ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1993, p. 1679–1684
0066-4804/93/081679-06$02.00/0

Vol. 37, No. 8

Therapy of Human Hydatid Disease with Mebendazole and Albendazole

ANTONELLA TEGGI,* MARCO GREGORIO LASTILLA, AND FRANCO DE ROSA

Second Chair of Infectious Diseases, Università degli Studi di Roma 'La Sapienza,' Policlinico Umberto I, Viale Regina Elena, 166, 00161 Rome, Italy

Received 27 October 1992/Accepted 26 April 1993

We report our experience in the treatment with benzoimidazole carbamates (mebendazole and albendazole) of 337 patients affected by hydatid cysts with different localizations. The treated cysts showed degenerative modifications in 50.6% of the cases after mebendazole treatment and in about 80% after albendazole treatment. Relapses after therapy were observed in 30% of the cases; about 95% of the recurring cysts showed good susceptibility to a further cycle of therapy with benzoimidazole carbamates. Side effects observed with either drug were not severe and always reversible, consisting mainly of abdominal pains and increased levels of transaminases in serum. Among the factors that may influence the therapeutic results are the drug employed, the age of the cysts, the age of the patient, and the localization of the cysts and their morphological characteristics. Moreover, it can be hypothesized that each hydatid cyst has an intrinsic sensitivity to benzoimidazole carbamates.

In the early 1970s, some benzoimidazole carbamates were proved to be effective against *Echinococcus granulosus* and, since then, many investigators have employed mebendazole and albendazole for the treatment of human hydatid disease (4, 8, 14, 20, 21, 24, 27, 28, 31). These drugs inhibit tubulin and induce blockage of glucose absorption, glycogen depletion, and degenerative alterations in the endoplasmic reticulum and mitochondria of the germinal layer, increasing lysosomes and producing cellular autolysis (6, 13, 18, 20, 32).

Preliminary experimental data on natural hydatidosis in sheep treated with benzoimidazole carbamates frequently reveal an inflammatory process very similar to that observed in cases of spontaneous recovery on histological examination of cysts (2). These data may suggest that benzoimidazole carbamates do not simultaneously affect different parts of hydatid cysts but that they first attack external layers of the membrane, which leads to a marked inflammatory reaction altering the parasite-host equilibrium until the protoscolices and germinal layers gradually become devitalized (2).

After encouraging experimental results observed both in vitro and in laboratory animals for the treatment of adult and larval stages of cestodes (6, 12, 15, 17), mebendazole, a broad-spectrum anthelmintic drug, was the first benzoimidazole carbamate used in the treatment of human hydatidosis (9, 13, 16, 20, 24, 28).

Mebendazole is poorly absorbed after oral administration, producing low levels in plasma, even lower concentrations in cysts (levels in blood, 10%), and liver metabolism leading to inactive metabolites (28). In this regard, experimental data for animals suggest that plasma mebendazole levels of at least 72 ng/ml should be considered effective (28).

Albendazole is the most recent benzoimidazole compound for the treatment of human hydatid disease (21, 27). This drug appears to be highly effective in humans and other species against several larval and adult stages of nematodes, trematodes, and cestodes (21, 25, 26). In humans, albendazole is better absorbed than mebendazole, and its hepatic metabolite, albendazole sulfoxide, is also active. Levels of this metabolite in serum may be as much as 10 times higher than those produced by equivalent therapeutic doses of mebendazole (7, 20, 21, 27). In addition, experimental data suggest that a concentration of at least 250 μg of albendazole per liter for 7 to 10 days or 50 μg/liter for 30 days in in vitro cultures is required for complete protoscolex devitalization (23).

Results in the treatment of human hydatid disease have been encouraging, though not always comparable because of the different schedules used. To solve this problem, some years ago the World Health Organization promoted two controlled multicentric trials to evaluate the usefulness of mebendazole and albendazole according to standard criteria (33, 34). In this paper, we report our experience in the treatment of 337 cases of human hydatid disease.

MATERIALS AND METHODS

Patients. From January 1982 to December 1991, 337 patients with hydatid cysts located in various parts of their bodies were treated; 121 of them were treated with mebendazole, and 216 were treated with albendazole. The characteristics of these patients are shown in Table 1.

Criteria for enrollment. World Health Organization protocols were used for indications and contraindications for chemotherapy (33, 34). Chemotherapy was indicated for patients who were inoperable, who were subjected to nonradical surgery, and who refused surgery. Contraindications for chemotherapy were hydatid disease complications, pregnancy, impaired liver, hemopoietic, and/or kidney function, and lack of cooperation of the patient.

Randomization method. Patients for whom medical therapy was indicated were treated with mebendazole or albendazole according to randomized criteria. Because of its greater effectiveness, albendazole was selected as first-choice treatment for liver cysts only 3 years ago; thus, the last 90 patients studied were treated with albendazole without randomization.

Drug schedules. One hundred eighteen patients were

* Corresponding author.

TABLE 1. Characteristics of 337 patients with hydatid cysts treated with benzoimidazole carbamates

Characteristic	No. of patients treated with:	
	Mebendazole	Albendazole
Total patients	121	216
Sex		
Female	71	122
Male	50	94
Age (yr)		
1–10	4	3
11–20	8	8
21–30	14	28
31–40	18	34
41–50	30	65
51–60	22	33
>60	25	45

TABLE 2. Effects of mebendazole treatment of cysts considered singly

Outcome	No. or % of cysts		
	Liver	Abdomen	Lung
Total cysts	172	55	16
Interruption of therapy[a]	13	4	1
Disappearance of cyst	8	4	4
Volumetric reduction	30	11	6
Morphologic modification	54	17	2
No modification	85	21	5
Any modification(s)[b]	46.5%	58.8%	66.6%
Further modification after therapy	28	2	1
Recurrence[c]	22	1	2
Surgical removal	30	23	1

[a] The cysts of the patients who stopped treatment were excluded from the statistic evaluation.
[b] Some cysts showed more than one modification (see "Criteria for assessment" in the text). 50.6% of the cases considered showed at least one modification.
[c] Relapses occurred in 21.9% of the cases.

treated with 50 mg of mebendazole per kg of body weight per day, two were treated with 30 mg/kg/day, and one was treated with 100 mg/kg/day. Treatment ranged from 3 to 12 months, and 30 patients were subjected to further cycles of treatment. Albendazole was administered at a dosage of 10 to 12 mg/kg/day without intervals for 3 months; 99 patients were subjected to further cycles of therapy.

Controls during therapy. Clinical, radiological, immunological, and biochemical controls were periodically performed, and liver, kidney, and hemopoietic function tests were carried out every 10 to 15 days during treatment. For patients with lung cysts, chest X rays were performed every 1 to 3 months during treatment; for those with liver, abdominal, subcutaneous, and muscular cysts, ultrasonography was performed every 1 to 3 months during treatment; and for some patients, computerized tomography and nuclear magnetic resonance tests were also performed. In addition, 4 h after administration of morning doses, plasma drug levels were measured in some patients by radioimmunoassay and high-pressure liquid chromatography. Thirty-five of seventy-six cysts surgically removed after medical therapy were further studied to evaluate the presence and characteristics of scolices and their eventual cystic evolution after inoculation in BALB/c mice, the morphology of membranes by optic and electron microscopy studies, and endocystic drug levels. The follow-up of the patients ranged from 6 to 103 months.

Criteria for assessment. The evaluation of the results was based on objective criteria, mainly those provided by imaging methods and, in particular, ultrasound monitoring of hepatic and abdominal cysts. To evaluate the effectiveness of therapy, the following changes were considered: the volume of the cyst (with a decrease of at least 10% up to complete disappearance), the morphology of the cyst, the increase of the solid component of the cyst (partial or total solidification corresponding to the pseudosolid ultrasonic pattern), the decrease in the number and/or size of daughter cysts, detachment and/or collapse of membranes (split wall or water lily sign), and calcification.

These findings were considered degenerative alterations of the hydatid cyst, which were probably caused by a reduced ratio between fluid secretion of the parasite and its reabsorption by the host parenchyma, in turn causing reduced endocystic pressure (5, 29).

Some of the hydatid cysts were clearly defined and therefore easily measurable; however, some patients had widespread hydatidosis with ill-defined cysts that were difficult to measure, and these cases were investigated separately. Moreover, in patients with both cysts which were easily measurable and others which were not clearly defined, the measurable cysts were investigated individually.

In order to evaluate the efficacy of treatment in cases of widespread hydatidosis, the following general criteria were used: success, defined as the disappearance or clear decrease in size of cysts and/or distinct degenerative changes in cyst morphology; partial success, defined as the successful treatment of a cyst(s) of one organ but not of others or of some cysts but not of others; improvement, defined as slight changes in cyst morphology and/or clinical improvement; and failure, defined as no change in cyst size or morphology and/or no change in the clinical stage. The same criteria were also applied for summarized results obtained for patients with singly evaluable hydatid cysts. Relapses were diagnosed on the basis of volumetric increase of cysts and/or disappearance of pseudosolid ultrasonic patterns, replaced by anechoic areas, and/or disappearance of split walls (5).

Statistical analysis. Statistical evaluation was performed by the X^2 test and, when required, by a comparative proportional test; values of $P < 0.05$ were considered significant.

RESULTS

Hydatid cysts observed. Overall, 172 liver cysts, 55 abdominal cysts, 16 lung cysts, 1 bone cyst, 1 subcutaneous cyst, and 1 mediastinic cyst were treated with mebendazole; 300 liver cysts, 42 abdominal cysts, 56 lung cysts, 5 bone cysts, 6 subcutaneous cysts, and 2 pericardic cysts were treated with albendazole. Furthermore, 68 patients with multiple or disseminated hydatidosis were treated (22 with mebendazole and 46 with albendazole). Results observed for the treatment with mebendazole and albendazole of hydatid cysts investigated singly are shown in Tables 2 and 3 and in Fig. 1. Only data for cysts of patients who completed the treatment schedule were evaluated.

Results of mebendazole treatment of cysts investigated singly. On the whole, apart from localization, 50.5% of the hydatid cysts treated with mebendazole showed degenerative modifications (listed in "Criteria for assessment" above) after therapy; this improvement sometimes continued after the suspension of treatment. Twenty-two percent of cysts recurred between 2 and 54 months after the end of

TABLE 3. Effects of albendazole treatment of cysts considered singly

Outcome	No. or % of cysts		
	Liver	Abdomen	Lung
Total cysts	300	42	56
Interruption of therapy[a]	18	1	2
Disappearance of cyst	15	4	12
Volumetric reduction	75	10	24
Morphologic modification	180	13	21
No modification	56	15	12
Any modification(s)[b]	80.1%	63.4%	77.7%
Further modification after therapy	68	6	11
Recurrence[c]	67	14	10
Surgical removal	18	1	3

[a] The cysts of the patients who stopped treatment were excluded from the statistic evaluation.
[b] Some cysts showed more than one modification (see "Criteria for assessment" in the text). 77.9% of the cases considered showed at least one modification.
[c] Relapses occurred in 30.9% of the cases.

TABLE 4. Effects of mebendazole treatment of disseminated hydatidosis

Outcome	No. of patients with infection of:			
	Liver	Lung	Abdomen	Bones and/or subcutaneous and/or muscular tissue
Total patients	7	3	9	3
Interruption of therapy	1	0	0	0
Success	1	2	1	0
Partial success	3	0	4	1
Improvement	1	0	1	1
Failure	1	1	3	1
Relapse	2	1	2	0

therapy. With regard to localization, 46.5% of the hepatic cysts, 66.6% of the lung cysts, and 58.8% of the abdominal cysts showed degenerative modifications after mebendazole treatment. Overall, success was achieved for 15.6%, partial success was achieved for 14.4%, and improvement was achieved for 21.6% of the patients and failure resulted for 48.1% of the patients.

Results of albendazole treatment of singly investigated cysts. On the whole, irrespective of their localization, 77.9% of the hydatid cysts treated with albendazole showed degenerative modifications (listed in "Criteria for assessment" above) after treatment; this improvement sometimes continued after treatment was stopped. After the end of therapy, 30.9% of the cysts recurred, and over one-half of the cases relapsed more than once. Overall, success resulted for 49.3%, partial success resulted for 13.1%, improvement resulted for 5.9%, and failure resulted for 31.5% of the patients.

Results of widespread hydatidosis treatment. The results of treatment of patients with widespread hydatidosis are shown in Tables 4 and 5; in these cases, the effects of therapy were evaluated by subjective rather than objective criteria.

Treatment of recurrent cysts. Table 6 illustrates the results obtained after a further cycle of treatment with mebendazole or albendazole of the cysts that recurred after treatment. These results demonstrate that recurring cysts showed good susceptibility (of about 94.9%) to a further cycle of therapy with the same drug or with the other benzoimidazole compound.

Studies of cysts removed after treatment. Data relating to the characteristics of scolices and membranes of 35 cysts surgically removed from 24 patients and examined after a cycle of therapy with mebendazole (23) and albendazole (12) are reported in Table 7. These data demonstrate that most of the treated cysts had reduced numbers of scolices which

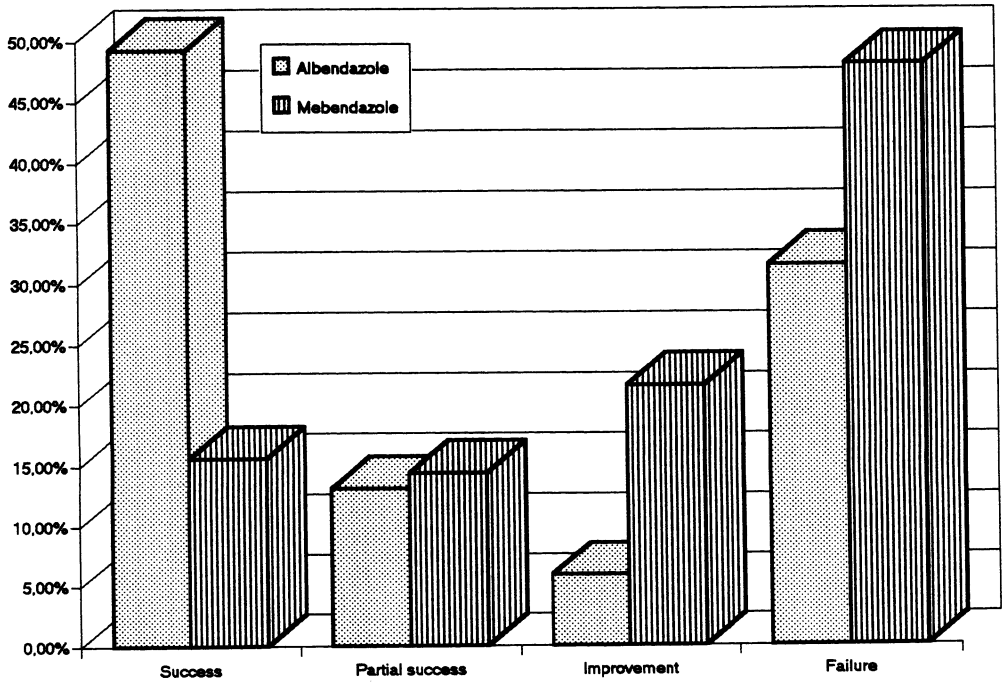

FIG. 1. Percentages of patients with singly evaluable hydatid cysts for whom treatment with mebendazole and albendazole resulted in the indicated outcomes.

TABLE 5. Effects of albendazole treatment of disseminated hydatidosis

Outcome	No. of patients with infection of:			
	Liver	Lung	Abdomen	Bones and/or subcutaneous and/or muscular tissue
Total patients	13	7	11	15
Interruption of therapy	0	1	0	0
Success	4	3	1	0
Partial success	5	3	4	4
Improvement	2	0	2	5
Failure	2	1	4	6
Relapse	2	1	1	4

were not colored by neutral red and showed a reduced capacity for cystic development when inoculated into the peritoneum of BALB/c mice. In the surgically removed cysts, electron microscopy demonstrated marked signs of degeneration of germinal layers; sometimes these alterations were also present in cysts that did not show macroscopic modifications.

Side effects. On the whole, treatment was well tolerated; the observed side effects are reported in Table 8. During treatment with mebendazole, rupture of cysts occurred in two patients, one with abdominal and one with hepatic hydatidosis. Such ruptures were not considered side effects of therapy, since the correlation with treatment was very doubtful: in the first case, trauma was involved, and in the second case, the rupture occurred after only a few days of treatment.

Six children with lung hydatidosis had repeated vomica or expectoration of membranes during or soon after treatment. Vomica was observed more than once (up to three times) in two of these children. In all cases, vomica was followed by anatomic cure (i.e., disappearance of cysts); further intrapulmonary dissemination was never observed.

Immunological survey. Regarding the immunological reactions of patients treated with mebendazole and albendazole, antibody levels detectable by routine serological tests (indirect hemagglutination, double diffusion, and counterimmunoelectrophoresis) are not correlated with therapeutic results in short-term follow-up.

DISCUSSION

Since the natural history of hydatidosis is not well documented and because of the many different factors related to both the host and the parasite, an evaluation of the results observed is difficult. Furthermore, it is hard to establish objective criteria to quantify therapeutic effectiveness, especially in the cases of widespread hydatidosis. Anatomic cure, i.e., disappearance of cysts followed by restitution ad integrum, should be the ultimate goal of treatment, but it can rarely be reached after medical treatment, and in only 8% of the cases reported in this paper did all cysts disappear.

Up to now, no immunological marker of prognostic value

TABLE 6. Results of further treatment of recurring cysts with benzoimidazole carbamates

Treatment group (*n*)	No. of cases with result[a]	
	Positive	Negative
Original mebendazole treatment (30)		
Mebendazole follow-up (14)	11	3
Albendazole follow-up (16)	13	3
Original albendazole treatment (103)		
Mebendazole follow-up (4)	1	3
Albendazole follow-up (99)	94	5

[a] Positive, degenerative modifications of the cysts (see "Criteria for assessment" above) after treatment; negative, no modification of the cysts after treatment.

TABLE 7. Viability of membranes and scolices from liver cysts surgically removed after chemotherapy

Patient	Treatment	Histology of membranes	% Living scolices[a]	No. of infected BALB/c mice/ no. inoculated
1	Mebendazole	Degenerated	0[b]	
2[c]	Mebendazole	Normal	60	0/10
3	Mebendazole	Degenerated	30	0/8
4[c]	Mebendazole	Degenerated	0	
5[c]	Mebendazole	Degenerated	10	0/10
6	Mebendazole	Degenerated	40	1/8
7[c]	Mebendazole	Normal	10	1/10
8	Mebendazole	Normal	0	
9	Mebendazole	Degenerated	0	
10	Mebendazole	Normal	40	4/8
11	Mebendazole	Degenerated	0	
12[c]	Mebendazole	Degenerated	20	0/10
13[c]	Mebendazole	Degenerated	0	
14	Mebendazole	Degenerated	0	
15	Mebendazole	Degenerated	20	0/10
16	Mebendazole	Degenerated	0	
17[c]	Albendazole	Degenerated	0	
18[c]	Albendazole	Normal	40	4/10
19	Albendazole	Degenerated	0	
20[c]	Albendazole	Degenerated	10	
21	Albendazole	Degenerated	0	
22	Albendazole	Degenerated	0	
23	Albendazole	Degenerated	10	
24	Albendazole	Degenerated	20	

[a] Determined by a positive reaction to the neutral red test.
[b] No living scolices.
[c] Some patients had more than one cyst; in these cases, a pool of hydatid fluid was made before performing the neutral red test and the inoculation of BALB/c mice.

TABLE 8. Side effects of mebendazole and albendazole[a]

Side effect	No. of patients	
	Mebendazole (*n* = 121)	Albendazole (*n* = 216)
Elevated SGOT and SGPT[b]	14	36
Abdominal pain	14	21
Headache	3	4
Distension	5	3
Vertigo	1	4
Urticaria	3	2
Jaundice	1	1
Alopecia	5	4
Thrombocytopenia	0	2
Tachycardia	0	1
Dyspepsia	4	1
Fever	0	1

[a] Several side effects were observed in some patients. Eight patients treated with mebendazole and six treated with albenzadole stopped treatment because of side effects.
[b] Serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels were considered elevated at 20% of the normal upper limit.

in a short-term follow-up has been identified, perhaps because medical treatment leads to biological recovery (death of the parasite) more often than to an anatomic cure, with persistence of the host's antigenic stimulation. In fact, in our experience, specific immunoglobulin E determination is more useful in a long-term than in a short-term follow-up (3).

More-promising results could perhaps be obtained by studying cellular immunity by the peripheral blood mononuclear cell proliferation assay (30) (which showed a decreased activity in patients with better therapeutic results) and by testing histamine release from basophils; the latter test is still being investigated (1).

In our experience, reported in previous papers, the levels of benzoimidazole carbamates in both plasma and cysts are poor and do not show a linear correlation with the effectiveness of the therapy (9, 11).

Most of the cysts treated with benzoimidazole carbamates show degenerative modifications (volumetric reduction and/or morphological alterations, such as solidification, detaching of membranes, and calcification) whose further evolution can hardly be predicted: in some cysts these degenerative modifications progressed until the parasite's death (biological recovery), while some cysts recurred after the end of treatment.

Anatomic cure after therapy with benzoimidazole carbamates is more frequent for lung cysts of children or for cysts dating back less than 2 years, since they are more easily expectorated (10, 19).

Calcification in liver cysts, as previously reported both by our group and by other authors (3, 31), is generally observed later in the follow-up and is not indicative of the parasite's death.

Treatment with benzoimidazole carbamates can sometimes sterilize the cysts and kill the parasite without also causing modifications detectable by imaging methods. A prolonged follow-up period (for at least 10 years, if not for life) for patients treated with benzoimidazole carbamates is needed before a definitive evaluation of the effectiveness of the therapy can be made.

Factors influencing therapeutic results. Many factors can influence the therapeutic results, and it was possible to elaborate statistical evaluations for some. These statistics, however, must be studied with caution, since they consider only one parameter a time and it is known that therapeutic results can be influenced by several factors, including the following.

(i) **Drug employed.** When the percentages of cyst modifications after treatment were compared, for our patients albendazole was significantly ($P < 0.001$) more effective than mebendazole in the treatment of whole hydatid cysts and liver cysts (50.6 versus 77.9% and 46.5 versus 80.1%, respectively); furthermore, the cysts treated with albendazole showed degenerative modifications in shorter periods than the cysts treated with mebendazole (means of 1 to 3 versus 3 to 6 months).

In our experience, the effectiveness of albendazole in the treatment of liver cysts was greater than in other studies reported (8). This may be correlated to the different dosage schedules used; in fact, in our series, albendazole was administered for uninterrupted cycles of 3 months, while other investigators used three cycles of therapy of 1 month with 15-day suspensions of therapy between cycles.

In our study, uninterrupted administration of albendazole was preferred since, in our opinion, intermittent administration could be more useful to the parasite than to the host.

(ii) **Age of cyst and age of patient.** Hydatid cysts dating back less than 2 years and cysts of patients less than 20 years old were significantly more responsive to therapy with benzoimidazole carbamates than comparable cysts dating back more than 2 years or in patients more than 20 years old (10). It can be hypothesized that the younger cysts have thinner fibrous envelopes (28) and/or higher metabolic activities with greater susceptibility to the action of benzoimidazole carbamates.

(iii) **Morphology of the cyst.** The occurrence of solidification was significantly more frequent among cysts with daughter cysts (164 of 310 versus 43 of 223) ($P < 0.005$), while volumetric reduction and detaching of membranes were more frequently observed among cysts without daughters (98 of 223 versus 46 of 310, respectively) ($P < 0.005$).

(iv) **Localization of the cyst.** In our experience, mebendazole therapy seems more effective for lung and abdominal cysts than liver cysts, even though results were not statistically significant ($P = 0.5$). This hypothesis, also reported by other authors, has been correlated with the envelopes of the cysts localized in the lung and abdomen being less fibrous (28, 31). On the other hand, there were no differences in sensitivity on the basis of cyst localization for albendazole therapy.

(v) **Differences in strains of *E. granulosus*.** The wide range of the observed results can also be influenced by the existence of different strains of *E. granulosus* with several degrees of sensitivity to benzoimidazole carbamates in the same way that schizomycetes reactions to antibiotics vary.

(vi) **Intrinsic sensitivity of the cyst.** Every hydatid cyst probably has intrinsic sensitivity to benzoimidazole carbamates; this hypothesis is supported by the not infrequent observation of very different therapeutic outcomes obtained for cysts of the same patient, even when the cysts have the same morphology and are localized in the same organ.

Conclusions. From a qualitative point of view, our results are similar to those reported in the literature (4, 14, 21, 22, 27, 31) regarding the findings of degenerative modifications in the cysts treated with benzoimidazole carbamates, relapses, and side effects. On the other hand, in our study, albendazole showed significantly more effective results than mebendazole in liver cysts, which differs from the findings of other authors (8). Finally, no positive correlation between drug levels and the effectiveness of therapy was found in our investigation (9), in disagreement with the findings of other authors (21, 22, 24, 27).

Benzoimidazole carbamates sometimes have a parasitocidal and sometimes a parasitostatic action, as suggested by the relapses frequently observed after suspension of treatment, as if the drugs can sterilize and stop the growth of echinococci but not completely kill them (2, 17, 20, 24).

After medical treatment, hydatid cysts show the same morphologic changes that can occur in the natural development of these cysts; nevertheless, the frequency of such changes is undoubtedly much higher than that observed for untreated cysts. Furthermore, these degenerative alterations take place and progress over shorter periods.

The treatment of cysts with further cycles of benzoimidazole carbamates after relapses proved to be effective in about 95% of the cases. Some cysts showed signs of recurrence more than once during follow-up (up to eight times in one case of a subcutaneous cyst), but they maintained equal sensitivity to further treatment.

Concerning the relationship between surgical and medical therapy of patients with hydatid disease, surgery should be indicated for patients with complications (infection or rupture of cysts or symptoms of compression or obstruction).

On the other hand, medical therapy is indicated when surgery is not possible or is unlikely to be effective, in patients who refuse surgery, or as a first therapeutical approach. Medical therapy should not be considered in opposition to but rather complementary to surgery, and the choice of therapy should be individual for each patient.

In our experience, patients who have never been subjected to surgery generally choose surgical treatment, while patients who have had operations in the past choose medical therapy. Even though definitive data on the effectiveness of mebendazole and albendazole for the prophylaxis of postsurgical relapses have not yet been reported, treatment with benzoimidazole carbamates at the same dosage used in therapeutical trials is advisable in all patients undergoing surgery to prevent cystic evolution of scolices which may be disseminated during the operation. A long-term follow-up for patients treated with benzoimidazole carbamates, as is usual for surgical patients, is advisable.

Many questions on the medical treatment of hydatid disease are still unsolved, and the most important are about the individualization of the best treatment and the management of relapses. Nevertheless, our experience appears to be encouraging, and benzoimidazole carbamates can be regarded as drugs producing objective degenerative modifications in hydatid cysts.

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