Triclabendazole in the treatment of established human fascioliasis

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استخدام ترايكلابندازول في معالجة الإصابات المؤكدة بداء المتورقات (الفاشيولا) البشرية

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خلاصة : تم تقييم درجة تحمُّل ونجاعة مستحضر تريكلابندازول (CGP 23030) المحضَّر خصيصاً للاستعمال البشري ، وذلك بإعطائه لخمسين مريضاً في الطور المزمن لداء المتورقات . فبعد أن تم الفحص السريري والتحري المخبري للمرضى ، تصوير الكبد والقنوات المرارية بالموجات فوق الصوتية ، أعطي المستحضر بجرعة وحيدة أو مقسمة قدرها عشرة ميليغرامات لكل كيلوغرام من وزن الجسم . ثم فحصت الحالة السريرية المرضى يومياً لمدة ستة أيام ، وأعيدت التحريات المخبرية بعد إعطاء العلاج بستة أيام ثم ثلاثين يوماً ثم ستين يوماً . ولوحظ أن المرضى قد تحملوا الدواء . وحدثت آثار جانبية اعتبرت طفيفة ، شملت آلاماً في أعلى البطن ، وحمى خفيفة وتغيرات محدودة في وظائف الكبد . وبلغ معدل الشفاء بعد شهرين 94% مقدراً باختفاء البيوض من البراز ، كما بلغ 88% مقدراً باختفاء البيوض من البراز والديدان من القنوات المرارية . وهكذا يستنتج أن من المفيد استعمال الترايكلابندازول في معالجة داء المتورقات (الفاشيولا) البشرية .

ABSTRACT The tolerance and efficacy of triclabendazole CGP 23030, specially prepared for human use, were assessed in 50 patients in the chronic phase of fascioliasis. After clinical examination, investigation and ultrasonography of the liver and biliary system, triclabendazole 10 mg/kg, either as a single or split dose, was administered. The clinical picture was studied daily for six days and the investigations were repeated 6, 30 and 60 days after treatment. The drug was tolerated. Its side-effects, which included upper abdominal pain, mild fever and limited derangement of liver function, were considered negligible. The cure rate at 2 months was 94% when assessed by the disappearance of eggs in stools and 88% when assessed by both the absence of eggs in stools and of worms in the biliary system. The use of triclabendazole for the treatment of human fascioliasis was found to be justified.

Le triclabendazole dans le traitement de la fasciolase humaine établie

RESUME La tolérance et l'efficacité du triclabendazole CGP 23030, spécialement préparé pour utilisation chez l'être humain, ont été évaluées chez 50 patients atteints de fasciolase en phase d'état chronique. Après examen clinique, investigation et échographie de la sphère hépato-biliaire, le triclabendazole a été administré à la dose de 10 mg/kg en une prise unique ou fractionnée. Le tableau clinique a été étudié quotidiennement pendant six jours et les investigations ont été répétées 6 jours, 30 jours et 60 jours après le traitement. Le médicament était bien toléré. Ses effets secondaires, qui comprenaient des douleurs siégeant dans la région supérieure de l'abdomen, une fièvre légère et un dérèglement limité de la fonction hépatique, ont été considérés comme négligeables. Le taux de guérison à 2 mois était de 94% lorsqu'il était évalué d'après la disparition des œufs dans les selles et de 88% lorsqu'il était évalué par l'absence d'œufs dans les selles ainsi que de vers dans les voies biliaires. L'utilisation du triclabendazole pour le traitement de la fasciolase humaine a été jugée justifiée.

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Received: 20/5/97; accepted: 16/10/97

Introduction

Human fascioliasis is becoming a public health problem of increasing importance in Egypt. In some places, the disease has become endemic and prevalence rates have reached 13% and 17% [*1*]. The infection is also reported in over 60 countries throughout the world [*2*]. However, the drugs used for treatment of human fascioliasis, dehydroemetine, bithionol and praziquantel, have substantial side-effects or are not effective [*3,4,5*].

Triclabendazole is considered the fasciolicide drug of choice in veterinary medicine. It has been proven effective against adult worms, as well as against immature stages of the parasite [*6*]. Preliminary trials in humans using the veterinary form of the drug have been encouraging [*7*].

This study is an evaluation of the tolerability and efficacy of a form of triclabendazole (CGP 23030) specially prepared for human use.

Materials and methods

Fifty (50) patients in the established phase of fascioliasis were enrolled in this study. All were 10 years of age or older and had a negative history concerning treatment of the liver fluke in the month preceding this study. They did not exhibit signs of any acute or chronic illness and they were generally not in poor physical condition. Informed consent to participate in the clinical trial was obtained from all.

Clinical and laboratory examinations

Upon hospitalization (day 0), all patients were subjected to:

- clinical examination;
- stool examination (Kato–Katz technique);
- blood picture: haemoglobin, total leucocytic count and absolute eosinophilic count;
- liver function tests: alkaline phosphatase, SGOT, SGPT and serum bilirubin;
- kidney function tests: blood urea and serum creatinine;
- indirect haemagglutination test for fascioliasis using IHAT kits (Fumouze, France);
- ultrasonography focusing on the liver and gall bladder.

Treatment

Triclabendazole was supplied in the form of tablets of 250 mg active principle. Patients were assigned randomly to two groups according to the schedule of treatment:

- Group I: 25 patients were given triclabendazole 10 mg/kg in a single morning dose after breakfast.
- Group II: 25 patients were given triclabendazole in a split dose of 5 mg/kg at 6 hour intervals after eating.

Patients were clinically examined daily and, when necessary, were given appropriate treatment. On the sixth day, stool examinations and all investigations were repeated and the patients were discharged from the hospital. The patients were asked to present on days 30 and 60 for repetition of examination and laboratory investigations.

Results

The complaints and abdominal signs of the 50 patients are presented in Table 1. The characteristics of the sample and the com-

Table 1 **Symptoms and abdominal signs in 50 patients with fascioliasis**

Symptom and signs	Patients	
	No.	%
Right hypochondrial pain	28	56
Abdominal colic	25	50
Anorexia, nausea and vomiting	20	40
Headache	4	8
Fatigue	3	6
Sweating	3	6
Urticaria	2	4
Constipation	2	4
Diarrhoea	1	2
Hepatomegaly[a]	5	10
Splenomegaly[b]	2	4

[a] *Three of these five patients had histories of treated schistosomiasis*
[b] *These two patients had histories of treated schistosomiasis*

parability of the two groups were studied (Table 2). There was no significant difference between the two groups in any of the parameters.

Tolerability of triclabendazole was assessed clinically and by follow-up of laboratory investigations. On the first day after treatment, clinical examination revealed a mild increase in right hypochondrial pain, abdominal colics, dyspepsia and nausea. Complaints were more frequently reported from the group receiving the single dose. In the following examinations, the intensity of colics and the frequency of complaints decreased gradually.

Results of vital signs are presented in Table 3. Some changes from basal values were observed 1 day after treatment but at the end of the week values regained their pre-treatment level.

Levels of eosinophilia and haemoglobin are also presented in Table 3. Before treatment, 36% of patients had eosinophilia. One week after treatment, the mean eosinophilic count was found to be higher, but 2 months post-treatment it had dropped back to normal in most patients. Furthermore, before treatment, 50% of the patients were considered anaemic; after treatment, haemoglobin levels showed a gradual rise.

Values of the liver function tests by regimen are presented in Table 4. Alkaline phosphatase was above normal in most patients before treatment; significant improvement with lower values were noted after treatment. SGOT and SGPT were within normal before treatment; 1 week after triclabendazole, the two enzyme levels were elevated particularly after the single dose, but at 1 and 2 months they regained gradually the pre-treatment values.

The mean bilirubin level was normal and did not change after treatment. Only one patient had jaundice and that disappeared at 1 month.

Results of IHAT are presented in Table 5. Changes in the mean titre 1 month after treatment were insignificant.

Efficacy of treatment

The cure rate after triclabendazole was assessed by two methods: the absence of eggs from stools and the absence of eggs from stools coupled with the absence of worms from the biliary system as revealed by ultrasonography (Table 6). The split dose resulted in higher cure rates at 1 and 2 months, while at 6 days the single dose showed higher cure rates.

Ultrasonographic examination uncovered mild changes in the liver tissue of 30% of the cases and the wall of the gall bladder was thick in 6% of cases. Table 7 indicates the

Table 2 **Characteristics of the study sample**

Parameter	Single dose (Group I)	Split dose (Group II)	*P* value
Demographic data			
Age in years			
Range	10–49	10–55	
Mean ± *s*	22.8 ± 11.51	19.9 ± 12.84	> 0.05
Sex (No. of males)	15	9	> 0.05
Stool examination			
Egg count			
Geometric mean ± *s*	50 ± 2.45	54 ± 2.35	
Arithmetic mean ± *s*	96 ± 129	82 ± 114	> 0.05[a]
Blood picture			
Haemoglobin (g/dl)			
Range	9–15.5	8–15.5	
Mean ± *s*	12.6 ± 1.59	11.7 ± 1.89	> 0.05
WBC/mm^3			
Range	4300–11 200	4050–13 000	
Mean ± *s*	6800 ± 1920	6900 ± 2170	> 0.05[a]
Eosinophilic count/mm^3			
Range	90–5225	0–6600	
Mean ± *s*	749 ± 1141	712 ± 1386	> 0.05[a]
Liver function tests			
Alkaline phosphatase (normal 3–13 KA units)			
Range	3–30	4–27	
Mean ± *s*	15.7 ± 7.44	13.5 ± 6.53	> 0.05
SGPT (normal up to 40 RF units)			
Range	2–52	4–64	
Mean ± *s*	13.2 ± 1152	19.3 ± 13.86	> 0.05
SGOT (normal up to 40 RF units)			
Range	2–78	4–36	
Mean ± *s*	17.9 ± 15.39	20.8 ± 9.18	> 0.05
Serum bilirubin (normal 0.1–1 mg/dl)			
Range	0.2–0.8	0.2–1.6	
Mean ± *s*	0.43 ± 0.11	0.47 ± 0.27	> 0.05
Kidney function tests			
Urea (normal 20–40 mg/dl)			
Range	18–33	18–34	
Mean ± *s*	24 ± 2.0	23 ± 2.0	> 0.05
Creatinine (normal 0.4–1.3 mg/dl)			
Range	0.5–1.2	0.5–1.1	
Mean ± *s*	0.82 ± 0.18	0.80 ± 0.16	> 0.05
Immunologic test			
IHA (titre)			
Range	< 80–2560	< 80–1280	
Mean ± *s*	313.6 ± 695.10	205 ± 303.99	> 0.05[a]

[a] *Mann-Whitney non-parametric test was used to compare the groups*
s = *standard deviation*

Table 3 **Values of vital signs before and after treatment with triclabendazole**

Variable	Range	Mean ± *s*	No.	%
Temperature (°C)				
Before treatment	36.5–37.5	36.7 ± 0.27	4	8
1 day after treatment	36.5–37.8	37.3 ± 0.33*	33	66
1 week after treatment	36.4–38.0	36.8 ± 0.28	2	4
1 month after treatment	36.5–36.8	36.7 ± 0.10	–	–
2 months after treatment	36.5–36.8	36.7 ± 0.09	–	–
Pulse rate (/min)				
Before treatment	75–100	83.2 + 5.26	2	4
1 day after treatment	72–105	88.7 ± 5.78*	6	12
1 week after treatment	78–100	82.3 ± 3.96	1	2
1 month after treatment	75– 90	81.3 ± 3.86	–	–
2 months after treatment	75– 90	81.2 ± 3.20	–	–
Cases with eosinophilia [a]				
Eosinophilic count (per mm³)				
Before treatment	90–6600	748 ± 1141	18	36
1 week after treatment	50–3451	857 ± 886	21	42
1 month after treatment	80–3570	702 ± 1052	13	26
2 months after treatment	56–2470	408 ± 532	10	20
Cases with anaemia [b]				
Haemoglobin level (g/dl)				
Before treatment	8.0–15.5	12.0 ± 1.89	25	50
1 week after treatment	8.5–14.3	12.0 ± 1.53	27	54
1 month after treatment	9.0–14.4	12.1 ± 1.31	21	42
2 months after treatment	9.5–15.0	12.2 ± 1.37	19	38

**P < 0.05 (for the difference between the means)*
The respiratory rate and systolic and diastolic pressure were normal in all patients
[a] Eosinophilia is considered present if eosinophilic count >440/mm³
[b] A patient is considered anaemic if haemoglobin <13 g/dl in males or <12 g/dl in females

presence of *Fasciola* worms in the gall bladder and biliary ducts.

Discussion

Faced with the problem of human fasciliasis and the absence of a certified drug for its treatment, physicians found themselves obliged to administer triclabendazole in its veterinary form. Recently Ciba-Geigy provided a form of Fasinex for human use and recommended that clinical trials be undertaken in concerned countries. This study was carried out by the Medical Research Institute, Alexandria, Egypt.

Fifty consenting patients were entered in the study. Their clinical picture and the results of laboratory investigations, prior to treatment, matched those reported in studies reviewed by Chen and Mott [*8*].

Table 4 **Values of liver function tests before and after treatment with triclabendazole according to regimen**

Parameter	Single dose (Group I) (Mean ± s)	Split dose (Group II) (Mean ± s)	Patients with abnormal values No.	%
Alkaline phosphatase (KA units)				
Before treatment	15.3 ± 7.27	13.5 ± 6.35	27	54
1 week after treatment	14.0 ± 8.15	14.8 ± 7.47	25	50
1 month after treatment	11.1 ± 6.24*	12.3 ± 5.07	15	30
2 months after treatment	11.5 ± 7.07*	10.7 ± 4.01*	13	26
SGOT (RF units)				
Before treatment	17.9 ± 15.39	20.8 ± 9.18	1	2
1 week after treatment	56.4 ± 101.07	28.2 ± 24.12	10	20
1 month after treatment	23.2 ± 9.97	24.3 ± 14.26	2	4
2 months after treatment	15.2 ± 5.97	19.1 ± 8.33	0	0
SGPT (RF units)				
Before treatment	13.2 ± 11.52	19.3 ± 13.86	2	4
1 week after treatment	64.2 ± 111.15*	31.6 ± 35.80*	10	20
1 month after treatment	13.2 ± 5.63	24.9 ± 27.42	3	6
2 months after treatment	11.5 ± 5.11	19.0 ± 17.75	1	2
Bilirubin (mg/dl)				
Before treatment	0.4 ± 0.11	0.5 ± 0.27	1	2
1 week after treatment	0.5 ± 0.57	0.4 ± 0.14	1	2
1 month after treatment	0.4 ± 0.11	0.4 ± 0.12	0	0
2 months after treatment	0.4 ± 0.09	0.4 ± 0.12	0	0

** Difference is significant ($P < 0.05$) as compared with before-treatment value (paired t-test)*
s = standard deviation

Table 5 **IHA titre before and after treatment**

Time	IHA test Reciprocal of titre Range	Mean ± s	Patients with positive test No.	%
Before treatment	80–2560	267 ± 695	13	26
1 month after treatment	80–2560	256 ± 518	12	24

Positive titre > 1/320

The tolerance of triclabendazole was considered excellent. Side-effects were in the form of brief episodes of upper abdominal pain and slight fever and some mild and limited disturbances in liver function with one case revealing moderate icterus that disappeared after a few days. These effects may be due to the paralysis and/or death of the flukes resulting in the release of antigens or toxic products and the partial blockage of the

Table 6 **Cure rate after triclabendazole by the two regimens**

Group	Patients cured					
	6 days		1 month		2 months	
	No.	%	No.	%	No.	%
Assessment by absence of eggs						
Single dose (Group I)	22	88	22	88	23	92
Split dose (Group II)	18	72	24	96	24	96
P value	>0.05		>0.05		>0.05	
Assessment by absence of eggs and worms						
Single dose (Group I)	12	48	19	76	21	84
Split dose (Group II)	10	40	21	84	23	92
P value	>0.05		>0.05		>0.05	

Table 7 **Ultrasonographic detection of *Fasciola* worms before and after triclabendazole treatment**

Time	Patients with *Fasciola* worms[a]		
	No.	%	*P* value
Before treatment	34	69.4	
1 week after treatment	19	38.8	$P < 0.05$
1 month after treatment	5	10.2	
2 months after treatment	3	6.1	

[a] *49 patients were examined ultrasonographically*

bile ducts. Similar findings have been reported in various preliminary studies: the drug has been reported to decrease parasite motility, but the exact mode of action of triclabendazole is unknown [*9*].

In this study, which used a total dose of 10 mg/kg body weight, the cure rate could be considered very high. Taking the absence of eggs as the sole indicator of cure, the cure rate amounted to 94%; considering both the absence of eggs and the absence of worms from the biliary passages, the cure rate was 88% 2 months after treatment. The split dose was slower in action but slightly more effective. Cure rates from 79% to 100% have been reported in various studies in which a single oral dose or repeated doses totalling 10 and 20 mg/kg body weight were used [*10–12*]. Some of these studies were performed during the acute phase of infection and depended on serology as the parameter for assessment of cure.

Triclabendazole has been reported to be non-mutagenic and non-teratogenic [*13*]. These factors together with its effectiveness and tolerability could allow the recommendation of triclabendazole for human use.

Differences between the effects of single and split doses in this study were minimal, yet the latter could be considered more tolerable and more effective.

Acknowledgments

We thank the late Dr K. Mott, Chief, Schistosomiasis and other trematode infections, WHO headquarters, for suggesting and supporting this work. We thank Ciba-Geigy for supplying the drugs used in this study. We

thank the Ministry of Health and Population, Cairo, Egypt for supporting this work financially. The participation of Dr W.S. Ragab, Dr R. Khalil and Professor Dr A. Zaki in performing of the clinico-pathological study, ultrasonography and in the statistical analysis of the data is highly appreciated.

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