

Research Note

**Studies on Chemotherapy of Parasitic Helminths (XXVI).
Comparative *In Vitro* Effects of Various Anthelmintics on the
Motility of *Angiostrongylus costaricensis* and *A. cantonensis***

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Adult *Angiostrongylus costaricensis* is the etiologic agent of human abdominal angiostrongylosis (Morera, 1971). This species was first described from the mesenteric arteries of the ileocecal region of a child in Costa Rica (Morera and Cespedes, 1971). Since then many human cases have been reported throughout the Western Hemisphere, from Mexico to Brazil (Zambrano, 1973; Zilliotto *et al.*, 1975; Iabuki and Montenegro, 1979; Loria-Cortes and Lobo-Sanahuja, 1980). Diethylcarbamazine and/or thiabendazole were given to these patients (Loria-Cortes and Lobo-Sanahuja, 1980), though there have been few studies on the efficacy of these drugs *in vivo* as well as *in vitro*. In the present study we examined the *in vitro* effects of various anthelmintics including diethylcarbamazine and thiabendazole on the motility of adult female worms of *A. costaricensis*. Parallel tests with adult female *A. cantonensis* were run.

A. costaricensis (Costa Rican strain, Costa Rica University) and *A. cantonensis* (Hawaiian

strain) were obtained from mice (ddY strain) and rats (Wistar strain), respectively, experimentally infected in our laboratory. The isotonic transducer method previously described (Terada *et al.*, 1982, 1984) was used.

The comparative effects of 19 anthelmintics on the motility of *A. costaricensis* and *A. cantonensis* are summarized in Table 1. Except a few drugs such as piperazine, ivermectin Bia and ivermectin, almost all the anthelmintics showed basically similar effects on the motility of both nematodes, that is, inhibitory and/or stimulatory effects, or little effect were observed. Though 7 anthelmintics such as piperazine, ivermectin Bia, ivermectin, thiabendazole, praziquantel, niridazole and CGP-4540 (4-isothiocyano-4'-nitro-diphenylamine) had little effect on the motility of *A. costaricensis* at higher concentrations such as 10^{-4} M, others showed a particular type of the mode of action at certain concentrations. For example, nicotine, pyrantel, levamisole and mebendazole had stimulatory effects, and hexylresorcinol and Stibnal (sodium antimonyl tartrate) had inhibitory effects. Both inhibitory and stimulatory effects were seen at different concentrations of diethylcarbamazine, bithionol and niclosamide, and santonin in a given concentration caused an inhibitory effect followed by a stimulatory one. In addition to these, some drugs including pyruvium and oxamniquine showed two

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Table 1 Mode of action of various anthelmintics on the motility of *Angiostrongylus costaricensis* and *A. cantonensis*

<i>A. costaricensis</i>							<i>A. cantonensis</i>						
10^{-9}	10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4}		10^{-10}	10^{-9}	10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4}
3×10^{-9}	3×10^{-8}	3×10^{-7}	3×10^{-6}	3×10^{-5}	3×10^{-4}	Anthelmintic (M)	3×10^{-10}	3×10^{-9}	3×10^{-8}	3×10^{-7}	3×10^{-6}	3×10^{-5}	3×10^{-4}
						Piperazine							▼ ■
						Avermectin Bia [†]	■	■					
						Ivermectin ^{††}		■	■				
	▼	▼	▼△	▼△	▼△	Santonin			▼	▼	▼△	▼△	▼△
		▼	▼	▼△	△	Diethylcarbamazine					▼	▼	▼△
		△	○			Nicotine				△	○		
△	△	○				Pyrantel		△	△	○			
△	△	○		△		Levamisole	△	△	○				
			△	○		Pyruvolum					△	△	
				△	○	Mebendazole						△	△
						Thiabendazole							
				▼	■	Hexylresorcinol					▼	▼	■
		△	△	■		Bithionol				△	○		■
			○	■		Niclosamide			△	○	■		
				▼	○	Oxamtuine							△
				△		Praziquantel							△
						Niridazole							
				▼	■	Stibnal						■	
						CGP-4540							

Results from 4 to 7 experiments on each anthelmintic against each nematode.

Little effect: —, Inhibitory effect: ▼, ▼; slight inhibition, ■; complete paralysis, Stimulatory effect: △, △; slight stimulation, ○; complete spastic paralysis.

† and ††: Concentrations are shown as 3.6×10^{-n} M and 2.5×10^{-n} g/ml, respectively.

types of the mode of action and about 50% of worm preparations were either inhibited or stimulated by each of these drugs.

Comparing *A. costaricensis* with *A. cantonensis* in their sensitivity to drugs, the most remarkable difference was observed in the effects of piperazine, avermectin Bia and ivermectin. These drugs are known to stimulate the inhibitory gabergic mechanism in nematodes like *Ascaris suum* (Del Castillo and Morales, 1969; Kass *et al.*, 1980, 1982) and *A. cantonensis* (Terada *et al.*, 1982, 1984). In Tyrode's solution in the present study the visual motility of *A. costaricensis* was remarkably active, whereas *A. cantonensis* moved slightly. Therefore, it may be probable that *A. costaricensis* has a little influence by the gabergic mechanism, and that drugs acting on this mechanism have little effect on the motility of the nematode. Though these two nematodes belong to the same genus and have closely related morphological properties, they have different life cycles

and habitats. Hence, it seems interesting to study differences in their sensitivity to drugs in more detail.

From the viewpoint of chemical structures of anthelmintics examined, phenolic compounds (hexylresorcinol, bithionol and niclosamide) were all effective on the motility of *A. costaricensis*, but other derivatives having piperazine (diethylcarbamazine and piperazine), lactone (santonin, avermectin Bia and ivermectin) and benzimidazole (mebendazole and thiabendazole) were not always effective.

Upper 12 anthelmintics in Table 1 have been used as anti-nemathelminth drugs and lower 7 as anti-plathelminth ones. Out of 12 anti-nemathelminthics 5 or 6 showed some effects on both of the nematodes at the lower concentrations of 10^{-7} M or less. On the other hand, only 1 out of 7 anti-plathelminthics was effective at such lower concentrations. It thus seems more reasonable from the present *in vitro* study as well to examine anthelmintic effects

of anti-nemathelminth drugs against abdominal angiostrongylosis. As to drugs used in human cases (Loria-Cortes and Lobo-Sanahuja, 1980), thiabendazole had little effect *in vitro* but diethylcarbamazine had some effects on the motility of *A. costaricensis* at the concentrations of 10^{-7} M and higher. The effects were, however, rather slighter and reversed by washing with Tyrode's solution. From the present *in vitro* efficacy of drugs together with other findings on absorption and fate of drugs, it is suggested that there may be more promising anthelmintics including levamisole for the clinical treatment of abdominal angiostrongylosis. We are investigating further the *in vivo* effects of some anthelmintics on *A. costaricensis* in animals.

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短 報

寄生蠕虫症の化学療法に関する研究 (XXVI).

コスタリカ住血線虫および広東住血線虫の自動運動に及ぼす諸種駆虫薬の *in vitro* 作用の比較について

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コスタリカ住血線虫および広東住血線虫の自動運動に対する19種駆虫薬の *in vitro* 作用をアイソトニック・トランスデューサー法により、比較検討した。

Piperazine, avermectin B_{1a} および ivermectin など少数の駆虫薬が、コスタリカ住血線虫に対して

作用を示さなかった点で、両線虫間に差がみられた。しかし、その他の駆虫薬に関しては、基本的には両虫種間に差は認められず、用いられた濃度において、それぞれの駆虫薬に特異的な作用様式を示した。