

# ALBENDAZOLE IN THE TREATMENT OF HEPATIC HYDATIDOSIS

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## ABSTRACT

**Objective:** To evaluate the efficacy of albendazole, in the non-surgical treatment of hepatic hydatidosis.

**Material and Methods:** This study was conducted on patients with hepatic hydatidosis & meeting the criteria over a period of 4 years, in the surgical department of Khyber Teaching Hospital, Peshawar. All these patients were treated with albendazole for an uninterrupted period of 6 months and then evaluated up to 12 months with ultrasonography.

**Results:** Patients studied during the time period were 38 (25 male and 13 female), with age ranged from 18 years to 64 years. When evaluated up to 12 months ultrasonographically, 11 (28.9%) showed marked regression or disappearance (cure). In another 19 (50%), there was evidence of cyst degeneration with a size reduction (improvement). The last 8 (21.1%) patients showed no change (failure). An overall response was noted in 30 (78.9%) cases.

**Conclusion:** Albendazole has significantly changed the management of hepatic hydatidosis, and under certain circumstances can be employed as the sole treatment modality with satisfactory clinical outcomes.

**Key Words:** Hepatic hydatidosis, Echinococcosis, Albendazole, Benzimidazoles.

## INTRODUCTION

Hydatidosis is a widespread anthroozoonosis. The distribution of echinococcosis is influenced by agricultural, economic, educational levels, and cultural habits.<sup>1</sup> For the aforementioned reasons, and because of the custom of slaughtering sheep and cattle at home among dogs, echinococcosis, constitutes a continuing serious public health problem in hyper-endemic areas such as the N.W.F.P. Of the four known species of echinococcus, three are of medical importance in humans. These are echinococcus granulosis, causing cystic echinococcosis; echinococcus multilocularis, causing alveolar echinococcosis; and echinococcus vogeli. The former is the most common, alveolar echinococcosis is rare but is the most virulent, and echinococcus vogeli is the most rare. There are currently three treatment options for liver hydatidosis: surgery, which remains the mainstay of radical treatment; ultrasound guided aspiration; and chemotherapy. Each of these therapeutic modalities has limitations depending on the individual case.

Although surgery is still considered the "gold standard" for treating hepatic hydatidosis, it is however associated with the problems of

recurrence and dissemination of the disease, and a significant morbidity and mortality. Chemotherapy is a noninvasive treatment and is less limited by the patients' status than surgery. Albendazole (ABZ), the drug most often used, appears to have the greatest efficacy of any agent used so far. The aim of this study is to evaluate the efficacy of ABZ in the non-surgical treatment of hepatic hydatidosis in a select group of patients.

## MATERIAL AND METHODS

The study evaluated the outcome of ABZ therapy as the primary mode of treatment for hepatic hydatidosis. This study was conducted at the department of surgery, Khyber Teaching Hospital, Peshawar. The study spanned over four years from January 1999 to January 2003. Patients in the study had the following inclusion characteristics:

1. Uncomplicated cysts <than 10cms. in diameter.
2. Those who refused surgery.
3. Cysts located deep in the liver parenchyma, either in the central or the juxta-caval positions.
4. Recurrent cysts, and those with re-recurrent

- cysts.
5. Those with concurrent cysts in other organs, or the peritoneum, or both.
  6. Those who had previous upper abdominal surgery.
  7. Those considered high risk for anaesthesia and surgery.

Obviously there was a certain degree of overlap of different characteristics in different patients. The following exclusion criteria for the study:

1. Patients <than 15 years of age and those >than 65 years of age.
2. Complicated cysts.
3. Cysts measuring >than 10cms, especially if peripherally located.
4. Those classified as Gharbi Type IV and Type V cysts.
5. Calcified cysts.
6. Pregnant women.
7. Those with present or past history of chronic liver disease.
8. Those who were non-compliant with medication.
9. Those who defaulted follow-up.

All patients underwent routine haematology and biochemistry including liver function tests. Serological tests were performed in all, but not totally relied upon. All patients had plain chest and abdominal X-rays, to exclude calcified cysts and concurrent pulmonary hydatidosis. The mainstay investigation was abdominal US; C.T. scan was performed in just under half the cases. All patients were started on oral ABZ in a dose of 400mg twice a day, to be taken with cimetidine 400mg twice a day, and a fatty meal. The treatment was administered to them on an outpatient basis for an uninterrupted period of six months. Patients were instructed to report every 2 weeks for the first month and then monthly for the remaining 5 months to report any major adverse effects and for evaluation of their hepatic profile. On every visit an ultrasound was performed. Serological tests were omitted. All patients were followed up for a minimum period of one year after cessation of treatment for a final evaluation.

## RESULTS

A total of 38 patients (25 male and 13 female) with hepatic hydatidosis were recruited in this prospectively performed descriptive study. The

age of the patients ranged from 18 years to 64 years, with a mean age of 39 years.

The following findings were noted in 38 patients: right lobe involvement alone in 31(81.6%) cases, right and left lobe involvement in 3(7.9%), and left lobe involvement alone in 4(10.5%) cases. Single hepatic cysts were observed in 27(71.05%) cases, whereas multiple cysts were seen in 11(28.94%) patients. When evaluated ultrasonographically (US) up to 12 months, the results of ABZ therapy in the 38 patients are summarized in Table-1.

### OUTCOME OF PATIENTS TREATED WITH ALBENDAZOLE

Outcome	No. of Patients n=38	Percentage
Cure	11	28.9
Improvement	19	50
Failure	08	21.1

Table 1

Ultrasonographically, cure was defined as marked cyst regression or disappearance; improvement as evidence of cyst degeneration with a size reduction; and failure as no change. Included in the 8 failures were 2 patients (5.2%) in whom treatment had to be discontinued because of a rise in serum transaminase (SGPT). Their hepatic profiles reverted to normal within 2 weeks of stopping treatment. No other major side effects were recorded. In 2 (5.2%) of the 8 failures, the cysts actually increased in size by the end of treatment, and in another one (2.6%), medical treatment had to be stopped because of clinical evidence of suppuration in the cyst. What was conspicuous is that 5 (13.1%) of the 8 failures had US evidence of daughter cysts within mother cysts, as opposed to 2 in the improved group, and one in the cured group. What was found to be significant is that the average size of the cysts in the cured group was 5.5 cms; 6.5 cms in the improved group, and 9 cms in the failure group. It was inferred that the smaller cysts exhibited a better response to ABZ therapy. Another note worthy finding was that the mean age of the cured group was 34, whereas the mean age of the failure group was 56.

All together 7 of the 8 failures subsequently underwent surgery. It is pertinent to mention that at operation, it was observed that intracystic pressures had markedly reduced therefore making surgery easier and lessening the chance of dissemination. Furthermore it was noted that the laminated membranes in all operated cases was less exuberant and distinctly atrophic. All in all ABZ was successful in treating 11 out of 38

patients, and an over all response was noted in a total of 30(78.9%) cases.

## DISCUSSION

In human cystic echinococcosis, the liver is reported to be the most commonly involved organ (52%-77% of cases).<sup>2</sup> The right lobe is affected in 85% of patients, and in 70% cases the cysts develop deep in the liver parenchyma, in the central or juxta-caval position, usually in segments VII and VIII, and are relatively inaccessible during surgery.<sup>3</sup> Ultrasonography (US), a noninvasive, readily available, sensitive, and cost-effective imaging technique, should be the diagnostic method of choice. C.T. scan is essential when planning surgical treatment. MRI is generally not cost effective. US features and patterns of hydatid cyst of the liver have been defined by various authors.<sup>4,6</sup> US is helpful for defining the internal structure, number, and location of the cysts and the presence of complications. The specificity of US is in the range of 90%. The ultrasonographic classification proposed by Gharbi et al gives a morphologic description.<sup>7</sup>

### Gharbi Classification:

Type	Criterion
I-----	Pure fluid collection.
II-----	Fluid collection with a split wall (floating membrane).
III-----	Fluid collection with septa (honey comb image).
IV-----	Heterogenous echographic patterns.
V-----	Reflecting thick walls.

Surgery remains the cornerstone of radical treatment for cystic echinococcosis.<sup>8</sup> The development of medical treatment is important for several reasons:

- (1) Completely curative surgery, whatever the method, is not always possible with a 2% to 15% risk of relapse in hyper endemic areas.<sup>9,10</sup>
- (2) Even in ideal conditions the operative mortality rate ranges from 0.9% to 3.6% for the first operation, with considerable additional morbidity for subsequent surgery. This risk increases with further surgery reaching 6% for the second and 20% for the third operation in some series.<sup>9</sup> Postoperative hospitalization is often lengthy.
- (3) Cyst rupture may also occur spontaneously; and surgical damage (accidental or deliberate) of the cyst(s) can lead to spillage and

widespread dissemination in the peritoneal cavity. A major problem is recurrence due to incomplete removal or destruction of the cyst. It has been estimated that between 11.3% and 30% of patients have a recurrence within 5 years of the first surgical procedure.<sup>11,12</sup>

- (4) There are both temporary and permanent contraindications to surgery, linked to the difficulty reaching the lesion, the poor condition of some patients operated on several times, some patients' refusal to undergo surgery, and in some highly endemic regions long hospital waiting lists and a lack of adequate medical equipments or experienced staff.<sup>13</sup>

It has long been known that effective parasitocidal or at least parasitostatic chemotherapy is required for cystic echinococcosis. Antimony, arsenic, thymol derivatives, iodides, and mercury are among the many substances that have been tried as agents for the systemic treatment of hydatid disease.<sup>5</sup> None had shown the slightest evidence of success. A new era began when it was reported that benzimidazole compounds were effective against the cystic form of echinococcus granulosis.<sup>5</sup> Successful medical treatment of hydatid disease with mebendazole was reported in 1977 by Bekti et al, though subsequent studies were less conclusive.<sup>14,15</sup> Over the last 25 years, the treatment of hydatid disease has changed substantially. Of the benzimidazole carbamates, mebendazole (MBZ) is given as 500 mg tablets in a daily dose of 40-50mg/kg/day in 2-3 divided doses. It was designed as a broad-spectrum anthelmintic drug, and is poorly absorbed. It undergoes almost total first-pass metabolism to inactive metabolites with loss of antiparasitic activity. ABZ, instead showed better absorption and tissue distribution. It decreases ATP production in the worm, causing energy depletion, immobilization, and finally death.<sup>16</sup> It undergoes almost total first-pass metabolism to its effective protoscolicide metabolite ABZ sulphoxide.<sup>16-18</sup> Today ABZ is the drug most often used, it is recommended in an oral dosage of 400mg twice daily or 10-15mg/kg/day.<sup>19</sup> Its plasma concentration in hydatid infested patients is about 10 to 40 times higher than that of MBZ.<sup>20</sup> Preoperative treatment with benzimidazoles has been reported to soften the cysts, thereby reducing intracystic pressure and simplifying their removal. This was noted in the 7 failures that subsequently underwent surgery in our series. ABZ has also been shown to reduce significantly the protoscolex and cyst viability and hence the risk of secondary echinococcosis.<sup>21</sup>

With the WHO method of evaluation, clinical outcome is classified as cure,

improvement, no change, or worsening, irrespective of the number of organs with cysts. According to the WHO working group, when evaluated up to 12 months about 30% of patients showed cyst disappearance (cure), 30%-50% showed cyst degeneration or a significant size reduction (improvement), and 20%-40% exhibited no change (failure).<sup>22</sup> This compares closely with results of our study in which 28.9% were cured, 50% improved, and 21% failed to respond. The penetration of drugs across cyst walls depends on the nature of the cyst. "Recent" cysts and those with thin walls inside the hepatic parenchyma showing little or no appreciable pericystic fibrosis are more accessible to drugs than "old" cysts with thick, partially "cartilaginous" or calcified walls. For the same reasons, extra hepatic cysts are probably more accessible to these drugs.<sup>23</sup> Chemotherapy seems to be more effective in young than in old patients. This fact was confirmed in our study with a better response rate observed in the relatively younger population. Small cysts (<6cm) with a thin wall, without infection or communication, and secondary cysts are more susceptible to chemotherapy. Chemotherapy may, however, be less effective on daughter cysts within a mother cyst.<sup>15,17,21-23</sup> Once again our study concurred with both the aforementioned observations.

WHO working group in 1985 reported that with ABZ therapy 48.1% and 24.2% of cysts disappeared or shrank respectively (giving a total of 72.3% of "successes"), compared with 27.9% and 29.7% with MBZ (57.6% of "successes").<sup>24,25</sup> In one study, surgical data suggested that 50% of cysts were non-viable at surgery, whereas the figure rose to 72% and 94% in patients given a one month and three months preoperative course of ABZ.<sup>26</sup>

Imaging studies with ultrasonography (US) have the most important role in follow-up. Cyst size reduction, membrane disruption and increased echogenicity of the cyst matrix correlate with cyst non-viability. Other US signs are pseudotumour appearance, total disappearance, floating water lily sign, congealed water lily sign, ball of wool sign, yarn, and spin whirl signs.<sup>27,28</sup> These were the US changes relied upon in our study. Most follow-up measures especially clinical judgment are relatively insensitive for detection of cyst changes during medical treatment. Serological tests are also not suitable for this purpose because of relative initial insensitivity and slow, delayed unpredictable response even after successful treatment.<sup>27,29</sup> Therefore imaging studies and in particular US have the most important role in follow-up of hydatid cysts. The relation between US changes and cyst viability was clearly demonstrated in the

excellent work by Gill-Grande et al in which viability was assessed by surgical removal, pathologic examination, and inoculation to mice after ABZ treatment.<sup>30</sup>

In an extensive WHO study ABZ treatment was administered in 3 or 4 courses lasting 4 weeks separated by 14-day intervals.<sup>22</sup> With treatment lasting less than 3 months 59% of patients responded, compared to 74% and 83% with 3 to 5 months or more than 6 months of therapy, respectively. Additional benefit for most patients for more than 6 months of treatment was marginal for most patients.<sup>23</sup> In general, three courses are routinely recommended, a maximum benefit is not reached with less than 3 months of therapy; more than 6 months of treatment is rarely necessary.<sup>23</sup> Cyclic treatment was originally recommended, but more recent data on uninterrupted treatment, without holidays show that this approach could have better efficacy over 3 or 6 months or longer with no increase in adverse events.<sup>8,22,23,26,29-32</sup> The later and more current regimen was the one employed in our study. Recurrences after medical therapy range widely, but the lowest rate observed was 2.9% among 68 patients followed for up to 7 years.<sup>33</sup> The WHO guidelines recommend that preoperative benzimidazoles should begin at least 4 days before surgery and last one month (ABZ) or three months (MBZ).<sup>22</sup> The more recently developed PAIR-method (ultrasound guided cyst: puncture/aspiration/injection/re-aspiration) introduced in 1986 has opened a new frontier in the less intrusive management of cystic hydatid disease.<sup>34-36</sup> US guidance is employed with injection of protoscolicidal substances; it is minimally invasive and less risky than surgery. It confirms the diagnosis and removes a large number of protoscolices and antigens with the aspirated cyst fluid. In a randomized study comparing percutaneous drainage with ABZ to ABZ or drainage alone, Khuroo et al showed that a maximum size reduction was observed in cysts treated with a combination of percutaneous drainage and ABZ.<sup>36</sup> In a subsequent randomized study they demonstrated that percutaneous drainage combined with ABZ therapy is an effective, safe alternative to surgery for treating uncomplicated liver cysts (including multivesicular cysts) and requires a shorter hospital stay.<sup>37</sup> The same WHO recommendations apply to PAIR as the ones with concomitant surgery. It has however been discovered that because the peak serum level of ABZ is reached four hours after administration, it is sufficient to start treatment four hours before the procedure.<sup>38</sup>

The use of praziquantel (PZQ) an isoquinoline derivative has been proposed at a dose of 40mg/kg once a week concomitant with

benzimidazole. In a study of the effect on protoscolices viability using a combination of ABZ plus PZQ compared to ABZ alone as preoperative treatment in patients with intra-abdominal hydatidosis, ABZ plus PZQ was more effective than monotherapy with ABZ.<sup>39</sup> Another benzimidazole compound, oxfendazole, has been tested for cystic echinococcosis in naturally infested animals and seems at least as effective as ABZ and is easier to administer, in that it may offer weekly dosing.<sup>40</sup> The failure of the MBZ fluorinated analog flubendazole to penetrate hydatid cysts suggested that it did not offer a viable alternative to MBZ or ABZ for treatment of echinococcosis.<sup>13,20</sup> The main adverse events are related to changes in liver enzyme levels. Approximately 10% to 20% of patients develop rises in transaminases at some time during treatment, but these rises are mild to moderate, self-limiting, and reversible on cessation of treatment.<sup>41</sup> This phenomenon was observed in 2(5.2%) of our patients. The second major event is bone marrow suppression of unknown origin, but this is exceptional. Less severe adverse events are relatively frequent, the most noteworthy being alopecia followed by regrowth after treatment cessation. Other complaints include abdominal pain, loose stools, nausea, vomiting, and headaches. Better intestinal absorption of benzimidazole compounds is gained by administering it with a fat-rich meal, by combining it with cimetidine, or dexamethasone.<sup>42, 43</sup> Medical and laboratory examinations for adverse reactions are initially necessary every two weeks and then monthly.<sup>23</sup>

Based on the WHO guidelines, chemotherapy with ABZ offers new options for the treatment of hydatidosis, especially for inoperable primary liver hydatidosis, for high-risk patients, for patients with multiple cysts in two or more organs, and peritoneal cysts. Chemotherapy offers advantages in that it can be administered to outpatients and does not utilize much needed surgical facilities. Presurgical use of ABZ can reduce the risk of recurrence and facilitate the operation. Another important indication is the prevention of secondary echinococcosis after surgery. Chemotherapy is contraindicated for large cysts that are at risk of rupture (superficially situated, infected cysts) and for inactive or calcified cysts. Patients with chronic liver diseases and with bone marrow depression should not undergo benzimidazole treatment. Early and late stages of pregnancy are also a contraindication.

## CONCLUSION

Currently available treatment options for hydatid disease (surgery, ultrasound guided

aspiration, and chemotherapy) have limitations depending on the individual case. The search for non-surgical therapy for hydatid disease has been stimulated by a high recurrence rate from surgery and a significant morbidity. Progress in the treatment of hydatid disease by antimicrobial agents has been substantial. Chemotherapy is a non-invasive treatment that is less limited by the patient's status than is surgery. Chemotherapy is the preferred option when the disease is inoperable whatever the reason, when surgery or PAIR is not available, or if the cysts are too numerous. In humans benzimidazole treatment is a useful advance in the management of hydatid disease. Albendazole appears to have the greatest efficacy of any agent used so far.

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