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CLINICAL TRIAL OF TRICLABENDAZOLE ON HUMAN FASCIOLIASIS: LONG TERM FOLLOW UP

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ABSTRACT

Following an outbreak of human fascioliasis in Gilan province of Iran in 1989, the benzimidazole derivative triclabendazole (TCBZ) was suggested as the drug of choice after finding out that routine drugs were not effective. Two studies were performed: a clinical trial (before/after type) in 1989 and a historical cohort (1989-1995) to examine the efficacy of the drug.

TCBZ was administered to 94 patients in four groups (A, B, C and D) according to the drug's instructions (time, size and frequency of dose). The patients were followed up clinically and paraclinically for 60 days. The highest cure rate, i.e., omission of eggs and improvement of clinical symptoms (86.6%) was observed in Group A (5 mg/kg-NPO, 3 days). Minor epigastric pain and vomiting and some urticaria was reported a few days after administration of the drug. Just a few developed cholangitis and one toxic hepatitis who were all treated satisfactorily. The second study was a 6-year follow-up survey of 50 of the 94 patients. Five cases had epigastric pain, and eggs were detected in the stool exams of two of them. Thus, by demonstrating up to 94% efficacy in the treatment of human fascioliasis in Iran ($p<0.002$), TCBZ is recommended as the drug of choice.

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INTRODUCTION

The liver fluke *Fasciola hepatica* and *F. gigantica* are prevalent in livestock in Iran.[4,21] The human infection has been reported sporadically in different parts of the country particularly in the littoral of the caspian sea. [4,5,21] Anzali harbor, our study area, showed the highest infection rate (7.3%) in stool examination by random sampling. I.F.A. test indicated that 16.5% of the population was infected with fasciola.[1,4] The early clinical symptoms of fascioliasis were urticaria, abdominal discomfort, epigastric pain, right upper quadrant pain, and vomiting. Hematologic examination revealed hypereosinophilia.[4,6,21] In some cases even the cutaneous form of ectopic fascioliasis has been observed.[5,14] In ultrasonography of the liver in some patients the presence of the liver fluke was documented.[5,6] Even in a few cases after surgery adult flukes were recovered. The study revealed that anti-fascioliasis drugs e.g. emetin, bithional and praziquantel were not effective.[2,5,6,17] However TCBZ had excellent results.[5,6,8,12]

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MATERIAL AND METHODS

Two studies were performed; a randomized clinical trial and a historical cohort. The first study was a before/after type (a quazi-experimental survey), in which *Fasciola hepatica* eggs were detected in the stool examination of 94 patients. The variables of the study were age, gender and weight. 85% of the patients were female. The age range was between 15 to 65 years, of which 62.2% were young adults. The patients were divided into four groups (A, B, C and D) according to dosage and method of drug use (time, size and frequency of dose). Group A, 5 mg/kg NPO for 3 days, group B 10 mg/kg bid, Group C 10 mg/kg single dose NPO & Group D 10 mg/kg single dose after meal. Each group had 22-26 patients. The patients were strictly followed for 60 days. All of them were examined in 8 days within certain intervals (Table I). Routine tests were CBC diff, ESR, liver function test, urine analysis, kidney function test and stool exam with Katou & Telman's technique.

The second study was a historical cohort from 1989 to the end of 1995. Both clinical and paraclinical investigations were performed but only Telman's method was used in the stool exam. Ultrasonography was performed when necessary.[6]

RESULTS

During the epidemic phase of fascioliasis, none of the old principles or routine drug therapy were effective. For example, praziquantel therapy (70 mg/kg), administered in a trial with 100 infected cases, gave only a 2% cure rate. Bithional and emetin were considered to be very toxic and are thus not recommended for mass therapy.[5,6] Bithional (40 mg/kg for 15 days) was 69% effective but 60% of the patients were hospitalized due to severe intractable side effects. Thus TCBZ (a veterinary product) was recommended by the W.H.O. (World Health Organization).

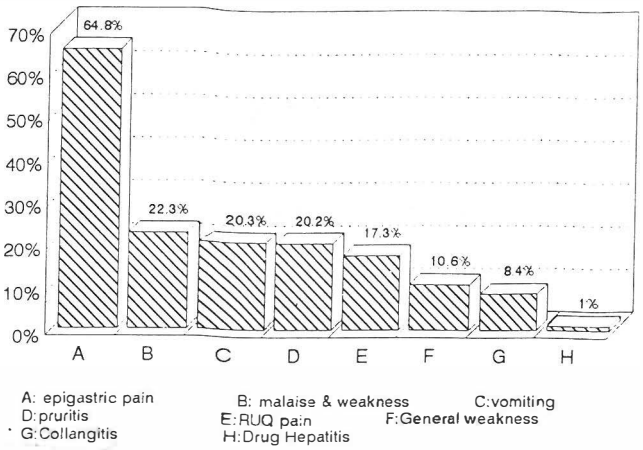

Fig. 1. TCBZ side effects.
A: epigastric pain
B: malaise & weakness
C: vomiting
D: pruritus
E: RUQ pain
F: general weakness
G: cholangitis
H: drug hepatitis

For clinical evaluation of TCBZ, 4 groups of patients were selected, and all of them were screened clinically and paraclinically before and after drug administration for 60 days (Table I). The cure rate, determined by omission of fasciola eggs in the stool exam and clinical improvement, was 86.6% in group A, 76.9% in group B, 70% in group D and 69% in group C. The clinical side effects were categorized in 4 classes (Fig. 1) : 1)Gastrointestinal tract effects (epigastric pain 64.8%, right upper quadrant pain 20.2%), the most common being epigastric pain which was colicky and intermittent, beginning a few days after taking the drug and sometimes requiring relief with antispasmodic agents. 2) Liver & biliary tract dysfunction (cholangitis & toxic hepatitis) in a few cases, 24 hrs after taking the drug. Temporary obstructive jaundice, which improved after 3-4 days, was observed due to parasites in the bile ducts. Just one case developed toxic hepatitis that was diagnosed with

Table I. Follow-up of fascioliasis patients.

Days	0	1	2	3	4	6	30	60
Clinical observation	+							
Physical exam	+	+	+	+	+	+	+	+
Drug effect survey		+	+	+	+	+	+	+
Lab	+				+	+	+	+
Chest X-ray	+						+	+
Ultrasonography	+						+	+

focal necrosis and cholestasis in liver biopsy. ERCP (endoscopic retrograde cholangio- pancreatography) detected parasites in the left hepatic duct. The patient had jaundice and pruritus, but the stool exam was negative. 3) Dermatologic disorders (urticaria, pruritus) were observed in a few cases. 4) General side effects (vertigo 22.13%, weakness and malaise 10.6%) were relatively mild. In general, the side effects were minor and transient, and the cure rate was 94%.[6]

The historical cohort study lasted for 6 years (1989-1995) after treatment with TCBZ and was carried out on 50 of the cases. Five of them still had some clinical symptoms (mild epigastric pain), however only 2 of the 5 cases were still passing fasciola eggs in feces. One patient died due to diabetes and another patient who was an old woman (70 years old) died due to liver cancer without any significant relation to TCBZ.[6] Two women aged 26 and 40 with right upper quadrant pain had undergone cholecystectomy.

DISCUSSION

After being tested, triclabendazole (Fasinex), a product of the CIBA-Geigy company, has been used voluntarily with the permission of the health authorities. TCBZ is effective on domestic animal fascioliasis.[4,7] It is also effective against both mature & immature stages of the parasite. The effect of this drug in it's active sulphoxide metabolite form on the tegumental surface of *Fasciola hepatica* has been examined.[20] While a randomized clinical trial (phase II) was being conducted in Iran, similar studies were being performed in Syria & Egypt. But unfortunately, only a few reports from Egypt are available. The reported results were similar to ours.[12] In a study performed in Spain, human fascioliasis cases with atypical & severe presentations were treated with single dose (10 mg/kg) TCBZ with suitable clinical response.[17] In a study reported from Thailand, praziquantel was the drug of choice in lung & liver trematode-parasitic disease but not in fascioliasis.[19] In another study in Gilan University of Medical Sciences, 96 patients were treated with a single dose of 10 mg/kg TCBZ, and after 2-4 weeks follow-up 58 of 60 patients had negative stool exams. Only 3 patients developed cholangitis which was treated with 5 days of Gentamycin injection. In our trial, TCBZ, compared with bithional and praziquantel, demonstrated a marked effect on human fascioliasis. Thus, triclabendazole is recommended as the drug of choice for human fascioliasis because it has good tolerance, and is both cheap and easy to administer with minimum side effects. [5,6]

REFERENCES

1. Asmar M, etal: Seroepidemiological investigation of fascioliasis in northern Iran. Med J Islam Rep Iran (1,2): 23-27, 1991.
2. Yadegary D, et al: Survey of praziquantel's effect on fascioliasis. Med J Islam Rep Iran (1,2): 43-4, 1991.
3. Adel AFM: Trematodes and Other Flukes. In: Mandell GL, Bennett JE, (eds.), Principles and Practice of Infectious Disease. 4th edition, part III, New York: Churchill- Living- stone, p. 2542, 1995.
4. Massoud J: Present status of human fascioliasis in Iran: food-borne trematodes. WHO manual, Manila Sch/SG/93 w, p. 19, Oct. 1993.
5. Yadegari D, Talaie H:Six years follow-up of triclabendazole in human fascioliasis. 7th Iranian Congress of Internal Medicine, Shahid Beheshti University of Medical Sciences, Abstracts (167), May 16-19, 1996.
6. Yadegari D, Talaie H: W.H.O. protocol: using triclabendazole in human fascioliasis in north of Iran. The First Parasitology Congress in Iran. Gilan Medical University, Abstracts (88-95), 1990.
7. Kinabo LD, Bogan JA: Pharmacokinetics & efficacy of triclabendazole in goats with induced fascioliasis. J Vet Pharmacol Ther 3 (9): 254-9, 1988.
8. Markwalder K, Goebel N, Wolf K: Successful therapy using triclabendazole in *Fasciola hepatica* infection. Sch Weiz Med Wochenschr 27-28: 1048-52, 1998.
9. Ramisz A, Urban E, Balicka laurans A: Usefulness of the preparation Fasinex (TCBZ, Ciba-Geigy) for the control of fascioliasis. Wiad Parasytol 32 (1): 93-8, 1986.
10. Overend D-DJ, Bowen FL: Resistance of *Fasciola hepatica* to triclabendazole. Aus Vet J 72(7): 275-6, 1995.
11. Apt W, Aguilera X, Veja F: Treatment of human chronic fascioliasis with triclabendazole: drug efficacy & serologic response. Am J Trop Med Hyg 52(6): 532(5), 1995.
12. Hammouda NA, el Mansoury ST, el Azzouni MZ: Therapeutic effect of TCBZ in patients with fascioliasis in Egypt. J Egypt Soc Parasitol 25 (1): 137-43, 1995.
13. Melero M, Rigau RC: Uncommon cause of prolonged febrile syndrome with hypereosinophilia. Medicine B Aries 51(3): 244-8, 1991.
14. Dowlati Y, et al: A case of cutaneous fascioliasis. Med J Islam Rep Iran 1: 62-65, 1987.
15. Echevarria FA, Corea MB: Experiments on anthelminthic control of *Fasciola hepatica* in Brazil. Ver Parasitol 43 (3-4): 211-22, 1992.
16. Osman MM, Helmy M: Studies of human fascioliasis in Egypt: some serum lipid parameters before and after treatment. J Egypt Soc Parasitol 215 (3): 769-72, 1995.
17. Merino AJ: Human fascioliasis with atypical severe presentation: treatment with TCBZ. Infec Microbiol Clin Jan 16: 28 - 30, 1998.
18. Montembault S, Serfaty L: Hemorrhagic ascites disclosing massive *Fasciola hepatica* infection. France Gastroenterol Clin Biol 21 (10): 785-8, 1997.
19. Harina Suta T, Keystone JS: Trematode infections: United States. Infect Dis Clin North Am Sep 7(3): 699-716, 1993.
20. Shitt AW, Fairweather I: Tegumental surface changes in adult and juvenile flukes following treatment *in vitro* with the sulphoxide metabolite of TCBZ. Germany Parasitol Res 79 (7): 529-36, 1993.
21. Rahimi-pour MD, Delkhosh J: Fasciola infection in man. Gilan Health Center Report, Rasht, I.R. Iran, 1995.