Br. J. Surg. 1987, Vol. 74, September, 805–806

Pre-operative albendazole therapy for hydatid cyst

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Surgical management of hydatid cyst is associated with recurrence in 10 per cent of patients. The role of perioperative chemotherapy in prevention of recurrence has not been extensively explored. Sixteen patients with Echinoccus granulosus *were treated with albendazole 10 mg kg^{-1} before operation; of fourteen patients who received albendazole for 1 month or more before operation only one (with doubtful therapeutic compliance) had viable protoscoleces, in contrast both of the two remaining patients who received only 1 and 3 weeks therapy had live disease at the time of operation. A 1 month pre-operative course of albendazole kills most if not all protoscoleces within hydatid cysts in man. This may allow pre-operative 'sterilization' of cysts and a reduction in the risk of recurrence.*

Keywords: Liver, hydatid cyst

One of the most significant problems in hydatid cyst surgery is recurrence which occurs in approximately 10 per cent of patients[1,2] and when recurrent disease occurs further surgery is associated with increasing operative morbidity and mortality[3]. The three most important causes of recurrent disease are small cysts missed at the first operation, re-infection and spillage. Improved pre- and perioperative imaging techniques may reduce the number of cysts which are missed and national or regional disease control schemes may reduce the risk of re-infection, but there has been little recent advance in the prevention of spillage/implantation. It is well established that spillage is dangerous; approximately 30 per cent of patients with peritoneal spillage can be expected to develop recurrent disease[4].

The use of scolicidal agents on operative packs to limit the consequences of spillage has become routine practice. However, significant systemic toxicity has been seen with formalin[5,6] and local toxicity in the form of adhesions has been recorded following the use of cetrimide[7]. Cyst–biliary fistulae are common in patients with large hepatic hydatid cysts[8] and injection of scolicidal agents into the cyst in order to sterilize its contents before opening the cyst is associated with a significant risk of developing sclerosing cholangitis, which has been seen following the use of formalin, ethanol, hypertonic saline and silver nitrate[9–11].

The purpose of this study was to determine the effect of pre-operative albendazole therapy on the viability of hydatid cysts in man.

Patients and methods

Sixteen patients with suspected *Echinococcus granulosus* were treated with albendazole 10 mg kg^{-1} day^{-1} orally. All patients had twice weekly liver function tests, white cell and platelet count and urinalysis. Female patients were warned of the potential teratogenic and embryotoxic properties of the drug.

The length of therapy used was variable. It was our policy to aim to treat for at least 1 month before planned surgery; six patients underwent surgery after apparent failure of chemotherapy. All patients in this study underwent surgery and at the time of operation cyst contents were aspirated after placement of packs soaked in 0·5 per cent silver nitrate by means of a syringe, needle and three way tap before the injection of any scolicidal agent. By altering the direction of the needle it was always possible to obtain an adequate sample. If bile stained fluid was aspirated (or if cyst–biliary fistula had been diagnosed previously by endoscopic retrograde cholangiopancreatography) no scolicidal agent was injected. The cyst was then emptied by a large diameter suction device which reliably removes daughter cysts and laminated layer without blockage[12]. Further operative management of the ectocyst cavity was conventional[8].

Viability assessment

Immediate microscopy of the aspirated cyst fluid was carried out to look for protoscoleces and their viability was assessed by flame cell activity, motility and ability to exclude 5 per cent aqueous eosin. Except for two of the first patients (when facilities were not available) gerbil intraperitoneal inoculation was also performed using 1 ml of the remaining fluid (approximately 5000 protoscoleces ml^{-1}) and also a preparation of daughter cysts or laminated and germinal layer. If the specimen was thought to be infected it was treated for 24 h in *in vitro* culture media containing antibiotics (gentamycin, streptomycin and penicillin) which do not affect parasite viability[13] and gerbils were treated with ampicillin for 24 h following inoculation.

Results

In all, 16 patients were studied (*Table 1*). The site of the cysts was hepatic in 12, bone in 2, peritoneal, retroperitoneal, anterior abdominal wall and cerebral in 1 each. The size of the cysts is shown in *Table 1*. Whilst it was intended to treat patients for at least a month before operation, two patients received 1 and 3 weeks therapy because delay was considered inadvisable in the first patient with a cerebral cyst and therapy was discontinued after 3 weeks owing to mild hepatotoxicity[14] in the other. One patient (no. 5) admitted taking her albendazole therapy erratically. All but one of the hydatid cysts were flaccid, in marked contrast to the tense cysts seen in untreated disease.

Macroscopic findings were not otherwise different from untreated hydatid cysts, all 12 hepatic cysts appeared to contain purulent or bile stained fluid and 10 had clearly identified biliary communications. Only one patient (no. 38) of the twelve patients where daughter cysts were found had tense daughter cysts.

Viability testing only identified three patients with live protoscoleses; all three were identified by microscopy and one was also positive by gerbil passage (three of four gerbils inoculated developed a total of eleven cysts). No patients have developed recurrent disease with a median follow-up of 15 months (range 2–34).

Discussion

The contribution of chemotherapy to the management of hydatid disease is growing. In 1977 Bekhti[15] described encouraging results in four patients treated with mebendazole, and considerable experience now exists with this compound[16]. Albendazole is another benzimidazole carbamate which achieves high serum and cyst fluid[17] concentrations of its principal metabolite albendazole sulphoxide. We have shown this metabolite to be an active scolicidal agent in *in vitro* cultures[13] in an animal model[18] and encouraging clinical and radiographic evidence of regression of cysts have been seen in man[19]. The possible contributions of perioperative chemotherapy in hydatid disease offer a prospect of reducing or perhaps completely preventing recurrent disease.

0007–1323/87/090805–02$3.00

Table 1 *Details of the 16 patients studied*

Patient	Sex	Site of cyst	Diamter (cm)	Therapy (weeks)	Biliary communications	Viability		Follow-up (months)
						Microscopy	Gerbil	
4	F	Pelvic peritoneal DC	10	12		–	–	15
5	F	Hepatic DC	20	4	+	+	ND	34
6	F	Hepatic	20	4		–	ND	34
11	F	Hepatic DC	25	12	+	–	–	24
18	M	Hepatic DC	15	8	+	–	–	21
21	F	Hepatic	10	8	+	–	–	12
27	M	Anterior abdominal wall	5	8		–	–	29
29	F	Hepatic DC	25	12	+	–	–	21
30	M	Hepatic + bone DC (femur)	10	12	+	–	–	14
36	F	Bone (vertebral) Retroperitoneal DC	10	4		–	–	18
37	F	Hepatic DC	15	4	+	–	–	15
38	M	Hepatic DC	15	3*	+	+	–	11
43	M	Cerebral	8	1*		+	+	9
45	M	Hepatic DC	15	4	+	–	–	8
47	M	Hepatic DC	10	8	+	–	–	5
48	F	Hepatic DC	15	8		–	–	2

ND, not done; DC, daughter cysts; * short course of therapy due to hepatotoxicity (38), urgency of surgery (43)

The viability rate of symptomatic cysts in man is not clear but 6 of 12 patients operated on following mebendazole therapy were found to have definitely viable disease[20]. In this study only 1 of 14 patients who had at least a 1 month course of therapy was found to have live disease at operation and this patient admitted (before operation) having taken her medication erratically. It is of importance that both of the two patients who received less than a month's therapy had viable disease at operation. All viability tests should be interpreted with caution; a positive finding has more meaning than a negative one but the finding of live disease in these two patients who had an inadequate course strengthens our belief that an adequate pre-operative course of albendazole does significantly reduce viability of cysts.

It is also interesting that the only patient who produced cysts when protoscoleces were passaged into gerbils had been treated for only 1 week. This may mean that whilst protoscoleces appeared alive on microscopy in patient 38, they may have already been irreparably damaged by the 3 weeks albendazole therapy.

Whilst these data are most encouraging, pre-operative therapy may not be the optimum way of preventing recurrence. In the postoperative setting only a 'few' spilled protoscoleces need to be killed and problems with penetration of the drug into the cyst are avoided. We have previously shown that very short courses of albendazole following peritoneal spillage in gerbils significantly reduces the number of cysts which develop[21].

These concepts will require large long-term controlled clinical trials to establish that perioperative chemotherapy does prevent recurrence but this paper strongly suggests that a pre-operative course of albendazole $10\,mg^{-1}\ kg^{-1}\ day^{-1}$ for 1 month significantly reduces viability of hydatid cysts in man.

Acknowledgements

I am grateful to Smith Kline and French Laboratories Ltd for their support of my work and to all the physicians and surgeons who have helped me by their generous cooperation in allowing me to treat their patients.

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Paper accepted 23 March 1987