United States Patent Office

2,868,692

Patented Jan. 13, 1959

2,868,692

ANTHELMINTIC POLYMETHYLENEPIPERAZINE AND METHOD OF USING SAME

Frederick L. Bach, Jr., and Redginal I. Hewitt, Pearl River, N. Y., assignors to American Cyanamid Company, New York, N. Y., a corporation of Maine

No Drawing. Application May 16, 1956
Serial No. 585,160

6 Claims. (Cl. 167—55)

This invention relates to new compositions of matter. More particularly, it relates to therapeutic compositions of polymethylenepiperazine and a carrier for the elimination of helminths such as pinworms and ascarids.

An object of the present invention is to prepare a composition capable of producing a high blood level and being effective against helminths such as pinworms and ascarids. A further object is to prepare a composition which will maintain a high blood level of drug for a longer period of time. A still further object is to prepare a composition which will be absorbed less completely and/or more slowly in order to reach and affect helminths such as pinworms and ascarids in the more terminal portions of the digestive tract.

We have now found that the above objects can be attained by the use of polymethylenepiperazine, which is effective in removing helminths, particularly pinworms and ascarids. While piperazine hexahydrate has been used in the past for pinworms, it has the undesirable property of being hygroscopic, and, therefore, it is troublesome to combine with other materials, such as a carrier. On the other hand, polymethylenepiperazine is a stable, tasteless, granular powder, insoluble in water, which can be easily mixed with other materials. Polymethylenepiperazine, being substantially tasteless, is more palatable than piperazine hexahydrate. When both fed and fasted dogs are given a single oral dose of polymethylenepiperazine (50–100 mg./kgm.) the peak blood level was reached five to eight hours after administration. In contrast, piperazine, under similar conditions, reaches peak blood levels during the second hour after administration. Furthermore, the presence of polymethylenepiperazine in the blood was detectable up to 24 hours after administration; whereas the presence of piperazine was not so detectable. The following table summarizes this information:

TABLE I

Piperazine blood levels in non-fasted dogs

[Base equivalent dose: 100 mg./kgm. oral.]

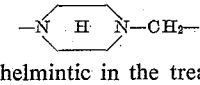
	2	4	6	8	11	14	24
Polymethylenepiperazine	1.7	2.2	2.45	2.45	1.5	1.0	0.7
Piperazine	3.0	1.3	0.3	0.2	0.15	0.13	0

Tests to determine excretion showed that 100% of the piperazine administered was excreted in the urine, whereas, of the polymethylenepiperazine administered, about

60% was excreted in the urine and about 30% detected by assay in the faeces. Polymethylenepiperazine offers therapeutic advantages over other forms of piperazine, since it gives desirable blood levels for longer periods of time against worms in the tissues, and its slower and/or less complete absorption favors greater effectiveness in treating pinworms and other worms infecting the lower intestinal tract.

The amount of single doses or daily doses to be given will vary with the size of the man or animal to be treated, but should be such as to give a proportionate dosage of 1 to 500 mg. per kgm. of body weight. In terms of total weight of drug, this is usually from about 0.1 g. to 10.00 g. per dosage unit. In larger animals, obviously, larger dosage units may be desirable.

The compound polymethylenepiperazine was described in Beilstein, volume XXIII, page 6, 1936, quoting Rosdalsky, J. Prak. chem. (2) 53, p. 22 (1896) and Berichte, volume 30, pages 3043–3045. The compounds described in these references are a polymethylenepiperazine of the following unit structure



Its use as an anthelmintic in the treatment of pinworms or ascarids has not been described. Methods of preparing the compound are described in the above reference and in the chemical literature.

Polymethylenepiperazine was given in a single, oral dose to mice naturally infected with pinworms of the species *Aspicularis tetraptera*, which resembles human pinworms. The mice were killed and necropsied several days after treatment and the intestinal tract examined for pinworms. Activity is indicated when a large proportion of the treated mice reveal few or no worms at necropsy, as compared with untreated controls. The following Table II illustrates the results obtained:

TABLE II

Compound	Test No.	Single oral dose, mg./kgm.	No. Survivals	Percent of mice with 0–5 worms at necropsy. Aspiculuris
Polymethylenepiperazine.	3453B-39	500	10/10	100
Do	3453B-39	200	10/10	100
Do	3453B-39	100	10/10	90
Do	3453B-55	100	10/10	100
Do	3453B-86	100	10/10	80
Do	3453B-55	50	10/10	50
Do	3453B-86	50	10/10	90
Do	3453B-55	25	10/10	60
Do	3453B-86	25	10/10	40
Controls	3453B-39		10/10	30
Do	3453B-55		10/10	20
Do	3453B-86		9/10	22
Polymethylenepiperazine.	Totals	500	10/10	100
Do	do	200	10/10	100
Do	do	100	30/30	90
Do	do	50	20/20	70
Do	do	25	20/20	50
Do	do		29/30	24

The present compositions containing polymethylenepiperazine are effective against dog ascarids (*Toxocara canis*), as shown in Table III illustrating the results obtained and also comparing them with piperazine hexahydrate and piperazine hydrochloride.

TABLE III

Effects of polymethylenepiperazine against dog ascarids (Toxocara canis), *as compared with piperazine hexahydrate and hydrochloride*

Dog. No.		Oral Dose, mg./kgm.	After—			Total	No. Ascarids Retained at Necropsy [d]	Percent Ascarids Passed (Total)
			1st Dose	2nd Dose	3rd Dose			
214	Polymethylene-piperazine	12.5, [b] 25	19	[c] 4	------	23	0	100
209	----do----------	12.5, 25, [b] 50	7	3	3	13	1	93
244	----do----------	12.5, 25, [b] 50	0	1	3	4	0	100
142	----do----------	[a] 100	10	------	------	10	6	63
906	Piperazine hexahydrate--	[a] 100	9	------	------	9	1	90
922	----do----------	[a] 100	4	------	------	4	4	50
130	----do----------	[a] 100	6	------	------	6	1	86
127	Piperazine hydrochloride-	[a] 100	9	------	------	9	15	40

[a] Single dose.
[b] Sequential treatment, single doses, with seven days' rest between increments.
[c] Died third day after second dose—cause of death unknown.
[d] Three-eight days after last dose.
No emesis noted with any of the doses used.

Polymethylene piperazine is also effective against *Ascaris lumbricoides* in guinea pigs. A summary of tests carried out is shown in Table IV.

TABLE IV

Effects of polymethylenepipearzine against larval Ascaris lumbricoides *in guinea pigs* [a]

Dose, Mg./kgm. b. i. d., 4 days, Orally	No. of Survivals to Necropsy [b]	Median and Range of Larvae per Gram of Lung	Percent Reduction of Larvae-Treated Pigs
50	17/27	11 (1-23)	78
Untreated	21/29	45 (14-206)	----------
25	7/7	8 (2-16)	83
12.5	6/7	14 (7-36)	71
Untreated	8/9	48 (27-185)	----------

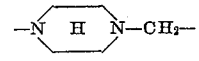
[a] Experimentally infected with 2000 embryonated *A. lumbricoides* ova per animal.
[b] Approximately one week after inoculation.

The compound polymethylenepiperazine can be combined with a carrier and dispensed in any of the usual dosage unit forms of pharmaceutical preparations; for example, tablets, capsules, pills, suspensions, as a powder, or in any other desirable form in the therapeutic quantities hereinbefore given. It may be in a dosage unit form for a single, daily, therapeutic dose or in smaller units for multiple doses or in larger units for division into single doses. Obviously, in addition to the therapeutic product, there may be present excipients, binders, fillers and other therapeutically inert ingredients necessary in the pharmaceutical preparation.

For use in treating animals it may be combined with edible carriers, such as feed stuffs, etc.

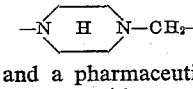
We claim:

1. A therapeutic composition useful in the treatment of helminths in dosage unit form comprising from 0.1 g. to 10.00 g. of a polymethylenepiperazine of the following unit structure



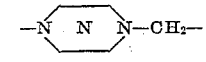
per dosage unit and an edible carrier.

2. A therapeutic composition for oral administration useful in the treatment and elimination of pinworms and ascarids in dosage unit form comprising from 0.1 g. to 10.00 g. of a polymethylenepiperazine of the following unit structure



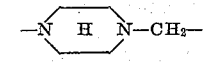
per dosage unit and a pharmaceutical carrier.

3. A therapeutic composition useful in the treatment of pinworms and ascarids in dosage unit form comprising from 0.1 g. to 10.00 g. of a polymethylenepiperazine of the following unit structure



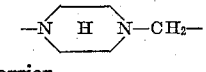
and a solid pharmaceutical carrier, said composition being in tablet dosage unit form.

4. A therapeutic composition in dosage unit form useful in the treatment of pinworms and ascarids comprising from about 0.1 g. to 10.00 g. of a polymethylenepiperazine of the following unit structure



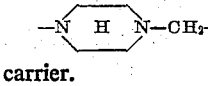
and a significant amount of pharmaceutical carrier.

5. A method of maintaining higher blood levels of piperazine useful in the treatment of pinworms and ascarids which comprises administering in dosage unit form from 1 mg. to 500 mg. per kgm. of body weight of a polymethylenepiperazine of the following unit structure



and an edible carrier.

6. A method of treating pinworm and ascarid infestations in animals which comprises introducing into the intestinal tract of the animals so infested a therapeutic composition containing from 1 mg. to 500 mg. per kgm. of body weight of a polymethylenepiperazine of the following unit structure



and an edible carrier.

References Cited in the file of this patent

White: British Med. Jour. No. 4839, October 3, 1953, pp. 755–758.