THE CURRENT STATUS OF THE CHEMOTHERAPY OF HYDATID DISEASE


Hydatid disease remains one of the few major parasitic diseases of man for which no adequate chemotherapy exists. However, the development of drug screening programs in laboratory animals provides a rapid, efficient, and economical means for testing potentially effective compounds.

Introduction

Since the chemotherapy of hydatid disease was last reviewed (1, 2, 3), the further development of laboratory animal models (4, 5, 6, 7, 8) has made it possible to design large-scale drug screening programs. Previously, testing of potentially useful drugs was carried out in vitro or via costly small-scale trials in humans and domesticated animals.

The difficulties involved in carrying out controlled clinical trials in humans severely compromise this method as a screening technique. In vitro testing is theoretically useful for identifying potentially effective drugs; however, extrapolation of the results to the situation in vivo remains uncertain, due mostly to insufficient basic information about the metabolism and permeability characteristics of hydatid cysts.

The purpose of this article is to point out certain problems that arise in interpreting the results of clinical trials in humans reported to date, and to review the progress of drug screening programs in laboratory animals.

Human Trials

Several attempts to sterilize or cure hydatid cysts through radiation therapy have met with only limited success (1, 9). Furthermore, the size of the cysts and the frequently large numbers involved make it very doubtful that radiation therapy will prove to be of any substantial use.

The theoretical rationale behind “biologic therapy” for hydatid disease and the results of clinical trials using it have recently been comprehensively reviewed (10, 11). As has been pointed out, no sound experimental or clinical evidence has emerged to demonstrate the efficacy of this mode of treatment.

Sporadic attempts to develop effective chemotherapy for hydatid disease over the past 50 years (12, 13, 14, 15) have, with the exceptions discussed below, encountered little success.

In 1951, Cuervo García (16) introduced chemotherapy using iodinized oil of thymol for treatment of hepatic and pulmonary hydatid...
FIGURE 1—The dog-sheep-dog life-cycle of Echinococcus granulosus. E. multilocularis, the other agent of hydatidosis, is commonly maintained by a fox-vole-fox cycle.

disease; his reported “cure” of 12 patients was ascribed to therapy with this compound. A critical review of this work, however, makes it difficult to connect the results observed with the therapy prescribed. The study lacked simultaneously matched controls; patient selection was biased toward those in whom a dramatic host response was probably occurring; diagnosis was often presumptive; and patient follow-up was uniformly short. Furthermore, as there is little reliable information on the natural history of hydatid disease in all of its forms and stages, it is possible to conclude that the results obtained by Cuervo García merely represent the natural course of the disease. The same comments can be made about subsequent clinical reports (17, 21) on the efficacy of iodinized oil of thymol.

For example, the frequency with which secondary hydatidosis develops after spillage of cyst contents during surgery is variable. Among the patients who Panaitesco treated with paludrin and followed for 2 years or more, 18 per cent remained infected. Schiller (23), however, reported an incidence of only 30 per cent of secondary hydatidosis in patients who received no therapy after spillage of cyst contents during surgery and who were followed for 5 years or more. Statistically, these results do not differ significantly ($p > 0.40$).

Trials in Laboratory Animals

Drug screening programs in laboratory animals have been easier to design and interpret, in that controls are easily included, objective criteria exist for judging drug efficacy at necropsy, and the natural history of infection in laboratory animal models has been thoroughly studied (7, 8). To date, the results of trials testing some 36 different compounds have been reported.

The results of those trials in which drug effectiveness was reported are summarized in Table 1. In addition, Lukashenko (27), in a review of his work, reports that various acridine derivatives (e.g., 2 methoxy-6-chloro-9-aminoacridine and 2 methoxy-6-chloro-9-methylaminoacridine) were effective, both $\textit{in vitro}$ and $\textit{in vivo}$; but details of the therapy provided and criteria for evaluating the effect of these drugs $\textit{in vivo}$ are not given.

It should also be noted that conflicting results have been reported by other investigators with respect to oil of thymol, cyclophosphamide, quinacrine and paludrin (Table 2). Results with the remaining compounds (rivanol, lucanthone, and dactinomycin) have yet to be confirmed. If these latter results are confirmed, dose response curves should first be established; trials should then be run in a variety of laboratory and domestic animals having both primary and secondary hydatidosis infections with certainty that Panaitesco’s patients were in fact cured.
**TABLE 1—Drugs reported to be active against hydatid disease in experimental animals.**

<table>
<thead>
<tr>
<th>Echinococcus species</th>
<th>Drug and reference</th>
<th>Dosage</th>
<th>No. of animals</th>
<th>Species</th>
<th>Infection age&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sacrifice&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. granulosus</strong></td>
<td>Thymol (16)</td>
<td>30 mg/kg intramuscularly, every other day for 3 months</td>
<td>1</td>
<td>Sheep</td>
<td>Months</td>
<td>–</td>
<td>Sheep: disappearance of cyst; Rabbits: cyst was converted into a small hard nodule (no controls).</td>
</tr>
<tr>
<td><strong>E. granulosus</strong></td>
<td>Quinacrine (26)</td>
<td>1 cc of a 1:1000 solution; intraperitoneally, once</td>
<td>20</td>
<td>Mice</td>
<td>1/2 hour</td>
<td>6 months</td>
<td>There were significantly fewer cysts in treated animals, but the same percentage of treated and control animals were infected.</td>
</tr>
<tr>
<td><strong>E. granulosus</strong></td>
<td>Rivanol (26)</td>
<td>1 cc of a 1:1000 solution; intraperitoneally, once</td>
<td>20</td>
<td>Mice</td>
<td>1/2 hour</td>
<td>6 months</td>
<td>In comparison to the controls, there were significantly fewer cysts among the treated mice, as well as significantly fewer infected individuals.</td>
</tr>
<tr>
<td><strong>E. multilocularis</strong></td>
<td>Lucanthone (24)</td>
<td>100 mg/kg; subcutaneously twice a week for 7 weeks</td>
<td>50</td>
<td>Mice</td>
<td>1 week</td>
<td>1 week</td>
<td>Cyst weight in treated mice was only 40 per cent of average cyst weight in the controls.</td>
</tr>
<tr>
<td><strong>E. multilocularis</strong></td>
<td>Cyclophosphamide (24)</td>
<td>200 mg/kg; subcutaneously, once</td>
<td>91</td>
<td>Mice</td>
<td>1 week</td>
<td>6-12 weeks</td>
<td>Cyst weight in treated mice was only 20 per cent of average cyst weight in the controls.</td>
</tr>
<tr>
<td><strong>E. multilocularis</strong></td>
<td>Dactinomycin (25)</td>
<td>0.35 mg/kg; intravenously, once a week for 3 weeks</td>
<td>40</td>
<td>Mice</td>
<td>1 week</td>
<td>1 week</td>
<td>Cyst weight in treated mice was only 60 per cent of average cyst weight in the controls.</td>
</tr>
</tbody>
</table>

<sup>a</sup>Infection age when therapy started.

<sup>b</sup>Time elapsed between end of therapy and sacrifice.
TABLE 2—Negative results reported in mice, conflicting with results shown in Table 1. (Negative results indicate that there is no statistically significant difference in the number of infected animals or in the size or weight of cysts in treated animals with respect to the control groups.)

<table>
<thead>
<tr>
<th>Echinococcus spp.</th>
<th>Drug and reference</th>
<th>Dosage</th>
<th>No. of mice</th>
<th>Infection agea</th>
<th>Sacrificeb</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. granulosus</td>
<td>Thymol (3, 28)</td>
<td>50 mg/kg in 1% iodinized oil, 12 intramuscular injections, one every other day</td>
<td>20</td>
<td>1/2 hour</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>64 mg/kg in 1% iodinized oil; intramuscularly four times a week for 2 weeks</td>
<td>6</td>
<td>4 months</td>
<td>2 months</td>
</tr>
<tr>
<td>E. granulosus</td>
<td>Paludrin (28)</td>
<td>5 mg/kg; orally five times a week for 6 weeks</td>
<td>10</td>
<td>2 days</td>
<td>3 months</td>
</tr>
<tr>
<td>E. granulosus</td>
<td>Cyclophosphamide (26)</td>
<td>200 mg/kg; one intraperitoneal injection per day for 3 days</td>
<td>20</td>
<td>1/2 hour</td>
<td>6 months</td>
</tr>
<tr>
<td>E. granulosus</td>
<td>Lucanthone (34)</td>
<td>0.3 mg; subcutaneously twice a week for 2 months</td>
<td>8</td>
<td>1 month</td>
<td>2 months</td>
</tr>
<tr>
<td>E. multilocularis</td>
<td>Quinacrine (24)</td>
<td>100 mg/kg; subcutaneously twice a week for 6 weeks</td>
<td>25</td>
<td>1 week</td>
<td>1 week</td>
</tr>
</tbody>
</table>

aInfection age when therapy started.

bTime elapsed between end of therapy and sacrifice.

Conclusions

At the present time, surgery remains the only remedy for patients with hydatid disease. However, many patients are inoperable due to the extensiveness of their disease, while others are ineligible for surgery because of medical contraindications. Furthermore, surgical removal of hydatid cysts is a costly and time-consuming procedure, and even in the most experienced hands it is a hazardous undertaking. At the same time, improved diagnostic techniques, and increased awareness of the disease as a result of epidemiologic surveys and national control campaigns, are bringing more and more patients to medical attention. Clearly, if effective chemotherapy were developed it would find immediate application.

SUMMARY

If an effective chemotherapeutic treatment for hydatid disease were discovered, there are good reasons to believe it would find immediate application. Among other things, there is currently no sure remedy for hydatidosis except surgery, diagnostic techniques have re-
recently improved, and there is increasing awareness of the disease as a result of epidemiologic surveys and national control campaigns. Initial efforts to test the effects of drugs on the disease were limited to small-scale trials in humans and domesticated animals. However, recent work with laboratory animal models has made it possible to conduct large-scale drug screening programs. This article reviews the results obtained from trials testing over 30 different compounds.

REFERENCES

the author's summary supplied by Dr. Teodor Wikerhauser, Professor of Parasitology, Department of Parasitology and Parasitic Diseases, Veterinary Faculty, University of Zagreb, Yugoslavia.

(27) Lukashenko, N. P., F. P. Kovalenko, and M. O. Kolosova. "O vliianii nekotorykh khimi-
cheskikh soedinenii na zhiznesposobnost’i
dykhanie lichinochnykh skoleksov
Alveococcus multilocularis" (Effects of
Several Chemical Compounds on Viability and
Respiration of Larval Scolecies of Echino-
coccus multilocularis). Acta Vet Acad Sci

"Quimioterapia experimental en animales de
laboratorio infectados con Echinococcus
granulosus." Paper presented to the I National
Congress of Parasitology, Buenos Aires, Argent-
tina, 26 November-2 December 1972.

(29) Dévé, F., and I. Payenneville. "Echinococious et
arsénio-benzenes." C R Soc Biol 87: 129-130,
1922.

(30) Dévé, F. "Kyste hydatique et kamala." C R Soc
Biol 93: 409-410, 1925.

(31) Magud, I. "On the Influence of the Origin of the
Parasitic Material and on the Effect of a
Corticosteroid Treatment of the Mouse upon
the Development of Secondary Echino-
coccosis in That Host." Acta Parasit Iugol 2:

Alveolar Hydatid Disease: Treatment Failure

(33) Dévé, F., and I. Payenneville. "Greffe hydatique
et neosalvarsan." C R Soc Biol 76: 648-649,
1914.

(34) De Rosa, F., and S. Giunta. "Primi dati sulla
chimioterapia della idatidosi sperimentale del
topo studiata con metodi quantitativi." Paper
presented at the VII National Conference of the
Italian Society of Parasitology held at
Bologna, Italy, in May 1972.

BUBONIC PLAGUE IN THE UNITED STATES OF AMERICA

Human and animal plague has been controlled in the United States to a point
where it is now primarily a rural or wilderness area problem. Only rarely does it
pose the sort of threat to large urban centers that it did in the early part of this
century. Nevertheless, a record 13 cases of human bubonic plague associated
with rural exposure were reported in the United States during 1970; two more
were detected in 1971, another was found in 1972, and two more occurred in
June and July 1973.

Plague activity has remained high among wild rodent populations in those
states where human cases have often occurred, notably Arizona, California,
Colorado, and New Mexico. During the first half of 1973 epizootic plague was
reported among wild rodents from three widely separated California counties:
Siskiyou, Tulare, and Riverside. An epizootic among wood rats at Siskiyou
County’s Lava Beds National Monument, detected in March, forced temporary
closure of visitor facilities until vector control measures could be implemented
by state officials. In New Mexico, an epizootic among prairie dogs near
Shiprock, San Juan County, necessitated vector control operations over a
5,000-acre tract in order to protect the resident Navajo population. This latter
situation was directly related to epizootics among prairie dogs of southwestern

Because it is sporadic and uncommon, human plague is easily overlooked or
mistakenly diagnosed. Since it is readily treatable with appropriate antibiotics,
recognizing the current status of wild animal plague and the consequent
potential for human exposure should provide a basis for suspecting and
appropriately handling sporadic cases. [Morbidity and Mortality, weekly report
of the U.S. Center for Disease Control, Vol. 22, Nos. 25, 30, and 32, 1973.]