

Triclabendazole in the treatment of human fascioliasis: a community-based study

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استعمال ثلاثي كلابندازول في معالجة داء المتورقات البشرية: دراسة مجتمعية
هالة المرشدي وعزة فرغلي وثرية شرف وليلى أبو باشا ورشيدة بركات

خلاصة: تم تقدير مدى نجاعة ثلاثي كلابندازول في معالجة العدوى المزمنة بالمتورقات. فعولج عدد مجموعه 134 من الحالات المؤكدة من عدوى المتورقات الخالية من الأعراض، حيث تلقى 68 شخصاً جرعة واحدة مقدارها 10 مع/كغ، وتلقى 66 شخصاً جرعتين مقدار كل منهما 10 مع/كغ في يومين متتابعين. وتم تقدير مدى الشفاء بعد خمسة أسابيع من المعالجة، وتبين أن الشفاء قد تحقق في 79.4% من أفراد المجموعة الأولى وفي 93.9% من أفراد المجموعة الثانية. وتميز الدواء بدرجة تحمل جيدة ولم تلاحظ معه أية آثار جانبية وخيمة. ولقد حدث ركود صفراوي كيميائي حيوي في مريضة واحدة في اليوم الثالث بعد المعالجة، ولكن عادت إنزيمات إلى المستويات الطبيعية بعد شهرين. وخلاصة القول إن ثلاثي كلابندازول دواء مأمون و ناجع ضد داء المتورقات.

ABSTRACT The efficacy of triclabendazole in the treatment of chronic *Fasciola* infection was assessed. A total of 134 asymptomatic cases of established *Fasciola* infection were treated: 68 individuals received a single dose of 10 mg/kg and 66 individuals received 2 doses of 10 mg/kg on 2 consecutive days. Cure was assessed 5 weeks after treatment and 79.4% of the first group and 93.9% of the second group were cured. The drug was well tolerated; no serious side-effects were noted. One patient developed biochemical cholestasis the third day after treatment, but her enzyme profiles returned to normal after 2 months. We conclude triclabendazole is a safe and potent fasciolicidal drug.

Traitement de la distomatose hépatique chez l'homme par le triclabendazole: étude communautaire

RESUME L'efficacité du triclabendazole dans le traitement de l'infection à *Fasciola* chronique a fait l'objet d'une évaluation. Au total, 134 cas asymptomatiques d'infection à *Fasciola* établie ont été traités: 68 sujets ont reçu une dose unique de 10 mg/kg et 66 sujets ont reçu deux doses de 10 mg/kg deux jours de suite. La guérison a été évaluée cinq semaines après le traitement: 79,4% des sujets du premier groupe et 93,9% de ceux du second groupe ont été guéris. Le médicament a été bien toléré; aucun effet secondaire grave n'a été noté. Une patiente a développé une cholestase biochimique trois jours après le traitement mais son profil enzymatique est revenu à la normale après 2 mois. On conclut que le triclabendazole est un médicament sûr et efficace contre les douves du genre *Fasciola*.

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Introduction

Abis, a rural area in the vicinity of Alexandria, Egypt, has been reporting increasing rates of human fascioliasis since the late 1970s [1-3]. Factors underlying human infection are the prevalence of *Fasciola* infection among herbivorous animals and the presence of the intermediate host snail (*Lymnaea cailliaudi*) of the fluke. Farag reported an overall prevalence of *Fasciola* infection of 32% among herbivorous animals without control measures [4]. The temperate climate of the area and the consumption of contaminated leafy green vegetables, a cheap source of food for inhabitants of the area, favour persistence of infection.

Because of the increasing prevalence of fascioliasis among Egyptians [1-3], the need for treatment is pressing and vital. Several drugs have been proposed for the treatment of human fascioliasis. Emetine is used because of its high efficacy in the treatment of acute and chronic infection but has significant side-effects [5-7]. Praziquantel is not effective against *Fasciola* infection, probably due to the thick tegument of *Fasciola* which hinders drug presentation [5,8,9]. Albendazole, although effective against animal fascioliasis, has a high rate of failure in human infection [10]. Bithionol is used for chronic infection only, its cure rate is near 50% and treatment must be repeated for several days with higher doses given daily [11-13].

Triclabendazole (TCBZ) is a chlorinated benzimidazole derivative. Compared with other fasciolicides it is outstanding for its high efficacy against both immature stages and adult forms of the worm simultaneously [10,14,15]. The drug is very effective and specific against both acute migratory and chronic infections in cattle [16] and in sheep [10] given in single doses of 12 mg/kg and 10 mg/kg respectively. It

has been used in millions of animals in the field and proven to be extremely safe. It is currently the drug of choice in the treatment of livestock in Australia and elsewhere in the world.

The first successful human trial was in 1988 [17]; thereafter limited human trials have been reported. The drug was either given in a single dose of 10-12 mg/kg or in two doses 12-48 hours apart [18,19]. Drug tolerance was excellent and none of the patients had either secondary symptoms or important alterations in the levels of aspartate and alanine aminotransferases, alkaline phosphatase or bilirubin during or after treatment [11]. The drug, however, has never been assessed in a large sample in the field.

The present study evaluated different regimens of TCBZ for the treatment of chronic human fascioliasis under field conditions. A single or double dose each of 10 mg/kg was given for the treatment of established human *Fasciola* infection in Egyptians in an endemic focus.

Subjects and methods

The study protocol was approved by the Environmental Committee, High Institute of Public Health, University of Alexandria. A total of 134 individuals proven to have chronic *Fasciola* infection after repeated stool examinations were enrolled in the study. All were from Abis, a rural area 15 km from Alexandria. The area is endemic for *Schistosoma mansoni* infection. Detailed epidemiological data are described in the authors' previous cross-sectional study [3].

Study subjects included 87 females whose ages ranged from 2 years to 60 years (mean = 16.5 years) and 47 males whose ages ranged from 5 years to 52 years (mean

Table 1 Characteristics of individuals participating in triclabendazole treatment trial

Variable	Group I Single-dose therapy	Group II Two-dose therapy	Test of significance
No. of participants	68	66	
Mean age \pm s (years)	16.10 \pm 11.92	14.20 \pm 10.90	t = 0.98
Mean age of males \pm s (years)	12.40 \pm 6.90	13.80 \pm 11.01	t = 0.54
Mean age of females \pm s (years)	18.74 \pm 14.00	14.28 \pm 11.00	t = 1.65
GMEC (epg)	60	69	t = 0.73
Infection prevalence of <i>Schistosoma mansoni</i> (%)	47.0	56.1	Z = 1.14

s = standard deviation

GMEC = geometric mean egg count

epg = eggs per gram of faeces

= 12.9 years). Cases were randomly divided into two groups: group I included 68 individuals (40 females and 28 males) and group II included 66 individuals (47 females and 19 males). There were no statistically significant differences between the two groups in terms of age, sex, geometric mean egg count (GMEC) of *Fasciola* infection or the prevalence of *S. mansoni* infection (Table 1). All participants in each group were subjected to the following:

1. Egg count in stools by the modified Kato-Katz technique [20]: 4 slides were examined and *Fasciola* eggs were identified and counted. All egg counts were transformed to logarithm 10. The anti-log of the mean \log_{10} of positive slides was the GMEC.
2. Liver function tests: these included serum bilirubin, serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and serum alkaline phosphatase (SAP) (Beckman Astra System, AST Enzyme Reagent Kit, USA).
3. Treatment: participants were informed in detail about the protocol. TCBZ (Ciba-Geigy Laboratories, Basel, Switzerland) was offered to all participants after obtaining consent to participate in this study. Group I was given a single dose therapy, 10 mg/kg. Group II was given two doses each of 10 mg/kg on 2 consecutive days. Participants were instructed to report any secondary symptoms, such as nausea, vomiting, pain in the right hypochondrium, skin rash, jaundice, fever.
4. Follow-up: laboratory tests were repeated 5 weeks after treatment. Blood samples were taken to determine the effect of the drug on liver function tests. *Fasciola* eggs in faeces were detected using the Kato-Katz technique [20]; 4 slides were examined from a single stool sample. The persistence of eggs was considered to indicate treatment failure. In

these cases a second treatment consisting of 2 doses each of 10 mg/kg was offered. In addition, 40 of group II were followed up 1 year after TCBZ treatment.

Data were analysed using *Epi-Info* 5.

Results

The efficacy of TCBZ treatment is given in Table 2. The overall parasitological cure rate was 86.6%. Cure was achieved in only 79.4% of cases receiving the single dose regimen but was 93.9% in those receiving the two-dose regimen ($Z = 2.54$, $P < 0.05$). The 18 cases with persistent *Fasciola* eggs after therapy intervention included 5 males whose mean age \pm standard deviation was 14.2 ± 9.3 years and 13 females whose mean age was 16.2 ± 15.4 years. There were no statistically significant differences between the cured and uncured cases in terms of age, sex and *S. mansoni* infection. However, the GMEC of uncured cases [80 eggs per gram of faeces (epg)] was significantly higher than that of cured cases (63 epg) ($t = 2.29$, $P < 0.05$). Among the uncured cases there was a 63% reduction in GMEC 5 weeks after treatment. These pa-

Table 3 Liver function tests before and after triclabendazole treatment

Liver function test	Before treatment	After treatment
Total serum bilirubin (reference range 0.1–1.0 mg/dL)	0.3	0.3
SGPT (reference range 0–60 U/L)	14 ^a	16
SGOT (reference range 0–40 U/L)	19 ^b	20 ^b

^aOne patient had SGPT = 99 U/L.

^bFive patients had a mean value of SGOT = 50 U/L.
SGPT = serum glutamic pyruvic transaminase
SGOT = serum glutamic oxalacetic transaminase

tients received a second course (10 mg/kg for 2 successive days) and cure was achieved in all cases. The 40 cases of group II who received the two-dose regimen and were followed for 1 year all remained negative.

The effect of TCBZ on the liver was studied (Table 3). Before therapy, the mean values of serum bilirubin, SGOT and SGPT were found to be within normal range. No significant change was observed after ther-

Table 2 Cure rate 5 weeks after triclabendazole treatment

Drug regimen	Cured		Not cured		% cure ^a
	No.	Baseline GMEC (epg)	No.	Baseline GMEC (epg)	
One dose ($n = 68$)	54	59	14	65	79.4
Two doses ($n = 66$) ^b	62	67	4	165	93.9
Total ($n = 134$)	116	63	18 ^c	80	86.6

^aThere was a statistically significant difference between the cure rates for the two regimens ($Z = 2.54$, $P < 0.05$).

^b40 cases were followed up for 1 year after triclabendazole treatment. All remained negative.

^c18 cases remained positive after the first trial, although there was a 63% reduction in GMEC. All became negative after receiving a second round of treatment (10 mg/kg for 2 consecutive days).

GMEC = geometric mean egg count

epg = eggs per gram of faeces

Table 4 Liver function tests of a patient who developed jaundice following triclabendazole treatment

Liver function test	Time after treatment		
	1 week	2 weeks	2 months
Bilirubin (reference range 0.1–1.0 mg/dL)	1.7	1.2	0.7
SAP (reference range 90–290 KA units)	482	371	232
SGPT (reference range 0–60 U/L)	118	82	29
SGOT (reference range 0–40 U/L)	137	72	21

SAP = serum alkaline phosphatase

SGPT = serum glutamic pyruvic transaminase

SGOT = serum glutamic oxalacetic transaminase

apy. The drug was well tolerated; mild, colicky pain was the only complaint reported. In one case, however, clinical jaundice developed 3 days after treatment. The patient was cured parasitologically and sonographic examination revealed a distended and inflamed gall bladder. The case was followed for 2 months; the enzyme profiles returned to normal at the end of the follow-up period (Table 4).

Discussion

A total of 134 cases of established *Fasciola* infection were diagnosed parasitologically using the Kato-Katz technique [20]. Liver function tests, SGOT, SGPT and bilirubin were normal. This agrees with the findings of other investigators [21,22]. In 14 cases of *Fasciola*-positive Egyptian children, only 2 had apparently high levels of SGOT and SGPT. The mean values of these enzymes, however, were not significantly different from those of negative controls [23].

Cure was achieved in only 79.4% of cases receiving single-dose therapy, whereas 93.9% of cases treated with two doses 24 hours apart were cured. In previous studies, the drug has been tested on individual human cases with promising results [24,25]. It was either given in a single dose of 10–12 mg/kg or in two doses each of 10 mg/kg on 2 consecutive days, especially for chronic infections [18,19]. Similar to the findings of our study, Apt et al. reported parasitological cure in 19 of 24 individuals (79.2%) receiving a single dose of TCBZ [11]. After a second round of therapy, the cure rate was 100%.

The GMEC of cured cases (63 epg) was significantly lower than that of uncured cases (80 epg). A relationship between the intensity of *Fasciola* infection and the curative dose of bithionol has been reported by many investigators [13,26–28]; the same principle may apply to TCBZ. It is worth mentioning that all the cases that remained positive after the first drug trial achieved 100% parasitological cure after a second round of treatment.

Drug tolerance was excellent. Almost all the participants were without significant secondary symptoms or alteration in the levels of liver enzymes after treatment. Other investigators have reported excellent tolerance of the drug in addition to the absence of important alterations in liver biochemical markers [11,18].

One patient, however, developed jaundice with high counts for SGOT, SGPT, SAP and bilirubin 3 days after treatment. This patient was followed up medically with regular symptomatic treatment and all markers returned to normal within 2 months. The transient alteration in the liver biochemical markers observed in this patient was probably due to disintegrated dead parasites as evidenced by the inflamed, distended gall bladder revealed by

sonographic examination. Hammouda et al. reported a similar brief episode of fever, jaundice and right abdominal pain in one patient 4 days after treatment, which was also attributed to disintegrated dead parasites [18]. Although this complication is rare, patients must be made aware of it and instructed to report it immediately to their medical facilities to exclude the possibility of obstructive jaundice.

The outstanding cure rate of the double-dose regimen of TCBZ in a fairly large number of patients, the ease of oral administration and the excellent patient compliance under field conditions, in addition to excellent drug tolerance favours the use of

the double-dose regimen of TCBZ for the treatment of chronic human fascioliasis.

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