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Multicentre clinical trials of benzimidazolecarbamates in human echinococcosis*

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Studies coordinated by the World Health Organization were conducted in seven clinical centres on the chemotherapy of human echinococcosis with mebendazole, albendazole, and flubendazole. The first phase of these ended with the following conclusions.

*Treatment of 85 patients with mebendazole for cystic (*Echinococcus granulosus*) echinococcosis was successful in 8 patients and partially successful in 4 others. Flubendazole was effective in only one case of lung echinococcosis. Albendazole was successful in 5 of 30 patients treated and partially successful in 4 others. Further studies on new drugs or new formulations of existing benzimidazoles and on better forms of their application are needed. In the mean time, chemotherapy of human cystic echinococcosis should be restricted to inoperable cases.*

In 54 patients with E. multilocularis *echinococcosis, it was confirmed that mebendazole therapy may arrest the development of the lesions. This treatment is therefore indicated in most cases of alveolar echinococcosis with or without surgery. However, further studies are needed to clarify the optimal regimen for mebendazole treatment and to explore the effectiveness of albendazole therapy.*

In 1981, the WHO Parasitic Diseases Programme launched a programme of coordinated clinical studies on the treatment of human echinococcosis with benzimidazolecarbamates, because individual studies undertaken since 1977 had given inconsistent results. The patients were examined and treated according to a WHO protocol.[a] Data were processed by computer and evaluated centrally.

MATERIALS AND METHODS

Echinococcus granulosus *echinococcosis*

The WHO-coordinated studies on *E. granulosus* echinococcosis were performed in five clinical centres (Beirut, Paris, Rome, Sofia and Zurich)[b] during the period 1982–84.

A total of 121 patients were treated: 85 with mebendazole, 6 with flubendazole, and 30 with albendazole (Table 1). Mebendazole was used in tablets of 650 mg, each containing 500 mg of mebendazole base. Flubendazole was used in tablets of 1 g, each containing 500 mg of flubendazole base. Albendazole was used in tablets of 200 mg.

The patients were mainly adults; only 7% were below 15 years and 11% were over 60 years of age.

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[a] *Treatment of human echinococcosis*. Unpublished WHO documents, PDP/82.1 and PDP/84.6.

[b] See Acknowledgements, page 387.

Table 1. Chemotherapy of *E. granulosus* echinococcosis

	Mebendazole	Flubendazole	Albendazole	Total
No. of patients treated	85 (100)[a]	6	30 (100)	121 (100)
Age: 5–14 years	3 (3)	1	4 (13)	8 (7)
15–59 years	72 (85)	4	24 (80)	100 (82)
⩾60 years	10 (12)	1	2 (7)	13 (11)
Sex: females	47 (55)	3	8 (27)	58 (48)
males	38 (45)	3	22 (73)	63 (52)
With cysts: in liver only	32 (37)	1	14 (47)	47 (39)
in lungs only	11 (13)	1	1 (3)	13 (11)
in other organs only	3 (4)	2	10 (33)	15 (12)
mixed localization	39 (46)	2	5 (17)	46 (38)
With more than 10 cysts in one organ	20 (24)	–	7 (23)	27 (22)
Previous surgery	46 (54)	5	19 (63)	70 (58)
Daily dose: mg/kg (range)	13.0–136.4	37.5–54.5	9.8–15.4	
mg/kg (mode)	50	50	12.5	
g (range)	1.0–10.0	1.5–4.0	0.25–0.8	
Treatment: <3 months	13 (15)	–	6 (20)	19 (16)
3–6 months	14 (17)	6	7 (23)	27 (22)
>6 months	45 (53)	–	17 (57)	62 (51)
irregular, but >3 months	13 (15)	–	–	13 (11)
Observation time: <6 months	21 (25)	2	11 (37)	34 (28)
6–12 months	21 (25)	3	11 (37)	35 (29)
>1 year	43 (50)	1	8 (26)	52 (43)
No. of follow-up examinations:	348	18	36	402
mean number per patient	4.1	3.0	1.2	3.3
Adverse reactions:				
treatment stopped because of adverse reaction	2 (2)	–	–	2 (2)
SGOT and/or SGPT, >100 U/l	6 (7)	–	2 (7)	8 (7)
leukocyte count, $<4\times10^9$/l	11 (13)	–	1 (3)	12 (10)
haemoglobin, <9 g/l	1 (1)	–	–	1 (1)
gastrointestinal symptoms	18 (21)	1	1 (3)	20 (16)
allergic conditions	2 (2)	–	1 (3)	3 (2)
CNS symptoms	4 (5)	–	–	4 (3)
loss of hair	2 (2)	–	1 (3)	3 (2)
No. with ruptured cyst(s):				
in lungs	14/30 (47)	1/1	0/5 (0)	15/36 (42)
in liver	4/71 (6)	0/3	1/19 (5)	5/93 (5)
Results: success	8 (9.4)	1	5 (16.7)	14 (11.6)
partial success	4 (4.7)	–	4 (13.3)	8 (6.6)
improvement	40 (47.1)	–	14 (46.7)	54 (44.6)
no success	33 (38.8)	5	7 (23.3)	45 (37.2)

[a] Figures in parentheses are percentages.

The sexes were about equally represented: 52% males, 48% females. Most of the patients had inoperable *E. granulosus* cysts. Localization was in the liver (39%), lungs (11%) or other organs (12%); mixed localization was common (38%). Multiple cysts were common; more than 10 cysts in one organ were found in 22% of the cases. Unsuccessful previous surgery had been performed in 58% of the patients. In general, the patients selected for the studies were representative of more serious and complicated echinococcosis than that existing in the population at large. For ethical reasons there was no

untreated control group, which made the objective evaluation of the results difficult, especially in lung echinococcosis, in which spontaneous cures may occasionally occur.

In patients treated with mebendazole, either a fixed or flexible dose was used, varying from 13.0 to 136.4 mg/kg body weight/day; the most frequently used dose (mode) was 50 mg/kg body weight/day. The maximum daily dose given was in the range 3.0–4.9 g in the majority of the patients (73%), 1.0–2.9 g in 13% and 5.0–10.0 g in 14% of the cases. As a rule patients were treated for 3 months, but in several cases, especially those with liver localization or multiple cysts, the treatment was extended. Half (50%) of the treated cases were re-examined on a three-monthly basis for over a year; 25% were observed for 6–12 months, and only 25% were observed for less than 6 months.

Flubendazole was used in a fixed daily dose of 1.5 to 4.0 g daily, i.e., 37.5–54.5 mg/kg body weight (mode, 50 mg/kg body weight) and re-examinations were conducted in a similar way.

Albendazole was given in a daily dose of 0.8 g in adults and 0.25 or 0.4 g in children, i.e., 9.8–15.4 mg/kg body weight (mode, 12.5 mg/kg body weight). This drug was used in treatment cycles of 30 days and repeated two or three times with two-week intervals between courses. Patients treated with albendazole were re-examined for a shorter time: 26% for over one year, 37% for 6–12 months, and 37% for less than six months.

The results of treatment were classified into three groups:

— with success: successful treatment was indicated by disappearance or significant decrease in the size of *E. granulosus* cysts and/or distinct changes in cyst morphology seen by X-ray, ultrasound and/or computerized tomography. In patients with multiple localization, a partial success was recorded if the treatment was successful in one organ but not the other;
— no success: patients with no change in cyst size or morphology, or with progression of the disease, or with signs of drug intolerance;
— some improvement: all other patients who showed some amelioration in clinical symptoms or signs, or insignificant changes in cyst morphology.

Serological examinations based on antibody detection were used for the confirmation of clinical diagnosis; they were found to be of little practical value in evaluating the effectiveness of chemotherapy. Both morphological criteria (protoscolex morphology, presence or absence of intact germinal layer, etc.) and biological features (muscular movements of protoscoleces, flame cell activity) were used for viability testing of *E. granulosus* metacestode material obtained by surgery. In a study, the cysts were found viable in 6 out of 12 patients treated with mebendazole for periods ranging from 10 days to 15 months.

Table 2. Chemotherapy of *E. multilocularis* echinococcosis

	Mebendazole	Albendazole
No. of patients treated	54 (100)[a]	20 (100)
Age: 19–59 years	29 (54)	13 (65)
⩾60 years	25 (46)	7 (35)
Sex: females	29 (54)	11 (55)
males	25 (46)	9 (45)
With lesions in liver:	53 (98)	19 (95)
in liver only	37 (68)	16 (80)
in liver and other organs	16 (30)	3 (15)
in lungs only	1 (2)	1 (5)
Previous surgery	36 (67)	15 (75)
Daily dose: mg/kg (range)	26.8–169.5	
mg/kg (mode)	41.7	
g (range)	1.5–10.0	0.8
Treatment and observation time:		
<1 year	10 (18)	20 (100)
1–2 years	22 (41)	
3–12 years	22 (41)	
No. of follow-up examinations:	260	
mean number per patient	4.8	
Adverse reactions:		
treatment stopped because of an adverse reaction	5 (9)	1 (5)
SGOT and/or SGPT, >100 U/l	16 (30)	
leukocyte count, $<4\times10^9$/l	14 (26)	
haemoglobin, <9 g/l	2 (4)	
gastrointestinal symptoms	4 (7)	
allergic conditions	2 (4)	
CNS symptoms	2 (4)	
loss of hair	5 (9)	
Results: success	4 (7.4)	
condition stabilized or improved	38 (70.4)	
failures	12 (22.2)	

[a] Figures in parentheses are percentages.

Echinococcus multilocularis *echinococcosis*

Under the WHO-coordinated studies, 54 patients with *E. multilocularis* infection were treated with mebendazole in three clinical centres (Anchorage, Besançon, and Zurich).[c] All the patients were adults; 46% were over 60 years of age (Table 2). There were

[c] See Acknowledgements, page 387.

29 females and 25 males. All but one had confirmed lesions in the liver; 16 (30%) had additional lesions in other organs. Thirty-six (67%) of the patients had undergone previous surgery. Mebendazole was used in fixed or flexible doses; daily doses of mebendazole were 3, 4 or 4.5 g in 76%; five patients (9%) received less than 3 g and eight patients (15%) 6–10 g of mebendazole daily. Only 10 patients (18%) were treated with mebendazole and observed for less than one year; 22 patients (41%) were treated and observed for 1 or 2 years, and another 22 patients (41%) for 3 to 12 years.

RESULTS AND DISCUSSION

Echinococcus granulosus *echinococcosis*

Treatment with mebendazole was fully successful in 8 of 85 patients (9%) and partially successful in 4 others (5%) with multiple localization of the cysts (Table 1). Flubendazole was effective in only 1 case of lung echinococcosis, but not in 5 patients with liver or other organ involvement. Treatment with albendazole was fully successful in 5 of 30 patients (17%) and partially successful in 4 others (13%).

No success was observed in 39% of the patients treated with mebendazole and 23% of those treated with albendazole. The remaining patients showed some improvement in clinical symptoms or signs or insignificant changes in cyst morphology.

The success of treatment with benzimidazole-carbamates depended much on the localization of the cyst(s). In patients treated with mebendazole, successful results were observed in 21% of lung echinococcosis cases, only 7% of liver echinococcosis cases, and 7% of cases with other localization (peritoneum, spleen, etc.). Albendazole was successful in three out of four (75%) lung echinococcosis cases, in 21% of liver echinococcosis cases, and in 17% of cases with other localization.

The success rates of chemotherapy, especially in liver cysts, were slightly higher in patients treated with higher doses of mebendazole and albendazole and in those observed for more than a year. There is as yet no explanation why in sporadic individual cases chemotherapy with mebendazole or albendazole caused spectacular cures or improvements within a few weeks or months. This phenomenon seems to be independent of individual drug plasma levels or any of the patients' or parasite's characteristics observed to date.

Echinococcus multilocularis *echinococcosis*

In these 54 patients, 4 deaths were reported (three within 2 years of treatment and one after 10 years) and there were 8 cases where the infection progressed despite mebendazole treatment. These 12 patients (22%) were classified as treatment failures (Table 2). In one centre it was noted that progression of the disease occurred only in patients with plasma levels below 200 nmol/l (measured four hours after the morning dose). However, in the majority of patients with alveolar echinococcosis (70%), the condition was stabilized and improvements in clinical status and in the titres of serological tests were frequent. A definite reduction in the size of the lesion was observed in four patients (7%) only.

Adverse reactions

Although the doses of mebendazole and albendazole given were well tolerated by most patients, the following clinical symptoms and signs were interpreted as possible or probable adverse drug reactions (Tables 1 and 2): severe abdominal pain, nausea and/or vomiting (recorded in 24 out of all 195 patients); dizziness, vertigo and/or headache (6 patients); fever, skin eruptions and/or pruritus (5 patients); hair loss (8 patients); serum transaminase level above 100 U/l (24 patients); leukocyte counts below 4×10^9/l (26 patients); and haemoglobin level below 9 g/l (3 patients).

These adverse drug reactions do not include the complications observed during chemotherapy such as spontaneous rupture of cysts, anaphylactic shock after the rupture of a cyst, infection of cysts and septicaemia, blockage of biliary ducts, pneumothorax, haemoptysis, pulmonary abscesses, etc. Spontaneous rupture of the lung cyst(s) occurred in 14 (47%) of 30 patients treated with mebendazole (Table 1). Spontaneous rupture of cysts localized in the liver was relatively common (5%).

In 8 patients (4%), treatment was stopped temporarily or permanently because of suspected adverse reactions. In two patients with cystic echinococcosis and in five patients with alveolar echinococcosis treated with mebendazole, the reason for stopping therapy was: the high level of serum transaminase (4 patients), allergic conditions (2 patients), and gastrointestinal disorders (one patient). In one patient with alveolar echinococcosis, albendazole treatment was stopped because of depressed bone-marrow activity.

All these clinical observations strongly suggest that the chemotherapy of human echinococcosis with benzimidazolecarbamates requires close supervision in order to prevent serious complications.

CONCLUSIONS

Mebendazole was the first drug shown to be effective in human cystic echinococcosis, but is not an

optimal compound. Studies on new drugs or new formulations of the existing benzimidazoles should be intensified and better forms of their application (parenteral or local use, liposome-bonded particles) investigated. In the meantime, chemotherapy of human cystic echinococcosis should be restricted to inoperable cases, including multiple lung echinococcosis in areas where spontaneous cure rarely occurs. The use of benzimidazoles for the prevention of secondary peritoneal echinococcosis should be investigated.

In *E. multilocularis* infections the results of the present coordinated studies have confirmed that mebendazole therapy may arrest the infection in man and is therefore indicated in most of the cases of alveolar echinococcosis irrespective of surgery. However, further studies are indicated to clarify the optimal dosage, the method of application, and the duration of mebendazole therapy. The use of other benzimidazole formulations or compounds should be explored. In fact, twenty patients with *E. multilocularis* infection in a clinical centre in Paris have already started albendazole therapy but the follow-up time is too short at present to evaluate the results.

These WHO-coordinated studies are being continued in patients with *E. granulosus* echinococcosis. Courses of mebendazole or albendazole treatment will be randomly allocated and continued for 6 months; re-examination times will be extended to at least 12 months. In patients with *E. multilocularis* infections mebendazole or albendazole will be given by random allocation, or when the response to one of these drugs is poor, the other will be used.

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RÉSUMÉ

ESSAIS CLINIQUES MULTICENTRES DES CARBAMATES DE BENZIMIDAZOLE POUR LE TRAITEMENT DE L'ECHINOCOCCOSE CHEZ L'HOMME

Dans le cadre d'essais cliniques multicentres, l'OMS a coordonné sept études sur la chimiothérapie de l'échinococcose humaine par le mébendazole, l'albendazole et le flubendazole. Ces essais ont eu lieu à Anchorage, AK, Etats-Unis d'Amérique; Beyrouth, Liban; Besançon, France; Paris, France; Rome, Italie; Sofia, Bulgarie; et Zurich,

Suisse. Les conclusions qui suivent ont été tirées de la première phase de ces études.

Le traitement par le mébendazole de 85 malades atteints d'échinococcose hydatique (*Echinococcus granulosus*) a guéri 8 malades et en a partiellement guéri 4 autres. Le flubendazole n'a été efficace que dans 1 cas d'échinococcose pulmonaire. L'albendazole a guéri 5 des 30 malades traités et en a partiellement guéri 4 autres. Il faudra poursuivre l'étude de nouveaux médicaments ou de nouvelles formulations des benzimidazoles existants, et rechercher de meilleurs modes d'application. En attendant, la chimiothérapie de l'hydatidose humaine devra être limitée aux cas inopérables.

Il a été confirmé, chez 54 malades atteints d'échinococcose à *E. multilocularis*, que le traitement par le mébendazole pouvait arrêter le développement des lésions. Ce traitement est par conséquent indiqué dans la plupart des cas d'échinococcose alvéolaire, qu'il y ait ou non intervention chirurgicale. Toutefois, il est nécessaire d'effectuer des études complémentaires pour définir la posologie optimale du mébendazole et pour tester l'efficacité d'un traitement par l'albendazole.