Chemotherapy of Gnathostomiasis

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OBJECTIVE: To continue the study on chemotherapy of gnathostomiasis by determining the effect of oral or parenteral administration of drugs on *Gnathostoma spinigerum* larvae. The drugs selected for the screening tests have been used effectively in the treatment of certain helminthic diseases but have yet to be used in treating gnathostome infection.

METHODS: Experimental white mice and/or white rats were orally infected with advanced third stage larvae of *G. spinigerum*. Mice were infected with 5 larvae, and rats with 20. The drug or combination of drugs tested was administered orally or by intramuscular injection, and the daily dose was calculated using the body weight of the test animal. In all instances the control animals were given distilled water. The drugs tested were Hetrazan (Diethylcarbamazine citrate) combined with Bithionol (Bitin); Fouadin (Pentasodium antimony 1, 1, 1—biscatechol—3,5—disulfonate); Flagyl (1—B—hydroxyethyl—1, 2—methyl—5—nitroimidazole); Dehydroemetine (racemic 2—dehydroemetine dihydrochloride); a combination of Dehydroemetine and Flagyl; and Metrifonate (0, 0—dimethylhydroxy—2, 2, 2—trichlorethyl—phosphonate). Following infection and the chemotherapeutic regimen, the test animals were autopsied, the parasites counted, and the results recorded.

RESULTS: 1. *Hetrazan combined with Bitin (oral administration)*: Infected mice were treated with 15 daily doses of Hetrazan (10mg/kg body weight) combined with Bitin (50 mg/kg body weight). The results of this experiment are shown in Table 1. No reduction in the number of larvae in treated mice was observed, and this combination of drugs is judged ineffective.

2. *Fouadin (intramuscular injection)*: The compound contains 13.5 per cent trivalent antimony in pyrogen—free redistilled water. Both mice and rats were used and a daily dose of drug administered at levels of 3.15, 6.3, 100, and 200 mg/kg body weight. The drug has been used in treating infection with *Schistoma hematobium*. The results of this experiment are shown in Table 2. No reduction in the number of larvae in treated mice was observed and this drug is judged ineffective.

3. *Flagyl (oral administration)*: This drug has been used with satisfactory results in treating intestinal and hepatic amebiasis, trichomoniasis and some other protozoal infections in man. Recently this drug has been used with good results in treating dracunculiasis in man.[1, 2] In this experiment, a daily dose of flagyl was administered to gnathostome—infected mice at levels of 200, 400, 800, and 1600 mg/kg body weight. The results are shown in Table 3. No reduction in the number of larvae in treated mice was observed and this drug is judged ineffective.

4. *Dehydroemetine combined with Flagyl (oral administration)*: This compound is chemically related to natural emetine and obtained by total synthesis. The drug has been used with good results in intestinal amebiasis (all forms), hepatic amebiasis, schistosomiasis (*S. haematobium* or *S. mansoni* or mixed infection) and distomiasis due to *Fasciola hepatica*. In this study, gnathostome—infected mice were each treated with 15 daily doses of dehydroemetine administered at levels of 10 or 15 mg/kg body weight. The results are shown in Table 4. There was no reduction in the number of larvae in treated mice and this drug is judged ineffective.

5. *Dehydroemetine combined with Flagyl (oral administration)*: Infected mice were treated with 20 daily doses of dehydroemetine (10 mg/kg body weight) combined with Flagyl (200 mg/kg body weight). The results of this experiment are shown in Table 5. No reduction in the number of larvae in treated mice was observed and this drug is judged ineffective.

6. *Metrifonate (oral administration)*: It has been reported that metrifonate was an effective drug in the treatment of *Schistosoma haematobium* infection by oral administration.[3] This drug is now being studied to determine its effectiveness at 2-week intervals for 5 doses in *G. spinigerum* infected experimental mice. The doses are 20, 40, 80, and 120 mg/kg body weight. Results at this time are incomplete.

REFERENCES:

1. Davis, A., and Bailey, D.R.: Metrifonate in urinary schistosomiasis. Bull. Wld. Hlth. Org. *41*: 209–224, 1969.
2. Antani, J.A., Srinivas, H.V., Krishnamurthy, K.R., and Jahagirdar, B.R.: Metronidazole in dracunculiasis: A preliminary report. Am. J. Trop. Med. Hyg. *19*: 821–822, 1970.
3. Antani, J.A., Srinivas, H.V., Krishnamurthy, K.R., and Borgaonkar, A.N.: Metronidazole in dracunculiasis: Report of further trials. Am. J. Trop. Med. Hyg. *21*: 178–181, 1972.

Table 1.

Hetrazan/Bitin Chemotherapy on Mice Infected with *Gnathostoma spinigerum*

Daily dose of Hetrazan (10 mg/kg body weight) combined with Bitin (50 mg/kg body weight) /mouse [1, 2]	No. mice treated	Autopsy findings			Remarks
		No. mice positive with advanced third stage larvae	No. advanced third stage larvae found (%)	Organs infected	
15	32	31 (97)	102 (64)	liver and/or body muscles	Autopsies 2—47 days after the last dose
Control—15 doses	9	9 (100)	29 (64)	" "	" "

[1] Drug dissolved in distilled water.

[2] Control was distilled water.

Table 2.
Fouadin Chemotherapy on Rats or Mice Infected with *Gnathostoma spinigerum*

Daily dose of Fouadin/rat or mouse [1, 2]	No. rats or mice treated	Autopsy findings			Remarks
		No. rats or mice positive with advanced third stage larvae (%)	No. advanced third stage larvae found (%)	Organs infected	
(3.15 mg/kg body weight) 15	12 rats	12 rats (100)	85 (35)	body muscles	Autopsies 17 days after the last dose
Control—15 doses	3 rats	3 rats (100)	20 (33)	" "	" "
(6.3 mg/kg body weight) 14	33 mice	33 mice (100)	112 (68)	liver and/or body muscles	Autopsies 14—16 days after the last dose
Control—14 doses	15 mice	15 mice (100)	45 (60)	" "	" "
(100 mg/kg body weight) 14	20 mice	20 mice (100)	73 (73)	" "	Autopsies 10—18 days after the last dose
20	20 mice	20 mice (100)	70 (70)	" "	Autopsies 3—26 days after the last dose
Control—20 doses	10 mice	10 mice (100)	39 (78)	" "	Autopsies 16 days after the last dose
(200 mg/kg body weight) 14	20 mice	20 mice (100)	69 (69)	" "	Autopsies 17—19 days after the last dose
Control—14 doses	10 mice	10 mice (100)	35 (70)	" "	" "
20	20 mice	20 mice (100)	70 (70)	" "	Autopsies 10—18 days after the last dose
Control—20 doses	10 mice	10 mice (100)	39 (78)	" "	Autopsies 2—20 days after the last dose

[1] Drug was dissolved in distilled water.
[2] Control was distilled water.

Table 3.

Flagyl Chemotherapy on Mice Infected with *Gnathostoma spinigerum*

Daily dose of Flagyl (200—1600 mg/kg body weight) mouse [1, 2]	No. mice treated	Autopsy findings			Remarks
		No. mice positive with advanced third stage larvae (%)	No. advanced third stage larvae found (%)	Organs infected	
(200 mg/kg body weight) 5	20	20 (100)	72 (72)	liver and/or body muscles	Autopsies 16—25 days after the last dose
Control—5 doses	10	10 (100)	35 (70)	,, ,,	Autopsies 25 days after the last dose
(400 mg/kg body weight) 5	17	17 (100)	54 (64)	,, ,,	Autopsies 18 days after the last dose
Control—5 doses	10	10 (100)	37 (74)	,, ,,	Autopsies 16—17 days after the last dose
(800 mg/kg body weight) 15	19	19 (100)	50 (53)	,, ,,	Autopsies 1—18 days after the last dose
Control—15 doses	10	10 (100)	29 (58)	,, ,,	Autopsies 18 days after the last dose
(1600 mg/kg body weight) 15	16	16 (100)	51 (64)	,, ,,	Autopsies 2—20 days after the last dose
Control—15 doses	10	10 (100)	31 (62)	,, ,,	Autopsies 21 days after the last dose

[1] Drug was dissolved in distilled water.

[2] Control was distilled water.

Table 4.

Dehydroemetine Chemotherapy on Mice Infected with *Gnathostoma spinigerum*

Daily dose of Dehydroemetine/ mouse [1,2]	No. mice treated	Autopsy findings			Remarks
		No. mice positive with advanced third stage larvae (%)	No. advanced third stage larvae found (%)	Organs infected	
(10 mg/kg body weight)					
15	19	19 (100)	57 (60)	liver and/or body muscles	Autopsies 3—19 days after the last dose
Control — 15 doses	10	10 (100)	30 (60)	" "	Autopsies 23 days after the last dose
(15 mg/kg body weight)					
15	11	11 (100)	44 (80)	" "	Autopsies 2—19 days after the last dose
Control — 15 doses	10	10 (100)	32(64)	" "	Autopsies 2—23 days after the last dose

[1] Drug dissolved in distilled water.
[2] Control was distilled water.

Table 5.

Dehydroemetine/Flagyl Chemotherapy on Mice Infected with *Gnathostoma spinigerum*

Daily dose of Dehydroemetine (10 mg/kg body weight) combined with Flagyl (200 mg/kg body weight)/ mouse [1, 2]	No. mice treated	Autopsy findings			Remarks
		No. mice positive with advanced third stage larvae (%)	No. advanced third stage larvae found (%)	Organs infected	
20	18	18 (100)	62 (69)	liver and/or body muscles	Autopsies 2—36 days after the last dose
Control—20 doses	10	10 (100)	31 (62)	" "	Autopsies 36 days after the last dose

[1] Drug dissolved in distilled water.

[2] Control was distilled water.