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

D. YADEGARI, M.D., H. TALAIE, M.D., AND J. MASSOUD, Ph.D.

From the Shahid Beheshti University of Medical Sciences & Health Services, the WHO Collaborating Center for Educational Development of Medical & Health Personnel (EDC), and the School of Public Health, Tehran Medical Sciences University, P.O. Box 6446-14155, Tehran, I.R. Iran.

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.

MJIRI, Vol. 13, No. 2, 89-91, 1999

INTRODUCTION

The liver fluke Fasciola hepatica and F. gigantica are prevalent in livestock in Iran.† The human infection has been reported sporadically in different parts of the country particularly in the littoral of the caspian sea.‡ Anzali

† D. Yadegari, M.D., Infectious Disease Specialist, Associate Professor
‡ H. Talaie, M.D., Infectious Disease Specialist, Assistant Professor
§ J. Massoud, Ph.D. Professor of Parasitology
Correspondence: H.Talaie, Faculty Member of EDC, Shahid Beheshti University of Medical Sciences, Tel: 240 10 21, Fax: 240 12 28, Email: Talaie @ hotmail. Com

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.¶ The early clinical symptoms of fascioliasis were urticaria, abdominal discomfort, epigastric pain, right upper quadrant pain, and vomiting. Hematologic examination revealed hyper eosinophilia.¶¶ In some cases even the cutaneous form of ectopic fascioliasis has been observed.¶¶ In ultrasonography of the liver in some patients the presence of the liver fluke was documented.¶¶ 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.¶¶¶ However TCBZ had excellent results.¶¶¶
Triclabendazole for Human Fascioliasis

MATERIAL AND METHODS

Two studies were performed; a randomized clinical trial and a historical cohort. The first study was a before/after type (a quasi-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 1). 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.

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. 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).

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 1). 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>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>30</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical observation</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Drug effect survey</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lab</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
focal necrosis and cholestasis in liver biopsy. ERCP (endoscopic retrograde cholangiopancreatography) 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%.* 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. 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.** It is also effective against both mature & immature stages of the parasite. The effect of this drug in its active sulphoxide metabolite form on the tegumental surface of Fasciola hepatica has been examined.** 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.** 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.** In a study reported from Thailand, praziquantel was the drug of choice in lung & liver trematode-parasitic disease but not in fascioliasis.** 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.**

**REFERENCES**

5. Yadegary D, Taleie 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.
THE EFFECT OF ANTIHYPERTENSIVE DRUGS IN THE SUPPRESSION OF ATHEROSCLEROSIS

HASSAN FALLAH HUSAINI, Ph.D., AND MANSURI SABERAH, * M.D.

From the Institute of Medicinal Plants and Natural Products, Tehran, I.R. Iran, and *B.J. Medical College, Ahmedabad 6, India.

ABSTRACT

The present investigation was undertaken to evaluate the effect of antihypertensive drugs on aortic atherogenesis in hypercholesterolemic rabbits. In enalapril and nifedipine treated rabbits aortic atherosclerotic plaque involvement was significantly decreased (p<0.01 and p<0.05, respectively) as compared to the control group. However, in hydrochlorothiazide treated rabbits aortic atherogenesis was marginally inhibited, whereas in clonidine treated rabbits it was similar to the control group. These results suggest that the inhibition of atherogenesis in enalapril and nifedipine treated rabbits is independent of hypercholesterolemia and may be relevant in the selection of antihypertensive drugs, provided their protective effect can be demonstrated in future clinical trials as well.

Keywords: Antihypertensive drugs, Atherosclerosis, Hypercholesterolemia.

INTRODUCTION

Atherosclerosis and its complications constitute a disease complex of major public health importance and, as a cause of myocardial and cerebral infarction, constitute the chief cause of death in industrialized societies. The incidence of atherosclerosis is correlated with age, male sex, cigarette smoking, obesity, diabetes, hypertension and hyperlipidemia. Although the actual mechanism by which hypertension aggravates atherosclerosis is not clearly known, the available evidence indicate that hypertension appears to induce a sequence of changes in connective tissue metabolism, smooth muscle cells, endothelial integrity, platelet function, lipid profile and changes pertaining to insulin and glucose metabolism which may be important in the genesis of atherosclerosis in hypertensive subjects.1 Hypertension is a long-term disorder, and one of the most perplexing problems in the management of hypertension is the adverse effect of antihypertensive drugs or their metabolites on the cardiovascular system. The effect may be small, but still blunt considerably the beneficial effect of blood pressure reduction.2 The present investigation was undertaken to find out the possible influence of diuretics (hydrochlorothiazide), centrally acting alpha 2-adrenergic agonists (clonidine), calcium channel blockers (nifedipine) and angiotensin-converting enzyme inhibitors (enalapril) on the development of atherosclerosis in cholesterol-fed rabbits.

MATERIAL AND METHODS

Fifty male New Zealand White rabbits aged 4 to 6 months weighing 1.5 to 2 kg were randomly selected. They were caged individually in five groups of 10 rabbits each, in
Effect of Antihypertensive Drugs on Atherogenesis

Table I. Serum triglyceride, HDL and total cholesterol levels (mg/dL) of control and drug-treated hypercholesterolemic rabbits.

<table>
<thead>
<tr>
<th>Experimental group (n=10)</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1904 ± 390</td>
<td>16.6 ± 4.3</td>
<td>284 ± 76</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>2062 ± 475</td>
<td>15.8 ± 5.1</td>
<td>450 ± 53</td>
</tr>
<tr>
<td>Clonidine</td>
<td>2246 ± 569</td>
<td>15.4 ± 4.4</td>
<td>381 ± 72</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>1980 ± 413</td>
<td>17.0 ± 6.3</td>
<td>230 ± 39</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1880 ± 411</td>
<td>17.5 ± 5.5</td>
<td>208 ± 37</td>
</tr>
</tbody>
</table>

Results are given as mean ± SD.

Table II. Tissue cholesterol content (mg/g wet weight) of control and drug treated hypercholesterolemic rabbits.

<table>
<thead>
<tr>
<th>Experimental Group (n=10)</th>
<th>Aortic cholesterol</th>
<th>Liver cholesterol</th>
<th>Adrenal gland cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>19.4 ± 5.8</td>
<td>58.3 ± 10.5</td>
<td>164.2 ± 21.3</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>18.0 ± 6.4</td>
<td>50.5 ± 12.2</td>
<td>145.0 ± 20.5</td>
</tr>
<tr>
<td>Clonidine</td>
<td>17.8 ± 5.9</td>
<td>54.7 ± 11.0</td>
<td>164.4 ± 18.8</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>12.8 ± 4.2*</td>
<td>51.2 ± 13.3</td>
<td>183.5 ± 25.8</td>
</tr>
<tr>
<td>Enalapril</td>
<td>5.2 ± 1.3**</td>
<td>59.9 ± 14.5</td>
<td>150.0 ± 17.5</td>
</tr>
</tbody>
</table>

Results are given as mean ± SD.

*p<0.05, **p<0.001 (significantly lower as compared to control).

After one week of initial adaptation to rabbit chow diet, each rabbit was fed 100 g of atherogenic diet (500 mg cholesterol+99.5 g rabbit chow) daily for a period of 10 weeks. Simultaneously, each group (except control group) of rabbits received one of the following antihypertensive drugs orally: hydrochlorothiazide 2 mg/kg/d, clonidine 0.013 mg/kg/d, nifedipine 1 mg/kg/d, enalapril 1 mg/kg/d.

Serum analysis

Blood samples were collected after overnight fasting for estimation of serum triglyceride, HDL and total cholesterol levels.

In vitro study

Rabbits were sacrificed at the end of 10 weeks and the aorta, adrenal gland and liver tissue were removed. The aortic atherosclerotic plaque involvement was measured.1

The liver, adrenal gland and aortic tissue cholesterol content was also determined.

RESULTS

The values of serum triglyceride, HDL and total cholesterol of control and drug treated groups are summarized in Table I. The results indicate that serum triglyceride, HDL and total cholesterol levels of control (284±76, 16.6±4.3, 1904±390 mg/dL, respectively) and drug treated groups were not significantly different.

As shown in Table II, the aortic tissue cholesterol content of enalapril and nifedipine treated groups were significantly (p<0.001 and p<0.05, respectively) lowered as compared to the control group.

The liver and adrenal gland tissue cholesterol content of enalapril and nifedipine treated groups were similar to the control group. Tissue cholesterol content of
H. Fallah Husaini and M. Saberah

Table III. Percent of aortic surface area covered by atherosclerotic plaque in control and drug treated hypercholesterolemic rabbits.

<table>
<thead>
<tr>
<th>Experimental group (n=10)</th>
<th>Percent of aorta covered by atherosclerotic plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>33 ±10</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>29 ±12</td>
</tr>
<tr>
<td>Clonidine</td>
<td>33 ±11</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>22 ±6*</td>
</tr>
<tr>
<td>Enalapril</td>
<td>8 ±2**</td>
</tr>
</tbody>
</table>

Results are given as mean ±SD.

\*p<0.05, **p<0.001 (significantly lower as compared to control).

hydrochlorothiazide and clonidine treated groups were not significantly different from controls.

The average extent of aortic atherosclerotic plaque involvement in enalapril (8 ±2%) and nifedipine (22 ±6%) treated groups was significantly lower as compared to the control group (33 ±10%). The aortic atherosclerotic plaque involvement in the hydrochlorothiazide treated group was reduced by 15.1% as compared to the control group but this difference did not reach statistical significance. However, in the clonidine treated group aortic atherosclerotic plaque involvement was similar to the control group.

**DISCUSSION**

The most interesting and important finding of this investigation was the prevention of atherosclerosis development and cholesterol accumulation in the aorta of enalapril and nifedipine treated rabbits. However, these preventive effects were independent of any changes in the serum cholesterol level. The accumulation of cholesterol in the adrenal gland and liver tissue were not influenced by these drugs. In hydrochlorothiazide treated rabbits atherosclerotic involvement of the aorta was marginally inhibited, whereas in clonidine treated rabbits it was similar to the control group.

The exact mechanism responsible for the antiatherosclerotic effect of calcium channel blockers is not yet clear. Calcium channel blockers appear to decrease the intracellular calcium concentration in the arterial wall smooth muscle cells (SMC). Reduced SMC calcium may decrease mitosis, collagen production, SMC migration and proliferation.\(^5\) Their anticalcinoic action and related pronounced effect on lipoprotein uptake and metabolism and prevention of noxious arterial calcium overload may also be identified as a possible vasoprotective mechanism.\(^3\) Calcium channel blockers may inhibit platelet activation as well as inhibit certain platelet functions such as calcium-dependent processes of adhesion, aggregation and release of platelet factors, which contribute to atherogenesis.\(^9,11\)

Several possible mechanisms may be proposed for the anti-atherogenic effect of angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors, by inhibiting angiotensin II formation, could theoretically be beneficial to the vasculature. Angiotensin II may act as a trophic factor stimulating the growth of vascular smooth muscle and myocardial cells and may alter the extra-cellular matrix in the arterial wall.\(^12,13\) Angiotensin II acts directly by stimulating the synthesis of new receptors for platelet derived growth factor (PDGF), thereby potentiating the mitogenic action of PDGF.\(^14\) Mas proto-oncogen product is an angiotensin receptor with mitogenic activity, and inhibition of angiotensin II could decrease the mitogenic activity mediated by this receptor.\(^13\) Furthermore, angiotensin II stimulates macrophage mediated oxidation of LDL secondary to cellular lipid peroxidation.\(^15\) However, the inhibition of angiotensin II synthesis by ACE inhibitors may explain the observed anti-atherogenic activity of enalapril.

The inhibition of atherogenesis in enalapril and nifedipine treated animals may be relevant in selection of antihypertensive drug therapy, provided their protective effect can be demonstrated in future clinical trials as well.

**REFERENCES**

Effect of Antihypertensive Drugs on Atherogenesis

(Suppl. 5): 1015-1020, 1990.


96