PRELIMINARY STUDY OF THERAPEUTIC EFFICACY OF A NEW FASCICOLIDAL DRUG DERIVED FROM COMMIPHORA MOLMOL (MYRRH)

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Abstract. Myrrh (from the stem of the Commiphora molmol tree) is an oleo gum resin that may prove efficacious for the treatment of fascioliasis. We studied 7 patients who were passing Fasciola eggs in their stools and treated them with myrrh. The drug (a formulation consisting of 8 parts of resin and 3.5 parts of volatile oils, all extracted from myrrh) was given in a dose of 12 mg/kg per day for 6 consecutive days in the morning on an empty stomach. Patients were followed for 3 months. The therapy proved to be effective, with pronounced improvement of the general condition and amelioration of all symptoms and signs. A dramatic drop in the egg count was detected at the end of treatment. Eggs were no longer detectable in the feces 3 weeks after treatment and after a follow-up period of 3 months. High eosinophilic counts, elevated liver enzymes, and Fasciola antibody titers returned to nearly normal. No signs of toxicity or adverse effects were observed. We conclude that the formulation of myrrh is safe, well tolerated, and effective for treating fascioliasis.

INTRODUCTION

Fascioliasis is a zoonotic disease caused by Fasciola (a liver fluke that infects sheep, goats, and cattle), for which humans act as an accidental host. Human fascioliasis is becoming an increasingly important problem in many countries, including Egypt, with increasing frequency in many governorates. Outbreaks have occurred in other countries.

Myrrh is an oleo gum resin obtained from the stem of Commiphora molmol (family Burseraceae), a tree that grows in northeastern Africa and the Arabian Peninsula. The drug is chiefly collected in Somalia. Much of the resin is obtained by collecting it from spontaneous exudation from the cracks and fissures that commonly form in the plant’s bark. Myrrh contains 7–17% volatile oil, 25–40% resin, 57–61% gum, and 3–4% impurities. Myrrh is approved by the U.S. Food and Drug Administration for food use (21 Code of Federal Registration–CFR 172.510) and was given generally recognized as safe (GRAS) status as a flavor ingredient (No. 2765) by the Flavor Extract Manufacturer’s Association (FEMA). The council of Europe included myrrh in the list of plants and parts thereof that are acceptable for use in foods.

Because drugs that act on schistosomiasis may also act on other parasites, and because myrrh was found to be effective in the treatment of schistosomiasis (with a high cure rate and without side effects), we decided to try a myrrh-derived drug on patients with fascioliasis to see if it proved beneficial. The present study was designed to investigate the efficacy of a new fascicidic that may offer a new promising approach in the treatment of fascioliasis.

MATERIALS AND METHODS

We chose 7 patients for inclusion in our study during the period January–October 1997. Patients were referred to us from different centers and hospitals and by colleagues. Patients presented with positive clinical or laboratory manifestations suggesting fascioliasis; all 7 patients were passing Fasciola eggs in their stools. All 7 completed the follow-up period of the study for 3 months. Their ages ranged from 10 to 41 years (mean, 23.7 ± 4.1 years). Five patients were boys or men and 2 were girls or women. All patients provided a full medical history, and all submitted to clinical examination and a number of laboratory investigations, as detailed below.

Full medical history included the following: age, sex, occupation, residence, dietary habits (including whether the patients ate raw green vegetables or drank from a contaminated water supply), family medical history, history of fever, abdominal pain, abdominal distension, and anorexia, vomiting, diarrhea, dysentery, jaundice, itching, fatigue, and chest symptoms (e.g., cough and chest pain).

Each patient was thoroughly clinically examined for fever, abdominal tenderness, jaundice, pallor, palpable liver and spleen, masses, and asci. Chest and heart examinations were performed.

Laboratory investigations included the following: each patient’s feces were analyzed by means of the modified Kato-Katz technique after the patient had maintained a liver-free diet for at least 7 days; complete laboratory investigations of blood included the following assessments: total leukocytic count, hemoglobin, eosinophilic count, and erythrocyte sedimentation rate; liver function tests included alanine transpeptidase (ALT), aspartate transpeptidase (AST), alkaline phosphatase, gamma glutamyl transpeptidase, and total serum bilirubin; renal function tests included blood urea and serum creatinine; and serologic diagnosis by use of indirect hemagglutination test (IHAT) was used to detect Fasciola antibodies.

A myrrh formulation consisting of 8 parts of resin and 3.5 parts of volatile oils was given orally in a dose of 12 mg/kg per day for 6 consecutive days in the morning on an empty stomach. The same dose was given to 10 normal, healthy volunteers (age and sex matched) with negative stool examinations and negative IHAT. All patients and normal volunteers were followed-up for 3 months. Clinical and stool examinations were performed at the end of treatment and then every week for 3 months. Other investigations were done at the end of treatment and every 2 weeks for 3 months.

Patients assumed responsibility for being treated with the myrrh-based drug. All patients gave informed consent. This study was approved by Al-Azhar Medical School Review Board.

Three infected members were from a single family, Farag...
and others\textsuperscript{2} and Ahmed and others\textsuperscript{9} have reported infection of more than one member of the same family with human fascioliasis; this may be explained by the fact that the family shares the same contaminated food, raw green vegetables.

### RESULTS

The most striking clinical symptoms in patients with fascioliasis included abdominal pain, fever, anorexia, weakness, loss of weight, fatigue, and asthenia. The most striking clinical signs included pallor and enlarged, tender liver (Table 1). Our therapy caused pronounced improvement of the general condition and amelioration of all symptoms and signs. The mean egg count in the infected group was 36 eggs per gram of stool. At the end of treatment (6 days), dramatic decrease in the egg count occurred, and eggs disappeared completely from stools 3 weeks after treatment and remained so for 3 months after treatment (Figure 1).

A mild to moderate degree of anemia in infected patients was nearly corrected 3 months after treatment. High erythrocyte sedimentation rate, leucocyte count, and eosinophilia returned to normal 3 months after treatment. Elevated alkaline phosphatase and gamma glutamyl transpeptidase in patients with fascioliasis were normalized 3 months after treatment. ALT, AST, and serum bilirubin were within normal ranges before and after therapy in patients with fascioliasis. Blood urea and serum creatinine values in patients with fascioliasis were within normal ranges before and after therapy. No signs of toxicity or adverse effects were observed. Before treatment, all patients displayed positive IHAT titer; 3 months after treatment, 1 of 7 patients still showed a positive titer, although it dropped from pretreatment levels (Table 2).

### DISCUSSION

Traditionally, myrrh has been used by Sumerians and Greeks to treat “worms,”\textsuperscript{18} by Chinese to relieve pain and swelling due to traumatic injury,\textsuperscript{20} and by Somalians to treat stomach complaints, diarrhoea, and wounds.\textsuperscript{21} In modern times, tincture of myrrh is used for therapy of aphthous ulcers\textsuperscript{22} and for reduction of cholesterol and triglycerides\textsuperscript{19,23}; myrrh also has cytotoxic and anticarcinogenic potentials.\textsuperscript{24}

Most fasciolicide treatments are either toxic, ineffective for parasites in both the mature and immature stages, or contraindicated; and efficacy still needs to be confirmed in human infection. Examples of fasciolicides include chloroquine,\textsuperscript{25,26} emetine and dehydroemetine,\textsuperscript{27,28} metronidazole,\textsuperscript{29} nicloflolan,\textsuperscript{30,31} bithionol,\textsuperscript{31} and praziquantel.\textsuperscript{32,33,34,37} Triclabendazole, a fasciolicide used effectively in veterinary medicine, has been proved to be effective and safe in treating human fascioliasis.\textsuperscript{33,38} However, the existence of more than a single drug that is effective and safe against such a disease is needed. Because drugs acting on schistosomiasis may as well act on other parasites, especially trematodes, and because myrrh was found to be very effective in treating schistosomiasis, with high cure rate and without side effects, even in cases complicated with hepatosplenomegaly,\textsuperscript{38} we thought that trying this drug as a fasciolicide might prove beneficial.

The crude material of myrrh is widely available on the market and can easily be imported from northeast Africa and the Arabian Peninsula. The price per dose is nearly one-fifth the price of triclabendazole. All the patients we studied were passing Fasciola eggs in their stools. We think this solid diagnosis is important, especially for documentation of a new fasciolicide such as myrrh. However, when trying the drug on patients with acute parasite infection, it is also important to know the effect of the drug on the immature stages of the parasite.

The main clinical presentations of the fascioliasis group were abdominal pain, pallor, fever, fatigue, asthenia, anorexia, loss of weight, tender liver, nausea, vomiting, enlarged liver, diarrhoea, and palpable spleen. No itching, jaundice, or ascites were noticed in the patients we studied. In our study, the common presentations were similar to those reported by Farid and others\textsuperscript{2} and Wessely and others.\textsuperscript{28} The patients had weekly check-ups after treatment over the course of 3 months. At the end of the follow-up period, physical examination revealed normalization of the liver and the spleen. The patients felt well and had no clinical symptoms of the presenting disease.

Pretreatment egg load was $36 \pm 4.8$ eggs per gram of stool. It decreased dramatically to $6.43 \pm 2.16$ eggs per gram of stool at the end of treatment. Complete disappearance of eggs from stools occurred 3 weeks after treatment, and remained so throughout the 3-month follow-up period.

Different methods have been commonly used for the evaluation of the effectiveness of treatment—for example, counting the eggs in stool samples and detecting serum antibody that is specific to the parasite.\textsuperscript{38} The present study showed that...
only 1 of 7 patients who received combined resin and volatile oil had positive IHA/3 months after treatment, although in this single patient, the titer was decreased significantly. However, in patients infected with Fasciola who are treated with praziquantel or bithionol, 90% of patients had high antibody levels 3 months after treatment. Hammouda and others reported that 50% of patients had high antibody titers 3 months after treatment with triclabendazole. We consider antibody titer to be a reasonable tool to assess the effect of therapy in fascioliasis; in this study, it was continually decreased, if not to be a reasonable tool to assess the effect of therapy in fascioliasis; in this study, it was continually decreased, if not normalized, after just a few months. IHA showed high positive titer in all patients, in comparison with the control group (mean, 1.188.57 ± 91.23 versus 96 ± 73.12). A significant drop of these values followed the specific therapy, but values returned to normal after 3 months in all patients except the single patient in whom the level decreased significantly but was not normalized. Values of IHA were correlated with the clinical and parasitologic cure. These findings are in agreement with those of Hammouda and others.

The present study showed that the hematologic disturbances consisted of increased total leucocyte count, high eosinophilia, decreased hemoglobin content, and accelerated erythrocyte sedimentation rate. All of these hematologic disturbances returned to normal values within 3 months after treatment.

Eosinophilic count in the present study was 10 to 40%, with a mean of 24.29 ± 3.86% of the total leucocytes. Eosinophilia was present in all patients. This was in agreement with the findings of Ahmed and others and El-Zawahy and others, who reported eosinophilia in all the patients they studied with human fascioliasis. However, Ragab and Farag reported detectable levels of eosinophils in only 87.5% of fascioliasis cases. Eosinophilia plays an important role in the immunity to fascioliasis. Duffus and Frank reported that eosinophils adhered in large numbers to the juvenile flukes and the major basic protein released from eosinophils induced damage and death in juvenile flukes. ALT and AST values were within normal ranges in patients in the present study. Similar findings were reported by Farag and others. However, Wessely and others reported moderately elevated transaminases. Total serum bilirubin in the patients in the present study ranged from 0.6 to 0.9 mg/dL, with a mean of 0.74 ± 0.23 mg/dL. Khsorsani reported slightly elevated bilirubin. Jones and others and Chen and Mott recorded higher levels of bilirubin. Serum enzyme levels were noticed in the present study to be compatible with cholestasis (elevated alkaline phosphatase and gamma glutamyl transpeptidase). Blood urea and serum creatinine values in patients in the fascioliasis group were within normal ranges before and after therapy, indicating that the drug will not harm the kidneys. In conclusion, despite the small number of patients in this pilot study, praziquantel has proven to be an effective drug in the treatment of fascioliasis. It resulted in no side effects, and the patients experienced marked improvement in the clinical and the laboratory results as well as complete parasitologic cure.

Acknowledgments: We thank Dr. Ibrahim El-Saedy for statistical assistance.

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REFERENCES


### Table 2

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<th>Variable</th>
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<th>Pretreatment</th>
<th>End of treatment</th>
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<td>Alkaline phosphatase</td>
<td>7 ± 2.65</td>
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<td>Gamma glutamyl transpeptidase</td>
<td>27.6 ± 4.74</td>
<td>93.0 ± 18.22**</td>
<td>90.14 ± 17.53**</td>
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<td>Alanine transpeptidase</td>
<td>19.8 ± 6.85</td>
<td>25.43 ± 6.48**</td>
<td>24.43 ± 6.25**</td>
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<td>Aspartate transpeptidase</td>
<td>19.9 ± 7.13</td>
<td>21.86 ± 7.25**</td>
<td>20.57 ± 6.94**</td>
<td>21.29 ± 6.27†</td>
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<td>Erythrocyte sedimentation rate</td>
<td>7.8 ± 3.24</td>
<td>41.71 ± 8.45**</td>
<td>34.57 ± 7.44**</td>
<td>30.29 ± 7.55†</td>
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<td>Total leucocyte count</td>
<td>6,208 ± 1,496.25</td>
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<td>11,142 ± 2,371**</td>
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<td>Eosinophilic count (%)</td>
<td>2.9 ± 1.8</td>
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<td>Indirect hemagglutination test</td>
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<td>1,005.57 ± 98.43**</td>
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<td>36 ± 4,819**</td>
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* Statistically significant ($P < 0.05$). ** Highly statistically significant ($P < 0.01$). † Not statistically significant ($P > 0.05$).

**TABLE 2**

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<td>594.3 ± 27.25*</td>
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