

REVIEW ARTICLES

NONSURGICAL TREATMENT OF CYSTIC ECHINOCOCCOSIS

Soheila Khazaei, Mohammad Ismail Motlagh**, Saeed Khazaei****

Abstract

The history of medical treatment of echinococcosis is intimately related to development and use of benzimidazole carbamates (e.g., mebendazole, albendazole, etc.) as a safe and effective class of antiparasitic drugs. The most important side effects include abnormality in liver enzymes, hair loss, drug allergy, bone marrow suppression. Factors predicting the cyst's response to treatment are size, site and dosage and method of use of the drug. Relapses occur in 3-25% of patients, the majority occurs within first two years. There are a few contraindications to the medical therapy of hydatid cyst, including: pregnancy, bone marrow suppression, liver diseases, diabetes mellitus and some cyst characteristics such as size and location of some of cysts.

Introduction

Treatment of cystic echinococcosis changed substantially during the past 20 years. Although surgery is still considered the first choice approach for radical care (1-3), medical treatment - both as adjunct and as sole treatment and also minimally invasive puncture techniques under sonographic and CT guidance gain increasing acceptance. Surgical treatment of the hydatid cysts have an inherent paradox, i.e. radical surgical procedures that have substantially less incidence of recurrences also are associated with increased morbidity, mortality, post-operative complications and hospital stay. Such invasive procedures are also impossible in substantial proportion of the patients because of co-morbid diseases, presence of multiple cysts in one or multiple organs and proximity of the cysts to major vascular or biliary structures.(2)

Mebendazole

Mebendazole is available as 100mg tablets. The drug is only slightly soluble in water and poorly absorbed after oral administration.(4-6) The rate of absorption increases (up to 8 folds) if the drug is taken during a meal specially one with a high fat content.(1,5) In plasma more than 95% of the drug is protein-bound.(5,6) Mebendazole is rapidly metabolized in liver to inactive metabolites, which are excreted via bile and urine. (1,5,6) It seems that the mebendazole itself rather than its metabolite is the active drug. (5,7) The elimination half-life is short (2.5-5.0 hours) but may be increased in patients with cholestasis. (5,7) The serum level of the drug show great inter-individual variability and not correlate with the dose given but serum level 4 hours after the morning dose have a high degree of predictability for the 24-hour average serum concentration. (1,7) Based on animal studies and therapeutic trials in human, the serum level of 200-250 nmol/L 4hours after the morning dose is suggested as the required concentration for anti-echinococcal effect (1,7), however several studies showed that such concentrations may not be attained by more than 30% of patients and lower (yet undetermined) levels may be sufficient. (1) Mebendazole have minimal and mild side

effects when used in low doses and for short courses (e.g.: 100mg bid for 3 days) including mild abdominal pain and diarrhea in those with high intestinal parasite burdens. (6) When the drug is used in high doses and for prolonged duration as in the treatment of echinococcosis, about 2/3 of patients experience one or more side effects but they are mostly of minor severity and importance. (1) The more important side effects include: alopecia, liver enzyme abnormalities and bone marrow suppression (with severe but reversible neutropenia). (6)

Albendazole

Albendazole (methyl-S-N- propoxy thio- 2-benzimidazole carbamate) has an exceptionally broad spectrum of anti-parasitic activity. (5,6) The drug is a white, odorless powder dispensed as 400mg human or 600mg veterinary tablets. It is practically insoluble in water and has erratic and variable absorption after oral administration. As for mebendazole the absorption of the drug can be enhanced by administration with a fatty meal. (5,6,8) Albendazole undergoes extensive first- pass metabolism in the liver and only albendazole sulfoxide which is primarily responsible for antihelminthic effect can be detected in serum. (5,6,8) The peak serum concentration of albendazole sulfoxide is reached within 2-4 hours following oral consumption. (7) It has plasma half-life of 9 hours and is 70% protein bound. (5,8) Albendazole sulfoxide is further oxidized to inactive sulfon metabolite. (5) The drug induces the cytochrome P450 responsible for its own metabolism and co-administration of cimetidine increases the serum levels. (8) It is also shown in animal experiments that co-administration of cimetidine and albendazole may increase the therapeutic effect on alveolar echinococcosis. (9) Co-administration of dexamethasone also increases the serum levels of Albendazole. (6) No human studies done to elucidate the incidence and clinical significance of albendazole resistance in hydatid cysts. Although about 2/3 of the patients experience one or more side effects, they are mostly of little importance and reversible (1,4,7,8,) and only in about 2.6 to 3.8 percent of patients drug was discontinued because of the side effects such as elevated serum transaminases, bone marrow suppression or alopecia. (4,7)

Choice of the benzimidazole drug for treatment of cystic echinococcosis

Mebendazole and flubendazole are used in the treatment of cystic echinococcosis. The success rate with flubendazole was very low (10) and therefore it is not considered a suitable drug for treatment of this disease. Mebendazole is the first benzimidazole drug used for treatment of cystic echinococcosis and success rate of 7-38% was reported for it. (3,4,10,11) In studies directly comparing mebendazole with albendazole, the success rate for albendazole was much greater (average 21%-30% versus 7%). (8,10-14) This was attributed to better bioavailability and greater tissue and cyst penetration

of Albendazole. (5,6,8,15) According to available data, albendazole can be considered as the drug of choice for medical treatment of cystic echinococcosis. (5,8)

Factors predicting the response of hydatid cysts to medical therapy

Size: There is general agreement that smaller cysts which are probably younger and have a thinner wall, show a more favorable response to chemotherapy (2,8,13) although some investigators disagree. (16)

Site: The best results are seen with hepatic, pulmonary and intra-abdominal cysts. (4,17) In some studies, the response of pulmonary cysts was even better than hepatic ones. (4,16,14) Poor responses are seen with bone cysts, which are unfortunately also very difficult to treat surgically. (13)

Sonographic appearance: Thick walls (8) and presence of daughter cysts (13) are associated with decreased response.

Dosage

Mebendazole is given in doses of 40-50mg/kg/day, usually in three divided doses. (13,14,17-19). According to clinical experience, daily doses of greater than 6g should not be applied to adults regardless of serum level achieved. (7) Albendazole is given in daily dose of 10-15mg/kg/day. (10,11,17,19). Animal studies showed that a total daily dose of 10mg/kg/day of albendazole produces cyst fluid concentrations of albendazole sulfoxide in excess of 100g/l, which is at the lower end of effective in-vitro parasitocidal concentrations. (15) Because of problems related to available dosage forms of the drug (400mg human and 600mg veterinary tablets), patients with body weight equal to or greater than 40kg receive 400mg bid and in those <40kg, dose is calculated according to body weight. It seems that efficacy of chemotherapy is higher in patients who received higher doses of albendazole (10,16) or mebendazole. (10,18) The maximum daily dose of albendazole given in experimental studies is 20mg/kg. (16)

Duration & method of treatment

For mebendazole the recommended duration of treatment is 3 months. (10,12) It is suggested that longer durations of treatment (up to 6 months) may be more effective and should be considered in cases predicted to be poorly responsive to antihelminthic therapy. (18) Albendazole is given in an intermittent treatment schedule with 4 week courses of therapy separated by drug free intervals of 2 weeks to decrease the incidence of adverse effects. (7) Usually three courses of therapy are given and it seems that more than six courses are usually not necessary. (1,10,17,19) Gill- Grande et al showed that 3 months of treatment is significantly more effective than 1 month course in reducing the viability of protoscolices (6% versus 24%). (20) There are emerging evidences that continuous treatment with albendazole for 3 to 6 month without drug holidays is significantly more effective and may not be associated with increased

side effects. (1,7,8,12,21)

Follow up of Medically Treated Patients

Most follow up measures especially clinical judgment are relatively insensitive for detection of cyst changes during medical treatment. Serologic tests are also not suitable for this purpose because of relative initial insensitivity and slow, delayed and unpredictable response even after successful treatment. (10,22) Therefore, imaging studies and in particular ultrasonography have the most important role in follow up of hydatid cysts. The relation between sonographic changes and cyst viability is clearly demonstrated in the excellent work by Gill- Grande et al (20) in which the viability was assessed by surgical removal, pathologic examination and inoculation to mice after albendazole treatment. They confirmed that size reduction of > 20%, membrane disruption and increased echogenicity of the cyst matrix are specific for non-viability (only one of 20 cysts showing these changes was viable but lacks specificity (only 41% of nonviable cysts show above sonographic changes. (20)

Efficacy and Outcome of Chemotherapy of Cystic Echinococcosis

Chemotherapy with benzimidazole carbamates results in complete cure in about 30% (9-43% in different trials), degenerative changes and/or significant decrease in size (improvement) in 30-50% and no morphological change in about 20-40% of patients in different studies. (1) In long term follow up of cases of cystic echinococcosis treated with benzimidazole carbamates, it is noted that some cysts which had no or minimal initial response may respond later even in the third post-treatment year with morphologic changes in sonography. (9) The differentiation of above late-appearing responses from spontaneous degeneration is difficult because of absence of control group in majority of trials.

Relapses

Relapses occur in 3-25% of cases in various studies and time of relapse varies from 1 to 100 months after end of the treatment, although majority of them occur during the first 2 years. (4,12,16,22). This relapse rate compares favorably with relapse rate of 11-30% reported with surgical treatment, especially with more conservative methods. (16) Signs of relapse on sonography include: reappearance of new daughter cysts or increase in the size. (22) There is no difference in relapse rate between treatment with mebendazole or albendazole but less recurrent cases are seen in younger patients and with extra hepatic cysts. (12) Further benzimidazole treatment of recurrent cysts results in high response rate of 75 to 90%, which is significantly higher than primary response. (4,12). This may be evidence against development of acquired albendazole resistance during treatment of cystic echinococcosis.

Measures to improve the efficacy of albendazole

Because of unpredictable and relatively low response rate with albendazole, attempts are made to

increase its efficacy. Continuous albendazole therapy may be superior to current method of intermittent therapy. Combination of praziquantel, an isoquinolone scolicide and albendazole used as both preoperative adjunct chemotherapy and sole treatment of cystic echinococcosis may be beneficial. Al karawi et al (1998) reported result of comparison between albendazole alone and albendazole plus praziquantel in a prospective, open label study. The complete response rate was 36.4% and 47.4% in albendazole and combination therapy groups respectively. It is of great importance that from total of 7 patients who did not respond to albendazole alone in a previous trial, 5 responded to combination therapy. (23) This combination also used as preoperative adjunct therapy resulted in significant decrease in percentage of viable protoscolices compared even with relatively high (20mg/kg/day) doses of albendazole alone. (24) Praziquantel was used in these studies in a daily dose of 20mg/kg -50mg/kg. (23,24). Praziquantel alone causes ultrastructural damage in parasite membranes but is not successful in treatment of hydatid cysts in animal studies (25) and its effect in improving the efficacy of albendazole is attributed to increased level of albendazole sulfoxide (24) which remains to be proven. Prescription of albendazole in a liposome-encapsulated form used as a method to increase bioavailability resulted in significant elevation of serum, hepatic tissue and cyst tissue concentrations of the parent drug and its active metabolite in experimental studies done on mice infected with E.Multilocularis. (9)

Indications for chemotherapy of cystic echinococcosis

Chemotherapy is certainly indicated for inoperable patients with primary lung or liver cysts, those with multiple cysts-specially in multiple organs making operative resection difficult or impossible and patients with peritoneal cysts which usually are multiple and result of secondary echinococcosis. (1) The use chemotherapy alone as the primary treatment of cystic echinococcosis in other patients as suggested by some authors (3,20,26) is not widely accepted because of relatively low and unpredictable cure rate. Chemotherapy also should be considered in patients with relapse of hydatid cyst after surgical treatment because of technical difficulties and relatively high complication rate associated with repeat surgery (27,28). Albendazole is widely used as adjunct pre- and post-operative chemotherapy with both surgery and percutaneous aspiration therapy to reduce incidence of secondary hydatidosis. Pre-operative chemotherapy not only decreases the number of viable protoscolices, but also results in significant reduction of intracystic pressure, which facilitates surgical removal and percutaneous aspiration (1,28). Different dosages and durations of preoperative chemotherapy have been given in different studies from single dose of drug given 4 hours before procedure (to attain maximum serum concentration at time of procedure) to 1-3 months of preoperative treatment (20,30,31). Although World Health Organization (WHO)

recommends preoperative chemotherapy for at least 4 days followed by continuous post-operative treatment for 1 and 3 months for albendazole and mebendazole respectively (1), prospective studies showed that increasing the duration of preoperative chemotherapy significantly increases the percentage of non viable cysts (20,30) and even 3 months of treatment was significantly more effective than 1 month. Combined regimen of albendazole plus praziquantel is also useful as preoperative therapy and apparently was more successful in decreasing the number of viable cysts compared with albendazole alone. (24)

It is shown in animal studies that post-spillage chemotherapy with albendazole for 1-2 weeks may be effective in reducing the implantation of protoscolices even in the absence of previous chemotherapy (32) but little data on this aspect of treatment is available.

Precautions and Contraindications :

- **Cyst characteristics:** Because of relatively long time required for effect of antiparasitic drugs and its unpredictability, large cysts that have a risk of rupture (especially those superficially located or infected) should be excluded from medical therapy. (1)
- **Pregnancy:** Benzimidazoles show teratogenic potential in animals and therefore their use in pregnancy especially during the third trimester is contraindicated. (1,4,6-8) It should be noted however that several pregnant women have been accidentally exposed to albendazole in early pregnancy and no fetal abnormalities reported to date. (4)
- **Bone marrow suppression:** Benzimidazoles are contraindicated in this situation. (1,4)
- **Liver disease:** Benzimidazoles should be given with extreme caution if at all to these patients and if benefits of chemotherapy outweigh associated risks. Dosage should be reduced specially in those with cholestasis or portal hypertension. (3) These patients also require frequent monitoring of serum drug levels and liver function tests.
- **Diabetes mellitus:** Mebendazole may reduce insulin requirement, therefore the serum glucose levels of diabetics should be carefully monitored during treatment. (1)
- **Lactation:** Exposure with mebendazole or albendazole during breast feeding does not appear to put the infant at risk of side effects. (1) However, they should be avoided if possible. (8)

Monitoring of patients (1)

Clinical examination and liver function tests are necessary initially every 2 weeks and then monthly. Leukocyte counts should be checked at 2 weeks intervals during the first 3 months. Although usually not possible, measurement of serum drug concentrations (albendazole-sulfoxide or mebendazole) is recommended after 2 weeks and 4 weeks of chemotherapy, respectively, in order to identify levels that are too high (possibly toxic) or too low (ineffective).

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From: *Pediatric infectious Diseases, Ministry of Health and Medical Education, **Department of Medicine, Ahvaz, *** Family Physician, Tehran, Iran.

Address for Correspondence: Dr Soheila Khazaei, Pediatric infectious Diseases, Ministry of Health and Medical Education, Tehran, Iran. Email: dr.s.khazae@gmail.com

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