Evaluation of two doses of triclabendazole in treatment of patients with combined schistosomiasis and fascioliasis

M.M. Osman,[1] A.Y. Shehab,[1] A. Zaki[2] and H.F. Farag[1]

تقييم جرعتي التريكلابندازول في معالجة المرضى المصابين بعدوى مشتـركة بداء البلهارسيات وداء المتورّقات

مرفت مصطفى عثمان، أمل يوسف شهاب،عادل زكي، هدى فهمي فرج

الخلاصـة: لتحديد سلامة ونجاعة جرعتين متتاليتين من التريكلابندازول في معالجة عدوى البلهارسية المنسونية في الحالات المصابة بكل من البلهارسية المنسونية والمتورّقة، أجرى الباحثون مسحاً ميدانياً اشتمل على 6314 شخصاً من 15 قرية. وكان إجمالي معدل انتشار البلهارسية وحدها 15.8٪، والمتورّقة وحدها 2.2٪، والعدوى المشتـركة بالاثنتين 0.7٪. وقد أُعطي علاج مكوّن من جرعتين من التريكلابندازول إلى 49 مريضاً لديهم عدوى مشتـركة. وبعد مضي ثمانية أسابيع من العلاج، بلغ معدل الشفاء 96٪ من المتورّقات، و32.7٪ من البلهارسية. وكان لدى جميع المرضى المصابين بالبلهارسية وشفوا منها، منخفضة الشدة. وأكدت اختبارات وظائف الكبد التي أجريت قبل العلاج وبعد العلاج بثمانية أسابيع على سلامة إعطاء العلاج بجرعتين من التريكلابندازول للمرضى المصابين بعدوى مشتـركة. ومع أن إعطاء التريكلابندازول يجب أن يسبق إعطاء البرازيكوانتيل في معالجة العدوى المشتـركة، إلا أن التريكلابندازول لا يمكن التوصية به لعلاج العدوى بالبلهارسية المانسونية وحدها.

ABSTRACT To determine the safety and efficacy of 2 consecutive doses of triclabendazole (TCBZ) in the treatment of *Schistosoma mansoni* infection in human cases infected with both *S. mansoni* and *Fasciola* sp., we conducted a field survey involving 6314 individuals from 15 villages. The overall prevalence of schistosomiasis alone was 15.8%, of fascioliasis alone 2.2%, and of combined infection 0.7%. Treatment with 2 doses of TCBZ was given to the 49 cases with combined infection. Eight weeks after treatment, the cure rate was 96% for fascioliasis and was 32.7% for schistosomiasis. All schistosomiasis cases cured had a low intensity infection. Liver function tests done before treatment and 8 weeks after substantiate the safety of 2 doses of TCBZ given to those with combined infection. Administration of TCBZ should precede praziquantel in treatment of combined infection, however TCBZ cannot be recommended for infection with *S. mansoni* alone.

Évaluation d'un traitement à deux doses de triclabendazole pour des patients atteints d'une schistosomiase associée à une fasciolase

RÉSUMÉ Afin de déterminer l'innocuité et l'efficacité de deux doses consécutives de triclabendazole dans le traitement de l'infestation par *Schistosoma mansoni* chez des patients atteints à la fois par *S. mansoni* et *Fasciola sp*., nous avons conduit une enquête de terrain impliquant 6314 individus provenant de 15 villages. La prévalence globale de la schistosomiase seule était de 15,8 %, celle de la fasciolase seule s'élevait à 2,2 %, et celle de l'infestation double à 0,7 %. Un traitement par deux doses de triclabendazole a été administré aux 49 cas atteints de la double infestation. Huit semaines après le traitement, le taux de guérison était de 96 % pour la fasciolase et de 32,7 % pour la schistosomiase. Tous les cas de schistosomiase guéris étaient des infestations de faible intensité. Les analyses de la fonction hépatique avant le traitement puis huit semaines après apportent la preuve de l'innocuité de deux doses de triclabendazole administrées aux patients atteints de l'infestation double. L'administration de triclabendazole doit précéder celle du praziquantel dans le traitement de l'infestation double, toutefois le triclabendazole ne peut être recommandé pour traiter une infestation unique par *S. mansoni*.

[1]*Department of Parasitology;* [2]*Department of Medical Statistics, Medical Research Institute, Alexandria University, Alexandria, Egypt (Correspondence to H.F. Farag: hfarag@link.net).*

Received: 08/04/09; accepted 16/09/09

Introduction

In Egypt, despite government efforts aimed at control, schistosomiasis remains an important public health problem. It is still endemic in rural areas and transmission is still ongoing [1].

Human fascioliasis has emerged in Egypt over the past 3 decades and prevalence rates in rural areas range between 2% and 19% [2–5]. As a result, schistosomiasis and fascioliasis co-exist in the same environment and they prevail in some villages [6,7]. A drug effective against both parasites would be highly welcome.

Praziquantel (PZQ) is still the ideal drug for control of schistosomiasis [8]. However, the extensive reliance on just 1 drug is of utmost concern due to the risk of possible development of drug-resistant parasites. In view of this concern, there is a great need for developing novel antischistosomal drugs.

Triclabendazole (TCBZ; Egaten), an effective and safe drug for *Fasciola* infection, was evaluated experimentally on schistosomiasis. *In vitro*, adult *Schistosoma mansoni* worms exposed to the drug were reported to show rapid destruction of the tegument; the damage was found to be irreversible and 100% of the worms were killed after 24 hours [9]. Studies performed on experimentally-infected mice revealed conflicting results; 2 have reported 84% and 87% of worms killed 4 weeks after treatment [10,11], however, a more recent study found low efficacy (18%–36%) for TCBZ *in vivo* [12].

No studies with high power on the effect of TCBZ on *Schistosoma* infection in humans are available. Recently, Barduagni et al. evaluated the use of TCBZ for treatment of patients co-infected with *Fasciola* sp. and *Schistosoma* sp. using a single dose of 10 mg/kg body weight [13]. They concluded that TCBZ was insufficiently effective on schistosomiasis. Further studies with 2 consecutive doses of TCBZ could be of value.

Methods

A field survey was carried out by the Parasitology Department of the Medical Research Institute in 15 villages near Alexandria in Beheira governorate. These villages were known to be endemic for both *Schistosoma* sp. and *Fasciola* sp. A census of the inhabitants was performed and demographic data were collected and recorded. All individuals over 5 years of age (n = 6314) were asked to submit a stool sample; there were no refusals to comply. We prepared 3 Kato–Katz slides [14] of 41.7 mg each for each sample and eggs were counted by trained technicians. Each technician examined 1 set of slides.

All positive cases with combined infection (n = 42) identified in the field survey, together with 7 cases which were referred to the Parasitology Department within the study period, were enrolled in the study. Interview and clinical examination were conducted. Participants included in the study had no past history of jaundice or viral hepatitis or history of receiving schistosomicidal or fasciolicidal drugs within the preceding 6 months.

Treatment and follow-up

Prior to treatment, a blood sample was obtained and liver function tests were performed. TCBZ for human use (Egaten, Novartis Pharma AG, Basle, Switzerland) was used. Each tablet contained 250 mg TCBZ and each case received 2 doses on 2 successive days after a fatty meal. Each dose was calculated at 10 mg/kg body weight. The maximum dose was 2.5 tablets.

For follow-up after treatment, all cases were asked to provide a stool sample after 1, 2, 3, and 8 weeks; 3 Kato–Katz slides were examined for each sample, and eggs were counted for positive cases.

Cases were considered cured of either *S. mansoni* or *Fasciola* sp. infection at any examination when no eggs of the corresponding parasites were found in stools after examination of 3 Kato–Katz slides. Actual cure was considered when eggs were absent on the 8th week after treatment.

Blood samples were taken at the 8th week and liver function tests repeated.

Statistical analysis

Data were processed using *SPSS*, version 11. Intensity of infection was expressed as geometric mean egg count (GMEC). Cure rates were calculated as the percentage of individuals becoming parasitologically negative. For cases remaining positive after treatment, percentage changes in egg counts were calculated using the formula:

$$\% \text{ change} = ((GMEC_b - GMEC_a)/GMEC_b) \times 100$$

where:

b = before and a = after treatment

The sign rank test was used to test the significance of changes in egg count, and the Cochrane test was used to assess changes in cure rates in the weeks of follow-up.

Ethics

The ethical aspects were respected throughout the study: informed consent was obtained from all participants and from parents of infected children. They were informed about the drug and the study protocol.

Results

The field survey covered a total of 6314 individuals from villages near Alexandria. Prevalence of schistosomiasis single infection was 15.8% (n = 996), of fascioliasis single infection was 2.2% (n = 142), and of combined infection was 0.7% (n = 42). For the 49 cases with combined infection (including the 7 referred ones) age ranged between 5 and 50 years; 27 (57%) of these were males.

Treatment of cases with combined infection

Cure rates for *Fasciola* and *Schistosoma* infection in combined cases were assessed. The cure rate for *Fasciola* was 98.0% (only 1 positive case) in the 1st, 2nd and 3rd week and decreased to 95.9% in the 8th week (2 cases).

Table 1 demonstrates the results for *S. mansoni* individually over time. Only 8 cases were negative on all examinations, 19 cases did not show negative results in any examination, all other cases gave varying results. The cure rate was around 40% at weeks 1, 2 and 3 and fell to 32.7% at week 8.

Only cases with low intensity of infection [< 100 eggs per gram (epg)] partially responded to TCBZ treatment (cure rate = 41.0% 8 weeks after triclabendazole treatment); not a single cure occurred in cases with moderate (100–400 epg) or heavy (> 400 epg) *Schistosoma* infection.

No significant changes in *Schistosoma* egg counts were found in cases remaining positive after TCBZ treatment (Table 2).

Liver function tests are presented in Table 3, showing no significant changes 8 weeks after treatment. No side effects were reported. Thus TCBZ is considered tolerable and safe in cases with combined infection.

Discussion

The efficacy and safety of TCBZ in treatment of *Schistosoma* infection was not sufficiently studied in human schistosomal infections. The existence of a relatively large number of patients infected with both *Schistosoma* and *Fasciola* detected in the present field study made it feasible and ethically accepted to assess the schistosomicidal effect of TCBZ while treating *Fasciola* infections in these patients. As some workers recommended the use of 2 doses of TCBZ (10 mg/kg each) in treatment

Table 1 Individual findings for *Schistosoma mansoni* infection in 49 combined cases 1–8 weeks after triclabendazole treatment

Combined cases	EPG	Cure rate			
		1st week	2nd week	3rd week	8th week
1	24	–	–	–	–
2	12	–	–	–	–
3	96	–	–	–	–
4	24	–	–	–	–
5	12	–	–	–	–
6	12	–	–	–	–
7	12	–	–	–	–
8	24	–	–	–	–
9	252	+	+	+	+
10	192	+	+	+	+
11	12	+	+	+	+
12	336	+	+	+	+
13	336	+	+	+	+
14	36	+	+	+	+
15	36	+	+	+	+
16	36	+	+	+	+
17	12	+	+	+	+
18	12	+	+	+	+
19	48	+	+	+	+
20	276	+	+	+	+
21	240	+	+	+	+
22	1440	+	+	+	+
23	96	+	+	+	+
24	96	+	+	+	+
25	72	+	+	+	+
26	36	+	+	+	+
27	24	+	+	+	+
28	24	+	–	–	–
29	36	+	–	–	–
30	12	+	–	–	–
31	60	–	–	+	–
32	528	–	+	+	+
33	36	–	+	+	+
34	84	–	+	–	–
35	24	–	+	+	+
36	12	–	–	+	+
37	12	–	–	–	+
38	204	–	–	–	+
39	36	–	–	–	+
40	36	–	+	–	+
41	60	–	–	+	–
42	12	+	+	+	–
43	84	+	+	–	–
44	156	+	–	+	+
45	36	+	+	–	+
46	12	+	+	–	+
47	12	+	–	+	+
48	36	+	+	–	+
49	36	+	–	+	+

+ = positive, eggs seen on stool examination; – = negative, no eggs seen on stool examination.
EPG = eggs per gram.

Table 2 Change in *Schistosoma* egg count in cases with combined infection remaining positive after triclabendazole treatment

When examined[a]	No. cases not cured[b]	Geometric mean egg count (95% CI)		% change	*P*-value
		Before treatment	After treatment		
1	30	56.31 (35.97–89.68)	64.02 (39.36–104.4)	+12.0	> 0.05
2	29	69.26 (42.88–111.87)	68.66 (42.14–111.87)	–0.9	> 0.05
3	29	65.30 (39.95–106.76	74.43 (46.48–119.20)	+12.3	> 0.05
8	33	60.34 (38.44–94.71)	58.48 (36.53–93.61)	–3.1	> 0.05

[a]*Weeks after treatment.*
[b]*Cases found positive differed from week to week.*
CI = confidence interval.

of *Fasciola* infection [15] this treatment schedule was followed to increase the possibility of detecting any potential schistosomicidal effect in cases with combined infection.

In our study, according to the results of the 8th week, TCBZ cured more than one-third of the patients with combined infection. It is important to note that cases cured from schistosomiasis were generally those with low egg counts (epg < 100). Some of them ceased to pass ova starting 1 week after treatment, others became negative starting from the second week. Some cases gave varying results in the different examinations, probably due to the low sensitivity of the Kato–Katz technique to detect light infection. In cases with moderate or heavy *Schistosoma* infection (epg > 100), TCBZ failed to cure any case, or even to reduce the intensity of infection. This latter finding is difficult to interpret, but it raises the possibility that TCBZ is not effective on immature worms, expected to be present more frequently in patients with higher intensity of infection.

In the 8th week, the reported cure rates for fascioliasis and schistosomiasis were slightly lower than those in the first few weeks. This is possibly due to the recovery of a few worms that were affected but not killed by the drug and resumed oviposition.

Considering cases that ceased passing eggs throughout the follow-up period, the actual cure rate would amount to 16.3%.

The variability in the effect of TCBZ on *Schistosoma* versus *Fasciola*, on high intensity versus low intensity infection, and *in vitro* versus *in vivo Schistosoma* infection needs more research. Pharmacokinetics in the host might play a key role in the differing susceptibilities to TCBZ between *Schistosoma* and *Fasciola*; it might also explain the difference in the *in vitro* and *in vivo* activity of the drug on schistosomes. TCBZ was reported to be highly protein bound in animal species and, while Fasciola is known to be very susceptible to drugs that mainly bind to plasma proteins, schistosomes might be less affected by the protein-bound TCBZ [16].

To sum up, this study emphasizes the fact that TCBZ, given in 2 consecutive doses cannot be recommended for treatment of *Schistosoma* infection alone because its efficacy is so inferior to that of PZQ. However, in areas where combined infection with both *Schistosoma* and *Fasciola* are prevalent, our findings indicate that the use of TCBZ followed by PZQ could be of value.

Table 3 Liver function indicators before and 8 weeks after triclabendazole treatment in 49 cases with combined infection

Parameter	Before treatment	After treatment	*t*	*P*-value
AST (≥ 12 U/L)[a]			0.76	> 0.05
Range	4–34	4–27		
Mean (SD)	12.55 (6.35)	12.0 (5.53)		
Cases with high values	21	17		
ALT (≥ 12 U/L)[a]			1.5	> 0.05
Range	4–63	4–35		
Mean (SD)	12.3 (9.23)	10.8 (4.63)		
Cases with high values	17	9		
AKP (9–35 IU/L)[a]			0.65	> 0.05
Range	7–557	7–289		
Mean (SD)	44.29 (83.94)	40.04 (49.30)		
Cases with high values	13	13		

[a]*Normal range.*
SD = standard deviation.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; AKP = alkaline phosphatase.

Acknowledgements

The authors acknowledge the TDR unit, World Health Organization, Regional Office for the Eastern Mediterranean, for funding and supporting this work. (Project ID: A 30049).

Thanks are due to staff members of TDR for their encouragement during the work. Special thanks are due to the late Professor Dr Laila Abou-Basha who spent a lot of effort in the initiation of this project.

References

1. Botros S et al. Efficacy of mirazid in comparison with praziquantel in Egyptian *Schistosoma mansoni* infected school children and households. *American Journal of Tropical Medicine and Hygiene*, 2005, 72(2):119–123.
2. *Control of foodborne trematode infections. Report of a WHO Study Group*. Geneva, World Health Organization, 1995 (Technical Report Series, No. 849).
3. Esteban JG, Bargues MD, Mas-Coma S. Geographical distribution, diagnosis and treatment of human fascioliasis: a review. *Research and Reviews in Parasitology*, 1998, 58:13–42.
4. Curtale F et al. Human fascioliasis, an emerging public health problem in the Nile Delta, Egypt. *Research and Reviews in Parasitology*, 2000, 60:129–134.
5. Haseeb AN et al. A review on fascioliasis in Egypt. *Journal of the Egyptian Society of Parasitology*, 2002, 32:317–354.
6. Esteban JG et al. Hyperendemic fascioliasis associated with schistosomiasis in villages in the Nile Delta of Egypt. *American Journal of Tropical Medicine and Hygiene*, 2003, 69(4):429–437.
7. Curtale F et al. Human fascioliasis infection: gender differences within school-age children from endemic areas of the Nile Delta, Egypt. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2007, 101(2):155–160.
8. Doenhof FMJ et al. Resistance of *S. mansoni* to praziquantel: is there a problem? *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2002, 96:465–469.
9. El-Sayad MH, Allam AF. Effect of triclabendazole on the tegument of *Schistosoma mansoni*: a scanning electron microscopic study. *Journal of the Egyptian Society of Parasitology*, 1997, 27:143–152.
10. Coles GC. Anthelmintic activity of triclabendazole. *Journal of Helminthology*, 1986, 60:210–212.
11. Khalil SS. On the schistosomicidal effect of triclabendazole: an experimental study. *Journal of the Egyptian Society of Parasitology*, 2000, 30:799–808.
12. Keiser J et al. Triclabendazole and its two main metabolities lack activity against *Schistosoma mansoni* in the mouse model. *American Journal of Tropical Medicine and Hygiene*, 2006, 75(2):287–291.
13. Barduagni P et al. Use of triclabendazole for treatment of patients co-infected by *Fasciola* spp. and *S. mansoni* in Behera Governorate, Egypt. *Parasitology Research*, 2008,102(4):631–363.
14. Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick smear technique in schistosomiasis mansoni. *Revista do Instituto de Medicina Tropical de São Paulo*, 1972, 14:397–400.
15. El-Morshedy H et al. Triclabendazole in the treatment of human fascioliasis: a community based study. *Eastern Mediterranean Health Journal*, 1999, 5(5):888–894.
16. Keiser J et al. Triclabendazole for the treatment of fascioliasis and paragonimiasis. *Expert Opinion on Investigational Drugs*, 2005, 14:1513–1526.

Global Health Observatory Map Gallery

The WHO Global Health Observatory map gallery includes an extensive list of maps on major health topics and covers all countries of the world. Maps are classified by themes, e.g. cholera, neglected tropical diseases and violence and injuries, and can be further searched by keyword.

Searches can be conducted from this page: http://gamapserver.who.int/mapLibrary/