

## Chemotherapy of Gnathostomiasis

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**OBJECTIVE :** To find drugs with chemotherapeutic activity against *Gnathostoma spinigerum*.

**BACKGROUND :** These studies are a continuation of work reported in previous years. Drugs with activity against other parasitic diseases are being evaluated for possible chemotherapeutic activity against *Gnathostoma spinigerum* in experimentally infected mice.

**METHODS :** ICR mice were infected by oral administration of 5 advanced third-stage larvae of *G. spinigerum*. After infection the test drug or combination of drugs, dissolved in distilled water, was administered orally in a predetermined regimen. Infected control mice were given distilled water orally. After completion of the treatment regimen, the mice were sacrificed at intervals and necropsied, parasites counted in the liver and/or body muscles, and results recorded.

The drugs tested were: Metrifonate (0, 0-dimethylhydroxy-2, 2, 2-trichlorethyl phosphonate); Flagyl or Metronidazole (1-B-hydroxyethyl-2-methyl-5-nitromidazole); Astiban (sodium antimony dimercaptosuccinate); Ambilhar or Niridazole (1-(5-nitro-2-thiazolyl)-2-imidazolidinone); and a combination of Astiban and Ambilhar.

### RESULTS :

**Metrifonate :** This drug was administered in 5 oral doses given at two week intervals. The results are shown in Table 1. Doses of 20, 40, 80, and 120 mg/kg were ineffective in reducing the number of larvae found in treated mice.

**Flagyl :** We previously administered 5 daily oral doses of 200-1600 mg/kg of Flagyl to gnathostome infected mice without effect. This year we administered a 5 day oral course of 200 mg/kg/day, but split the daily dose into 3 equal portions similar to the way in which this drug has been used with success in man for the treatment of dracunculiasis and amoebic liver abscess. The results are shown in Table 2. No reduction in the number of gnathostome larvae in treated mice was observed.

**Astiban :** Gnathostome infected mice were treated with 5 daily oral doses of 640 mg/kg, or with a single oral dose of 1920 mg/kg. The results are shown in Table 3. The drug is judged ineffective in these regimens.

**Ambilhar :** Daily oral doses of 25-100 mg/kg for 5 days have previously been judged ineffective in gnathostome infected mice. This year mice were treated with 5 daily oral doses of 640 mg/kg, or with a single oral dose of 1920 mg/kg. Results are shown in Table 4. At 1920 mg/kg, 8 of 15 mice developed diarrhea with streaks of blood in the feces as a result of drug toxicity, and one died. No reduction in the number of larvae was observed in the treated mice at either dose.

**Astiban and Ambilhar in Combination :** Infected mice were given a single oral dose of 1920 mg/kg of astiban, and beginning on the following day, ambilhar was given orally at 640 mg/kg every other day for 4 doses. Results are shown in Table 5. A lower percentage (44%) of advanced third-stage larvae was found in treated mice than in controls (58%), although no mice were cleared of larvae entirely. The possibility that this represents a chemotherapeutic effect is being investigated further.

**SUMMARY :** Oral administration of metrifonate, flagyl, astiban or ambilhar was ineffective in the chemotherapy of *Gnathostoma spinigerum* in experimentally infected mice. Combined therapy with astiban and ambilhar had a modest chemotherapeutic effect which is being investigated further.

TABLE 1 Treatment of *Gnathostoma spinigerum* Infected Mice with Metrifonate\*

Drug dose (mg/kg/day)	Number of mice treated	Mice positive with larvae Number (%)	Third-stage Larvae found Number (%)	Time of Necropsy** (days)
20	16	16 (100)	43 (54)	12-20
Control	10	10 (100)	26 (52)	21
40	15	15 (100)	48 (64)	5-20
Control	8	8 (100)	27 (68)	7-20
80	16	16 (100)	48 (60)	6-20
Control	10	10 (100)	33 (66)	4-20
120	19	19 (100)	51 (54)	4-20
Control	10	10 (100)	28 (56)	20

\* Five doses at two week intervals.

\*\* Days after last dose of drug.

Table 2 Treatment of *Gnathostoma spinigerum* Infected Mice with Flagyl

Drug dose (mg/kg/day)	Number of Mice treated	Mice positive with larvae Number (%)	Third-stage Larvae found Number (%)
200*	17	16 (94)	49 (58)
Control	7	7 (100)	18 (51)

\* Three doses per day for 5 days.

Table 3. Treatment of *Gnathostoma spinigerum* Infected Mice with Astiban

Drug dose (mg/kg/day)	Number of Mice Treated	Mice positive with larvae Number (%)	Third-stage Larvae found Number (%)	Time of Necropsy (Days)***
640*	15	15 (100)	38 (51)	18
Control	10	10 (100)	29 (58)	19
1920**	15	15 (100)	40 (53)	7-16
Control	10	10 (100)	28 (56)	7-15

Table 4. Treatment of *Gnathostoma spinigerum* Infected Mice with Ambilhar

Drug dose (mg/kg/day)	Number of Mice Treated	Mice positive with larvae Number (%)	Third-stage Larvae found Number (%)	Time of Necropsy (Days)***
640*	13	13 (100)	32 (49)	1-18
Control	10	10 (100)	28 (56)	19
1920**	15	14 (93)	43 (57)	1-15****
Control	10	10 (100)	30 (60)	7-15

\* For 5 days

\*\* For 1 day

\*\*\* Days after administration of last drug dose.

\*\*\*\* 8 mice developed bloody diarrhea after drug was administered indicating toxicity.

Table 5. Treatment of *Gnathostoma spinigerum* Infected Mice with an Astiban—Ambilhar Combination

Group	Number of Mice Treated	Mice positive with Larvae		Third-stage Larvae found		Time of Necropsy** (Days)
		Number	(%)	Number	(%)	
Treated	15	15	(100)	33	(100)	13
Control	10	10	(100)	29	(58)	14

\* One dose Astiban (1920 mg/kg body weight) followed on the next day by 4 doses of Ambilhar (640 mg/kg body weight) administered every other day.

\*\* Days after administration of last drug dose.