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Benzimidazoles in the treatment of alveolar echinococcosis: a comparative study and review of the literature

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Mebendazole and albendazole are the drugs of choice for the treatment of alveolar echinococcosis. In this open-labelled observational study we present and evaluate the outcome of long-term treatment with these drugs and present results of different treatment regimens. Thirty-five patients were started on either mebendazole or albendazole at the beginning of 1992 and followed for an average of 39 months (range 12–79 months). Treatment was classed as successful if the disease had not progressed for >1 year and if there were no side-effects necessitating a change of treatment. Lack of progression was evaluated mainly using ultrasound and computed tomography and was further substantiated by laboratory tests and clinical findings. The overall success rate was 97%. An initial regimen for cases of alveolar echinococcosis was recurrence-free in 71% of those treated with mebendazole and in 78% of those treated with albendazole. Four out of five cases with progressive disease stabilized after the therapeutic regimen was changed. Seven patients received a continuous regimen with albendazole. These patients were observed over an average of 28 months (range 13–50 months) without signs of progression or significant side-effects. This open-labelled prospective study demonstrates the high therapeutic efficacy of both mebendazole and albendazole with similar response rates in the treatment of alveolar echinococcosis. Albendazole reduced costs by >40% and is easier for patients to take, further arguing in favour of its preferred use. Albendazole in alveolar echinococcosis is only licensed for intermittent application. None the less, continuous treatment is safe and well tolerated and showed promising results when applied to patients in whom other treatment regimens had failed. It should thus be strongly considered in inoperable cases or progressive disease.

Introduction

The larval stage of *Echinococcus multilocularis* causes alveolar echinococcosis (AE), a disease primarily affecting the liver.[1] AE is endemic in regions of western and central Europe, Eastern Europe, North America and Asia.[1] Its incidence in central Europe is approximately 0.02–1.4 per 100 000 inhabitants per year.[2]

The WHO (Informal Working Group on Echinococcosis) guidelines for the treatment of AE[3] recommend that: (i) for patients with operable disease, surgical resection of the parasitic lesion is the treatment of choice, followed by chemotherapy for a limited time (minimum of 2 years); (ii) long-term chemotherapy is indicated in inoperable disease or after incomplete resection of lesions as well as after liver transplantation.

Without treatment, AE is fatal in >80% of cases[4] and operative resection of lesions is frequently incomplete because of the tumour-like growth of the parasite with diffuse infiltration of non-resectable structures or insufficient safety margins. As a result of this infiltrative multilocular growth, therapeutic puncture and instillation of parasitocidal agents are not valid options in AE.

Two drugs are licensed for therapy of AE: mebendazole (Vermox forte; Janssen-Cilag GmbH, Neuss, Germany) and albendazole (Eskazole; SmithKline Beecham, Harlow, UK). These two drugs, both benzimidazoles, are administered orally. Mebendazole[5] was first introduced as a veterinary anthelminthic against *E. multilocularis* in 1977 and soon proved to be effective in human AE as well.[6] The recommended daily dosage is 40–50 mg/kg/day taken with a fat-containing meal three times daily. Albendazole is

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taken together with a fat-containing meal twice daily (manufacturer's recommendation, 10–15 mg/kg/day). The drug is licensed for cyclic treatment only (i.e. 28 days of treatment followed by 14 days of interruption); continuous treatment was discussed as a promising alternative only recently.[7–9]

The present comparative study between mebendazole and albendazole was started in 1992, when albendazole[10] was first registered in Germany for the treatment of AE. Mebendazole and albendazole are presumed to have equally effective anthelminthic activities, but studies comparing their efficacies are scarce.[11–13] In the present open-labelled observational study, we compare the outcome of long-term benzimidazole treatment with cyclic and continuous regimens initiated after 1991 and we review the literature with regard to the clinical outcome of treatment with either drug.

Materials and methods

Each of the patients evaluated in the present study was treated with albendazole (Eskazole) or mebendazole (Vermox forte) and followed for >12 months in our outpatient department between 1 January 1992 and 31 December 1998. All patients were given the dosage recommended by the manufacturers: albendazole 10–15 mg/kg/day and mebendazole 40–50 mg/kg/day. If necessary, patients were also followed by our surgical consultant service. Data from 35 patients (average age 50 years when medical treatment was initiated and 54 years (median 56 years, range 13–80 years) at the time of data analysis) were included in the present study (Table I). This group consisted of 18 women and 17 men. The mean time of observation was 39 months (median 34 months, range 12–79 months). Seven patients had been cured by operation, while 13 had undergone palliative resection and 15 were inoperable. Extrahepatic lesions were observed in 12 patients.

For diagnosis and follow-up in half-yearly intervals we evaluated clinical parameters (hepatomegaly, icterus, upper abdominal complaints and others) and performed immunodiagnosis using antibodies against *Echinococcus* spp. with the indirect haemagglutination test (IHA) (bioMérieux, Marcy-l'Etoile, France), the CAP-RAST (cap radioallergosorbent test) (Pharmacia, Freiburg, Germany) and specific antibodies against *E. multilocularis* with Em2+ enzyme-linked immunosorbent assay (ELISA) (Bordier Affinity Products SA, Crissier, Switzerland). Biochemical parameters (complete blood count, parameters of cholestasis, CRP, immunological parameters and transaminases) and imaging techniques (ultrasound and computerized tomography) were also taken into account. The criteria for success of treatment were: lack of disease progression (i.e. stability or regression of AE lesions) and lack of side-effects necessitating a change of treatment. Whether the disease was stable or had progressed was evaluated mainly by ultrasound and computerized tomography, and was further substantiated by laboratory tests and clinical findings.

Results

A total of 452 months of mebendazole, 627 months of cyclic albendazole and 193 months of continuous albendazole were prescribed. The average time of treatment was 24 months for mebendazole, 25 months for cyclic albendazole and 28 months for continuous albendazole.

Between 1992 and 1998, of a total of 35 patients, seven patients were treated with mebendazole alone (four women and three men, median age 51 years) and 14 patients with albendazole alone (six women and eight men, median age 52 years), while the treatment regimen was changed in 14 cases (eight women and six men, median age 59 years) during the course of disease. First treatment with mebendazole was successful in 12/17 (71%) cases (95% CI: 52–94%) and first treatment with albendazole was successful in 14/18 (78%) cases (95% CI: 44–90%) (see Table I). The time between initiation of drug treatment and apparent progression varied between 4 and 36 months (median 11 months). Medication was changed in 14 cases either from mebendazole to albendazole (cyclic or continuous) or from cyclic albendazole to mebendazole or continuous albendazole. A change of treatment resulted from either suspected or confirmed progressive disease ($n = 5$) or intolerable side-effects ($n = 4$) (see Table II), while five cases were changed from mebendazole to albendazole for financial reasons or because albendazole treatment involved taking fewer tablets (not included in Table II). Four of five progressive cases were stabilized by changing the treatment regimen. In three of these four patients, the regimen had been changed from cyclic albendazole to continuous albendazole, while in the fourth it was changed from mebendazole to continuous albendazole. The regimen of the unsuccessful case had been changed from cyclic albendazole to

Table I. Numbers of patients with regard to success of initial medical treatment, classified by previous operative treatment

	Success[a]		No success		
	ABZ	MBZ	ABZ	MBZ	Total
Curative operation	6	1	0	0	7
Palliative operation	4	2	4	3	13
No operation	4	9	0	2	15
Total	14	12	4	5	35

Abbreviations: MBZ, mebendazole; ABZ, albendazole.
[a]Success of treatment was defined as stable disease and regression.

Table II. Outcome after change of drug treatment. A change of treatment was necessary because of progressive disease ($n = 5$) or intolerable side-effects ($n = 4$)

	Progression		Side-effects		
Change of treatment	success	failure	success	failure	Total
MBZ to ABZ (cyclic/continuous)	1	0	3	0	4
Cyclic ABZ to MBZ	0	1	1	0	2
Cyclic ABZ to continuous ABZ	3	0	0	0	3
Total	4	1	4	0	9

Abbreviations as in Table I.

mebendazole. The overall success of treatment was 97% (34/35).

There was no difference in response to treatment between patients in whom only the liver was affected ($n = 23$) and those with additional extrahepatic disease ($n = 12$).

While side-effects were observed in seven patients, they were intolerable in only four cases and led to a change of treatment in three patients being treated with mebendazole (alopecia, drop in performance, psychic conspicuousness) and in one being treated with cyclic albendazole (elevation of serum transaminases). After treatment was changed, all these side-effects disappeared. Mild vertigo, loss of hair, itching and queasiness were also observed, but they were only minor and were thus tolerated by the affected patients.

Seven patients were treated with a continuous dosing of albendazole for >12 months each and for an average of 28 months (median 26 months, range 13–50 months). All patients had a stable or regressive course of disease. One patient with extensive disease was started on continuous treatment with albendazole immediately after diagnosis. Two other patients were changed from mebendazole to continuous albendazole, one because of the easier mode of intake and the other because of persistently low serum concentrations of mebendazole. Four cases of progressive disease were successfully stabilized after changing medication to continuous albendazole. No significant side-effects were observed (only one case of minor, temporary, hair loss) with continuous dosing of albendazole.

Discussion

We did not have a control group of untreated cases for ethical reasons, as treatment could not be withheld from a patient once the diagnosis had been established. Untreated AE is fatal in >80% of cases[4] and operative resection of lesions is often incomplete because of the tumour-like growth of the parasite. It has to be emphasized that, in contrast to cystic echinococcosis, benzimidazole treatment in AE only has a parasitostatic effect and thus cannot kill the parasite in most cases. Ammann *et al.*[14] have shown that, in patients with unresectable disease, a significant number of relapses is to be expected after discontinuation of chemotherapy, even after long-term treatment. Chemotherapy for unresectable disease is, therefore, performed over many years, often throughout the patient's life.

The lack of early signs indicating progression or stability of disease make it difficult to evaluate the success of treatment in AE. The most reliable tools to date are imaging techniques: ultrasound is the standard screening method in AE. It is combined with computerized tomography every 12–24 months and, in the hands of an experienced physician, allows adequate follow-up evaluation of this chronic disease. Laboratory tests and clinical findings are less valuable for the detection of progressive disease and may only give additional hints.

Table III summarizes the results of major studies on the clinical outcome of AE treated with mebendazole and albendazole. It is difficult to compare the different studies directly, as most studies differ significantly with regard to their study protocols and results. In Table III we have therefore confined ourselves to differentiating between success of treatment and progression. Considering the unfavourable course of disease in untreated patients and the non-parasitocidal effect of benzimidazoles in most cases, non-progression is generally regarded as a success. Success of treatment thus includes stable disease and regression rather than regression alone.

Few studies have compared mebendazole and albendazole directly[11–13] (see Table III); the demand for such studies has been emphasized repeatedly.[1,15,16] All studies to date (see Table III) included patients treated before 1992 and had reported that mebendazole therapy was associated with a higher rate of progressive disease before 1992.[11,12] The rate of failure of treatment for cystic echinococcosis was also greater for mebendazole than for albendazole.[17]

The present study is the first to evaluate the outcome of medical treatment for AE started after 1991, since albendazole was licensed for the treatment of AE in Germany in 1992. Follow-up in a specialized outpatient service and an

Table III. Studies of the clinical outcome of alveolar echinococcosis treated with different long-term benzimidazole regimens

Author(s) and reference no.	Drug	Curative surgery vs non-curative or inoperable disease	Number of patients	Average duration of treatment (months)	Average time of observation (months)	Percentage success
Present study	MBZ	1 vs 16	17	24	39	97
	ABZ	6 vs 12	18	25	39	
Wilson *et al.*[13]	MBZ	0 vs 8	8	61	166	100
	ABZ	0 vs 5	5	3	53	80[a]
Reuter *et al.*[12]	MBZ/ABZ	8 vs 36	44	20	42	80
Ammann *et al.*[11]	MBZ/ABZ	0 vs 37	37	76	76	84
Bresson-Hadni *et al.*[31]	MBZ/ABZ	?	59	?	>36	88
Ammann *et al.*[14]	MBZ	0 vs 19	19	52	71	100[b]
	MBZ	14 vs 0	14	24	66	100
Ammann *et al.*[23]	MBZ	0 vs 60	60	51	84	76.7
Davis *et al.*[19]	MBZ	?	54	?	?	78
Junge & Rengstorf[24]	MBZ	8 vs 16	24	?	?	96[c]
Rausch *et al.*[15]	MBZ	0 vs 8	8	42	>42	75
Luder *et al.*[25]	MBZ	0 vs 6	6	53	58	100
Kern[26]	MBZ	0 vs 7	7	18	22	100
Müller *et al.*[27]	MBZ	6 vs 18	24	21	<20	96
Wilson & Rausch[5]	MBZ	5 vs 0	5	>60	>60	100
Ishizu *et al.*[28]	ABZ	3 vs 17	20	39	>39	55
Wang *et al.*[22]	ABZ	0 vs 6	6	?	?	100
Wen *et al.*[29]	ABZ	?	19	<24	?	74
Liu *et al.*[8]	ABZ	0 vs 14	14	36	95	91
Horton[30]	ABZ	0 vs 35	35	<24	?	88.6[d]

Abbreviations as in Table I.

[a]Progression was observed with albendazole treatment. However, the authors question the patient's compliance.

[b]Recurrence was observed in seven of 19 patients after stopping treatment (average time of treatment was 52 months). Their condition stabilized in all of six cases after reinitiation of treatment (one patient died after refusing treatment).

[c]Recurrence was observed in seven of nine patients after stopping treatment (average time of treatment was 26 months). Their condition stabilized in six of these seven cases after reinitiation of treatment.

[d]Data from a meta-analysis including patients from the Alaskan and European cohort.

Studies with five or more patients are included. Treatment failure was defined as either progression or a combination of progression and side-effects leading to a change of treatment. The present study is the first to directly compare benzimidazole treatment initiated after 1991.

intensified interdisciplinary cooperation were factors that improved the outcome of long-term treatment. In our specialized outpatient service, all ultrasound examinations are performed by the same experienced person and our radiologists are specially trained to evaluate imaging characteristics and follow-up in AE. These factors may have contributed to the high rate (97%) of successfully treated patients. Albendazole and mebendazole showed similar effectiveness against AE. It must be emphasized, however, that the two treatment groups differed with regard to their previous treatment and that there was more inoperable disease among patients in the mebendazole group (see Table I).

In 1994, Ammann *et al.*[11] reported slightly lower overall success rates, with successful treatment in 84% and progressive disease in 16% of cases. As in the present study, the criterion for success was morphological non-progression as assessed by computerized tomography. Although these data are not directly comparable with ours (only three of 37 patients had been treated with albendazole and the success of treatment was not analysed separately for the two drugs), they further substantiate the tendency towards higher success rates during the last few years.

According to the literature,[1,18] the most frequent adverse reactions associated with benzimidazole treatment are gastrointestinal disturbances, reversible alopecia, elevation of serum transaminases, proteinuria, neurological symptoms and neutropenia. In our study, adverse reactions were observed in seven patients. A change of treatment was necessary in four cases. In a study by Davis *et al.*,[19] side-effects led to a change of treatment in five of 54 cases receiving mebendazole and in one of 20 cases receiving albendazole. Other authors have observed a tendency towards higher rates of adverse reactions associated with mebendazole treatment,[20] but we observed only few side-effects. In general, both drugs were well tolerated and, in the few cases of severe side-effects, a change of treatment successfully stopped these adverse reactions.

One advantage of albendazole over mebendazole is its cost-effectiveness. Depending on the dosing regimen, albendazole is $\geqslant$40% cheaper than mebendazole.[12] In Germany, costs per year for mebendazole range between 8200 and 16300 Euros (approximately US$7450 and 14800), depending on dosage, while albendazole costs between 4700 and 7000 Euros (US$4300 and 6350) for cyclic and continuous dosing, respectively.

Patients are more likely to comply with the albendazole regimen as it involves taking fewer tablets (one tablet twice daily) than mebendazole (two to four tablets three times daily).

According to the manufacturer's recommendations, cyclic dosing is the regimen of choice for albendazole. One treatment cycle consists of 28 days of drug intake followed by 14 days without treatment ('washout' phase). This intermittent treatment is intended to reduce toxicity. However, the 'washout' phase of albendazole treatment may reduce the control of parasite growth,[9] and this may outweigh the need to avoid pharmacological adverse reactions. To date, cyclic dosing is the only licensed treatment regimen. Continuous dosing remains experimental and is reserved for severe and progressive cases. In the study described here, continuous dosing of albendazole in seven patients did not lead to increased toxicity or to higher rates of adverse reactions compared with cyclic dosing. After an average time of observation of 28 months, all of our patients treated with albendazole on a continuous regimen have stable or regressive disease and treatment is tolerated well without exception. It is of particular importance to note that four of our cases with progressive disease were stabilized by changing treatment to continuous albendazole. As only a small number of patients was studied, additional studies are needed to substantiate these promising results.

Several other studies have focused on the efficacy and adverse reactions of continuous long-term treatment with albendazole.[7–9,21,22] All studies found the same low rate of side-effects as observed under intermittent regimens. As was to be expected, the response to treatment was highly successful. Liu[9] noted progression in one of 20 patients with AE receiving continuous albendazole treatment. In the light of these favourable data, the manufacturer's recommendations of cyclic dosing might be revised. Continuous dosing should be strongly considered in AE patients with inoperable or progressive disease.

It has proven advantageous for AE patients to receive care from a family practitioner and to be followed regularly at longer intervals in a specialized outpatient department. This practice was presumably one reason for the high compliance and the high rate of success among our patients. It is essential for a successful long-term treatment of AE to build up the patients' motivation and to encourage compliance.

In summary, mebendazole and albendazole are both effective for the treatment of AE and both are well tolerated. A cost reduction of >40% and a simplified drug intake are advantages of albendazole. Although albendazole is not licensed for continuous dosing, this regimen is well tolerated and constitutes a promising alternative in cases of inoperable or progressive AE.

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