Studies on chemotherapy of parasitic helminths (V). Effects of niclosamide on the motility of various parasitic helminths

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Summary. Niclosamide, a well-known antitapeworm drug, caused spastic and/or paralytic actions on the motility of various preparations including parasitic cestodes, trematodes, nematodes, and host isolated tissues.

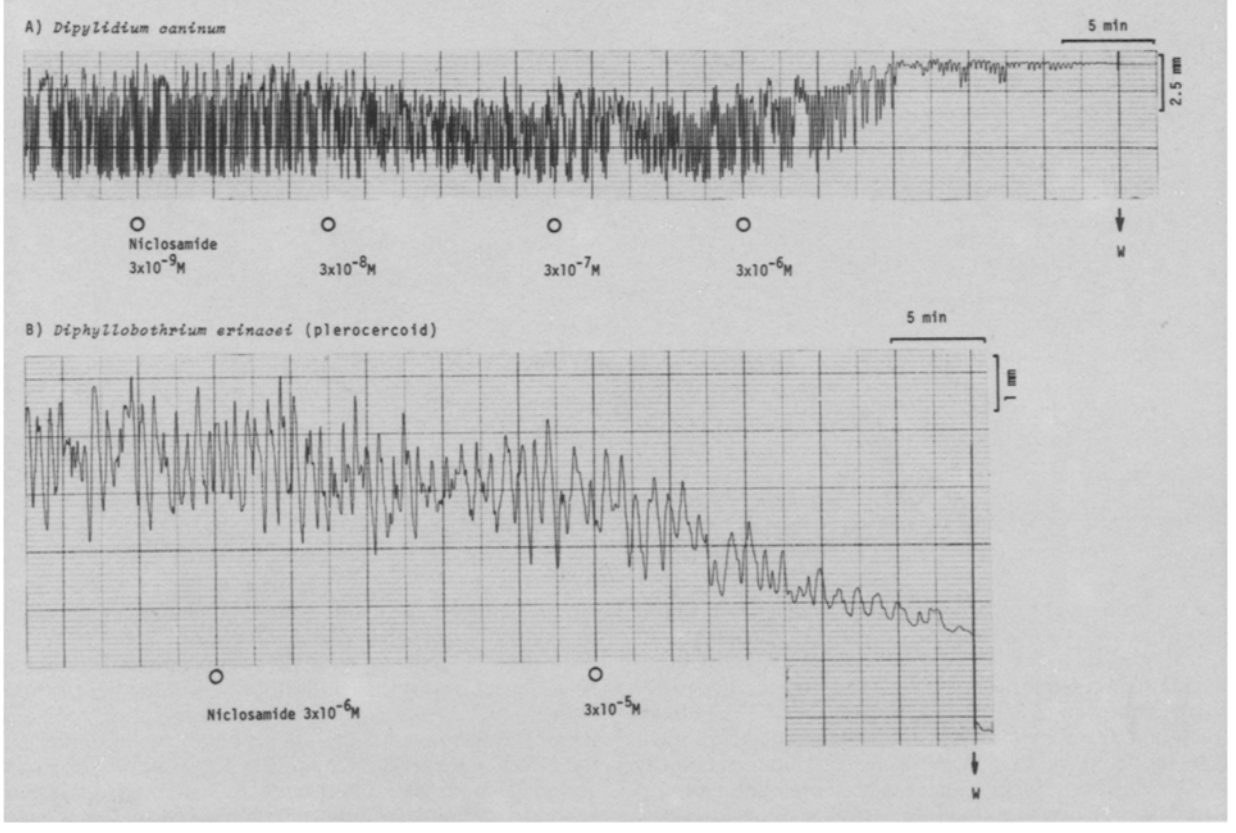
Niclosamide is a well-known antitapeworm drug and it has replaced other drugs for the treatment of most tapeworm (cestode) infections[1]. Since Gönnert et al.[2,3] reported that niclosamide was very active against *Hymenolepis diminuta* in their in vitro screening test for the development of antitapeworm drugs, both in vitro and in vivo studies on this drug seem to have been carried out exclusively on tapeworms.

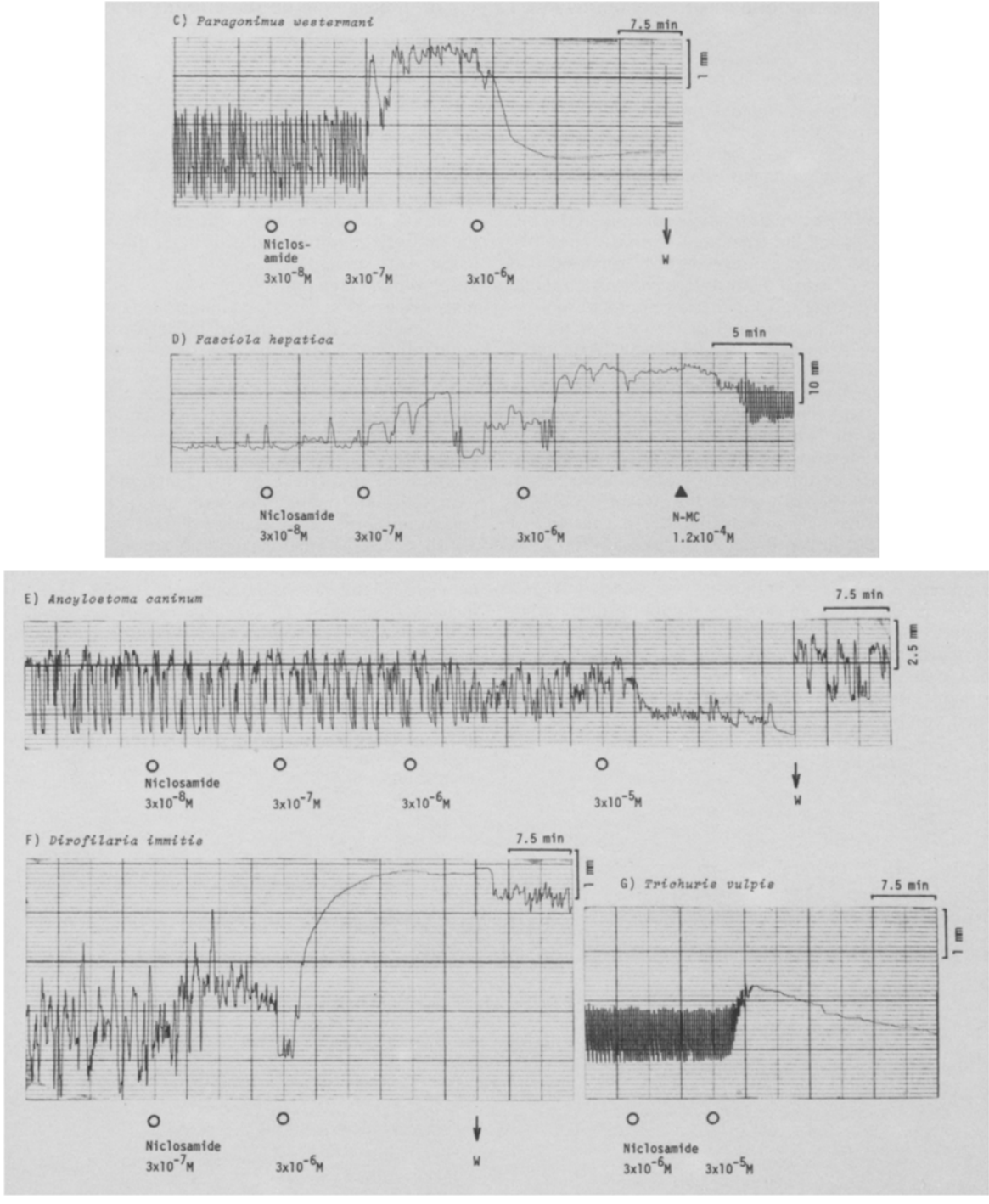
In a previous report[4], we describe the development of isotonic transducer and visual observation methods to study effects of drugs on the faint motility of smaller parasites in vitro. Using these methods, we have selected experimental model worms which permit us to study anthelmintic drugs systematically and rationally. From the practical point of view, considering such factors as availability, the easiness of experiments and the susceptibility to drugs, and also from considerations of phylogenic and pharmacological differences among 3 groups of helminths, we selected *Angiostrongylus cantonensis* as an excellent model for nematodes, *Dipylidium caninum* as an example of a cestode and *Fasciola hepatica* and *Schistosoma japonicum* as trematode[5]. Comparative systematic studies have been carried out in vitro using many preparations including these 4 essential parasites and smooth and skeletal muscles isolated from the host[6-9].

In the present study, the in vitro effects of niclosamide on the motility of various parasitic helminths and host isolated tissues were studied.

Materials and methods. Worms were obtained from the animals sacrificed at the Hamamatsu slaughterhouse or from those experimentally infected in our laboratory. The isotonic transducer and visual observation methods previously described[4,5,8] were used.

Results and discussion. There have been numerous reports regarding the in vivo effects of niclosamide against various cestodes in clinical[1,2,11,12] and animal[13-16] experiments. There have, however, been few reports regarding the in vitro and in vivo effects of this compound against parasitic trematodes and nematodes, with the exception of *Enterobius vermicularis*[17]. In our in vitro experiments, niclosamide did show spastic and/or paralytic actions against all preparations used including parasitic cestodes, trematodes, nematodes, and host isolated tissues (table). Many worms such as *D. caninum, Diplogonoporus grandis, Paragonimus westermani, Metagonimus yokogawai, F. hepatica,* and also host isolated tissues such as the frog rectus and the mouse ileum were affected by niclosamide at concentrations of 3×10^{-8} M or more. *A. cantonensis* was most susceptible to this drug, and was affected at concentrations of 3×10^{-9} M or more. On the other hand, some worms such as *Diphyllo-*





Effects of niclosamide on the motility of various parasitic helminths. Records show the motility of cestode: *Dipylidium caninum* (A) and *Diphyllobothrium erinacei* (plerocercoid, B), trematode: *Paragonimus westermani* (C) and *Fasciola hepatica* (D), and nematode: *Ancylostoma caninum* (E), *Dirofilaria immitis* (F) and *Trichuris vulpis* (G). N-MC: N-Methylcytisine, W: washed by Tyrode's solution.

bothrium erinacei (plerocercoid) and *S. japonicum* were less susceptible, and were affected by the drug at concentrations of 3×10^{-6} M or more. *Toxocara canis* and *Trichuris vulpis* were least susceptible, and were affected by the drug only at a concentration of 3×10^{-5} M. Figure 1 shows the effects of niclosamide on the motility of some parasitic helminths.

These results show that niclosamide acts non-specifically against parasitic cestodes, trematodes, nematodes, and host isolated tissues, and that the drug is similar to hexylresorcinol in its mode of action. Since niclosamide seems to be singularly free from any undesirable side effects[2,11,17], this drug may be able to be used as an anthelmintic with a broad spectrum against intestinal helminths besides tapeworms.

Regarding the mechanism of action of niclosamide, only the effects on energy metabolism, for example on glucose and oxygen uptake have been reported[2,18,19]. We have, however, obtained results suggesting that niclosamide eli-

Mode of action of niclosamide in various parasitic helminths and host isolated tissues

Preparation	Concentration of niclosamide (M) 3×10^{-9}	3×10^{-8}	3×10^{-7}	3×10^{-6}	3×10^{-5}
Cestoda					
Dipylidium caninum		▼	▼△	○	
Diphyllobothrium erinacei (plerocercoid)				▼	■
Diplogonoporus grandis		▼	△	○	
Trematoda					
*Metagonimus yokogawai**		▼	▼	■	
Paragonimus westermani		△	○	■	
Fasciola hepatica		△	△	○	
*Schistosoma japonicum**				△	○
Nematoda					
Angiostrongylus cantonensis	▼	▼	△	○	
Dirofilaria immitis			△	○	
Trichuris vulpis					○
Toxocara canis					△
Ancylostoma caninum			△	△	■
Frog rectus (guanidine-induced twich response)		△	○		
Mouse ileum		▼	■		

*Tested by the visual observation method. Inhibitory effect: ▼, slight affection; ■, complete paralysis. Excitatory effect: △, slight affection; ○, complete spastic paralysis.

cits its spastic and/or paralytic action through a neuropharmacological mechanism including acetylcholine (ACh) and 5-hydroxytryptamine (5-HT) in *D. caninum*[20]. Since Strufe and Gönnert[19] suggested that niclosamide acts on oxygen uptake and oxidative phosphorylation through its action on ATPases, the neuropharmacological effects of this compound may also be elicited through its action on the same sites and be related to the release of neurotransmitters.

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Studies on chemotherapy of parasitic helminths (IX). Effects of praziquantel on the motility of various parasitic helminths and isolated host tissues

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Summary. Praziquantel (PQ) caused spastic and/or paralytic actions on the motility of various parasitic helminths and isolated host tissue preparations, through a neuropharmacological mechanism.

Praziquantel (2-cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-2H-pyrazino [2,1a] isoquinolin-4-one, PQ) is a newly developed anthelmintic with a broad spectrum against trematodes and cestodes. Since Gönnert and Andrews[1] reported antischistosomal effects of PQ, there have been many reports regarding the in vivo effects of this compound in animal[1-3] and clinical[4-8] experiments against trematodes such as *Schistosoma mansoni*[1,2,4], *S. haematobium*[2,5], *S. japo-*