Zeitschrift: Acta Tropica
Herausgeber: Schweizerisches Tropeninstitut (Basel)
Band: 33 (1976)
Heft: 1

Artikel: Miscellanea : 4-Isothiocyanato-4'-nitrodiphenylamine (C 9333-Go/CGP 4540) : a new anthelminthic with potent antihookworm activity
Autor: Sen, H.G.
DOI: https://doi.org/10.5169/seals-312222

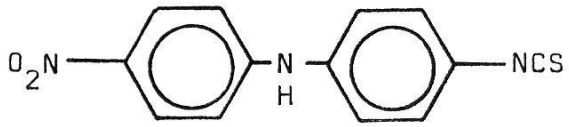
4-Isothiocyanato-4′-nitrodiphenylamine (C 9333-Go/CGP 4540) a New Anthelminthic with Potent Antihookworm Activity[1]

H. G. SEN [2]

Of all intestinal nematodes affecting man, the two main hookworm-species, *Necator americanus* and *Ancylostoma duodenale* produce the greatest morbidity. FAUST & RUSSELL (1963) considered hookworm infestation as one of the major diseases of mankind from the point of view of human misery and economic loss, only exceeded by malnutrition and malaria. It has been estimated (DAVIS, 1973, STANDEN, 1975) that between 726 and 907 millions of the world population are infested with hookworms. There is still a need for adequate chemotherapeutic agents for use on a wide scale in mass campaigns, requiring only a short period of drug administration and with a good tolerability.

We wish to report on a new compound first studied in experimental infections by *Necator americanus* in laboratory animals. These parasites, since their first isolation from a human patient several years ago, have been exclusively maintained in golden hamsters, *Mesocricetus auratus*. Methods for faecal culture, preparation and counting of larvae, animal inoculation and maintenance of infected animals have been reported earlier (SEN, 1972).

In the course of our routine anthelminthic screening programme, we have found that amongst several hundred isothiocyanates [3] tested in the primary screen, 4-isothiocyanato-4′-nitrodiphenylamine (C 9333-Go/CGP 4540) is highly promising.



4-Isothiocyanato-4′-nitrodiphenylamine is prepared from 4-nitro-4′-aminodiphenylamine by standard procedures for example by reaction with thiophosgene. It is a yellow crystalline compound, m.p. 198–199° (from acetone).

Repeated tests have revealed that both adult and immature stages of *Necator americanus* are highly susceptible to this compound. Single oral doses of 30–60 mg/kg administered to hamsters harbouring a non-patent, 37-day-old infection eliminated 94–99% of the total parasites, while single oral doses of 25 mg/kg and

---

[1] Contribution No. 434 from CIBA-GEIGY Research Centre, Goregaon.

[2] Department of Parasitology, CIBA-GEIGY Research Centre, Bombay 400063, India.

[3] These were prepared in the Research Department of CIBA-GEIGY Agrochemicals Division, Basle, and in the Chemical Laboratories of CIBA-GEIGY Research Centre, Goregaon. C 9333-Go/CGP 4540 was synthesized in the former laboratories.

Table. Oral activity of C 9333-Go/CGP 4540 against 37-day-old non-patent and patent *Necator americanus* infestation in golden hamsters (single dose)

	Dose mg/kg	No. of animals cured [1]/treated	% cured	% worm-load reduction as compared with controls	ED_{50} [2] mg/kg
37-day-old non-patent infection	200	10/ 10	100	100	
	100	5/ 5	100	100	
	60	309/357	86	98	
	50	24/ 36	67	99	28
	30	28/ 54	52	94	
	25	5/ 10	50	84	
	20	7/ 20	35	68	
patent infection	60	5/ 5	100	100	
	40	4/ 4	100	100	≈10
	25	15/ 15	100	100	
	10	13/ 24	54	67	

[1] Only animals which are completely deparasitized are classed as cured.
[2] The ED_{50} is taken as the dose that cures 50% of the infested animals.

above completely eliminated the worms in adult mature patent infestation (Table). Within the first three to six hours of treatment, hookworms were often detected intact in the large intestine, which suggests that the drug expels parasites from the small intestine by causing their paralysis.

Further tests in mice have shown that a single oral dose of 90–200 mg/kg can completely expel *Nematospiroides dubius* and *Hymenolepis nana* parasites, while in naturally infected mongrel dogs this compound (25 mg/kg orally) reduced faecal egg excretion of hookworms and ascarids by 90–100%.

The minimum effective dose against *Necator americanus* is 10 mg/kg and the maximum tolerated dose in laboratory animals (mouse, rat, hamsters, dog, cat, rhesus monkey) is greater than 5,000 mg/kg, giving a therapeutic index of over 500.

Preliminary results show that this anthelminthic is also effective in man against both *Necator americanus* and *Ancylostoma duodenale* thus suggesting that further clinical investigation is worthwhile.

References

DAVIS, A. (1973). Drugs for hookworms. In: Drug treatment in intestinal helminthiasis, p. 53. – Geneva: World Health Organisation.

FAUST, E. C. & RUSSELL, P. F. (1964). The human hookworms. In: Craig and Faust's Clinical Parasitology, p. 370. – Philadelphia: Lea & Febiger.

SEN, H. G. (1972). *Necator americanus:* Behaviour in hamsters. – Exp. Parasitol. *32,* 26–32.

STANDEN, O. D. (1975). Chemotherapy of intestinal helminthiasis. In: Progr. Drug Res. *19,* 158–165, ed. by E. Jucker. – Basel: Birkhäuser.