mean decrease averaging 0.16% · kg · mmol$^{-1}$ ± 0.14% · kg · mmol$^{-1}$. The effects of albendazole on conventional liver function tests are given in Table II: eight of 12 and 10 of 12 patients showed a significant increase in AST ($p < 0.01$) and ALT levels ($p < 0.005$), respectively. This increase in transaminase activity did not correlate with the decrement in microsomal aminopyrine demethylation ($r = 0.06$). Albendazole had no significant effect on the cholestatic parameters alkaline phosphatase (Table II), γ-GT, and serum bilirubin (data not shown).

Mean albendazole sulfoxide levels during the first and second half of the cycle are shown in Fig. 2. In 26 of 34 cycles, albendazole sulfoxide levels were lower in the second half of the cycle ($p < 0.002$); the decrease in the 12 patients averaged 0.84 ± 0.76 μmol/L (Table III). This phenomenon was particularly evident in patients with high initial plasma levels of albendazole sulfoxide (Fig. 2).

Albendazole was tolerated without major side effects in 17 patients. The three exceptions deserve some comment. Hepatotoxicity developed in one patient (Patient 10) after three cycles of the standard dose albendazole treatment. The course of transaminase activities in this patient is shown in Fig. 3. After two unremarkable cycles, transaminase levels slightly increased during the third cycle but returned to normal during the drug-free interval. After 2 weeks, rechallenge was undertaken, once with the standard dose and once with a reduced dose (755 μmol two times a day). On both occasions, there was a marked and prompt increase of transaminase activities that resolved when the drug was withdrawn. The patient remained asymptomatic throughout. He took no other drugs, and alcohol intake was minimal. Hepatitis serology remained negative, and eosinophil count was normal. Albendazole sulfoxide levels were within the therapeutic range.

In two patients (patients 8 and 20), a marked drop in leukocyte count during the first days of albendazole treatment was observed. In one of those patients, the drug had to be stopped when the neutrophil level decreased from 5200 to 980 μl$^{-1}$ after 12 days. In both patients white blood cell count returned to normal after withdrawal. One of these (patient 8) had complete biliary obstruction due to *Echinococcus alveolaris;* sub-

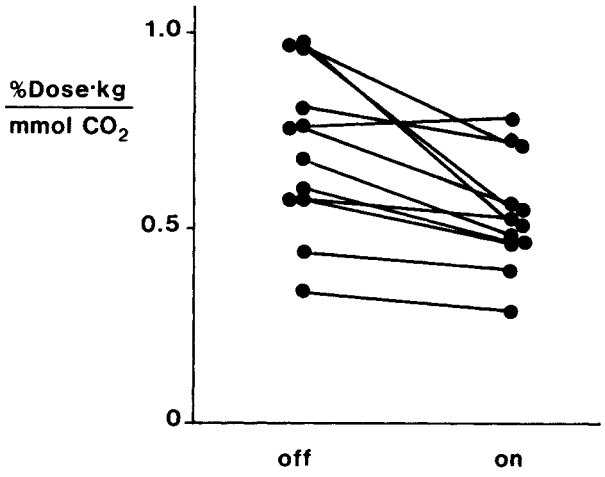


**Fig. 1.** Aminopyrine breath test without albendazole treatment *(off)* and during albendazole treatment *(on)*. The decrease was statistically significant ($p < 0.005$).

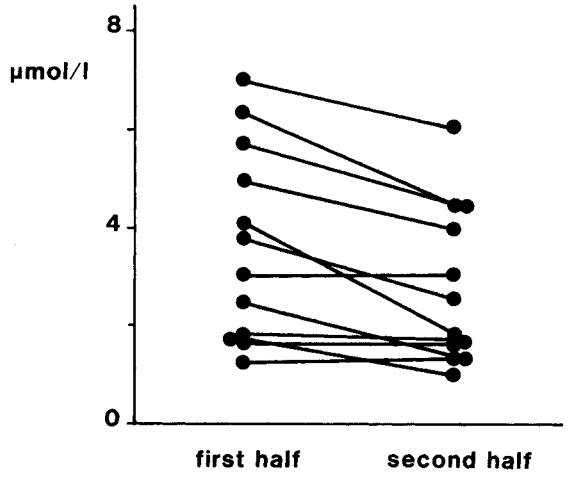


**Fig. 2.** Mean albendazole sulfoxide plasma levels during the first and second half of albendazole treatment cycles in 12 patients. Drug levels decreased by an average of 0.84 ± 0.76 µmol/L ($p < 0.02$). The number of observations for each patient is reported in Table III.

**Table III.** Effect of long-term albendazole treatment on albendazole sulfoxide plasma levels obtained 4 hours after the morning dose

| *Patient* | *Dose (mg/day)* | *Decrease in cycles observed* | *Averaged change in ASOX* (µmol/L)* |
|---|---|---|---|
| 8 | 3 × 200 | 6/6 | −1.89 |
| 9 | 2 × 200 | 2/2 | −1.25 |
| 10 | 3 × 200 | 2/2 | −0.73 |
| 11 | 2 × 200 | 2/2 | −0.95 |
| 12 | 3 × 200 | 2/2 | −2.25 |
| 13 | 3 × 200 | 1/1 | −1.12 |
| 14 | 3 × 200 | 1/3 | 0.08 |
| 15 | 3 × 200 | 2/3 | 0 |
| 16 | 3 × 200 | 3/6 | 0.26 |
| 17 | 3 × 200 | 2/2 | −0.95 |
| 18 | 3 × 200 | 2/4 | −0.05 |
| 19 | 3 × 200 | 1/1 | −1.22 |

*Albendazole sulfoxide levels were measured during the first and second half of 4-week cycles. Both the number of decreases and the average decrease were statistically significant ($p < 0.02$).

total diffuse alopecia developed in this patient in addition to leukopenia during the first weeks of albendazole treatment; at that time she was 4½ months postpartum. After a pause of 3 weeks, therapy was resumed, and hair growth returned under continued treatment. During the first cycle albendazole sulfoxide levels were above the therapeutic range; moreover, she was the first and so far the only patient in whom the parent compound was detectable in serum. Folic acid decreased with albendazole treatment from 21 to 6.7 nmol · $l^{-1}$ within 3 weeks. On further questioning, 6 of 12 patients reported hair loss during albendazole courses.

## DISCUSSION

The main findings of our study are that long-term treatment with albendazole significantly inhibits aminopyrine *N*-demethylation, induces an almost universal slight transaminase elevation, and induces its own metabolism as suggested by a decrease of albendazole sulfoxide levels during the second half of the treatment cycles. Finally, the incidence of serious adverse effects is substantial: hepatotoxicity, neutropenia, or alopecia occurs in three of 20 patients.

The first step of albendazole bioconversion is the rapid and virtually complete sulfoxidation of albendazole to its major active metabolite, albendazole sulfoxide. This is followed by sulfonation to the inactive sulfone, one among seven other metabolites identified so far.[15] Involvement of the both cytochrome P-450 and FAD monooxygenase system in albendazole metabolism have been demonstrated in rat and pig liver microsomes,[16-18] as well as in a well-differentiated human hepatoma cell line.[19] In rats, enhanced sulfonation of the sulfoxide has been observed after pretreatment with the parent compound, which suggests autoinduction.[10,18] In human hepatoma cells the sulfoxide and the sulfone induced cytochrome P-448 and UDP-glucuronyltransferase, whereas the parent compound inhibited the activity of these enzymes.[19] Our data,

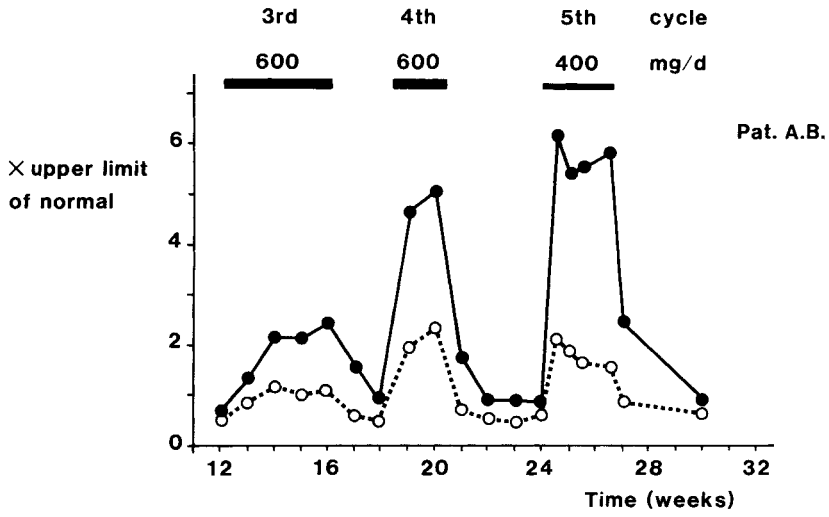


**Fig. 3.** Serum transaminase levels (times upper limit of normal range) in patient 10. *Black bars,* Cycle of drug administration and dose; *solid circles,* ALT level; *open circles,* AST level.

**Table IV.** Albendazole hepatotoxicity in humans

| *Reference* | *No. of cases* | *Type of hepatotoxicity reaction* | *Rechallenge* | *Liver biopsy* | *Hypersensitivity* |
|---|---|---|---|---|---|
| Chevrel B et al.[22] | 8/39 | Hepatocellular (8 cases) | Not done | Not done | * |
| Choudhurie G et al.[9] | 1/1 | Cholestatic (1 case) | +1/1 | Not done | * |
| Davis A et al.[2] | 2/20 | Hepatocellular (2 cases) | Not done | Not done | * |
| Morris DL et al.[5] | 6/32 | Hepatocellular (5 cases), Cholestatic (1 case) | +2/2 | 1/1, Moderately severe hepatitis with centrilobular and patchy focal necrosis | * |
| Wilson JF et al.[3] | 6/7 | Hepatocellular (6 cases) | +1/1 | 2/3, Mild hepatocellular necrosis with lymphohistiocytic infiltrates and multinucleated hepatocytes. 1/3, Normal biopsy | — |
| Present report | 1/20 | Hepatocellular (1 case) | +1/1 | Not done | — |

*No indications in report.

which show inhibition of aminopyrine *N*-demethylation on the one hand and suggest autoinduction of albendazole disposal on the other hand, agree with these in vitro data. Alternatively, the decrease of albendazole sulfoxide levels during long-term albendazole treatment could be caused by an inhibition of albendazole bioactivation to its sulfoxide. However, the fact that the parent compound was not detectable in serum (except in patient 8) militates against this hypothesis.

Both the parent compound and the primary metabolites have cytotoxic potential.[19,20] A recent toxicity study in human hepatoma cells showed albendazole to be more cytotoxic than the sulfoxide or the sulfone.[19] Elevations in transaminase activities have been described in 7% to 27% of patients treated with mebendazole,[2,4,21] but these elevations seem to be more frequent and potentially more severe with albendazole treatment.[5,7] Our study demonstrates an almost universal, albeit slight, transaminase elevation during albendazole; this does not predict severe hepatotoxicity, however. Several reports of hepatotoxicity of albendazole in humans have been published[2,5,7-9,22]; these reports are compiled in Table IV. The response to rechallenge and the absence of hypersensitivity reactions in our case suggest an idiosyncratic hepatotoxic drug reaction. Hepatotoxicity can occur during any course of albendazole treatment and does not appear to depend on albendazole sulfoxide levels.[7]

Reversible bone marrow depression caused by albendazole has been described in animals[23] and in humans[2,5,7,24]; it seems to occur less frequently with albendazole than with mebendazole.[2-3,25-26] Neutropenia was observed in two of 20 patients in our series, necessitating discontinuation of the drug in one patient. One of these two patients had excessively high plasma albendazole sulfoxide levels and a sudden drop in serum folic acid. Whether folic acid substitution could decrease the incidence of neutropenia without affecting therapeutic efficacy remains to be studied.

Alopecia as adverse drug reaction has been described for both mebendazole[2,27] and albendazole.[2,2,24] When questioned, 50% of our patients reported hair loss in our study. Total alopecia developed in one patient with high albendazole sulfoxide levels and detectable albendazole in serum. Whether this was caused by the drug itself, a Herxheimer reaction to parasite necrosis, or to pregnancy remains unclear.

In conclusion, albendazole partially inhibits microsomal enzyme function but induces its own metabolism. These findings provide a rationale for giving albendazole in cycles rather than continuously. The efficacy of cyclic therapy has been proved for *Echinococcus granulosus*[2] but not for *Echinococcus alveolaris*. The unpredictable time of onset of severe side effects, such as hepatotoxicity and neutropenia, emphasizes the need for close therapeutic monitoring of patients receiving albendazole.

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