POTENTIATION OF THIOPENTAL ANESTHESIA BY DERIVATIVES AND ANALOGUES OF PHENOTHIAZINE

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A SURVEY of some of the specific effects of phenothiazine derivatives has revealed that there are wide differences among these drugs which are available for clinical use. These differences should be defined so that selection may be facilitated.[1, 2] This report deals with the effect of several phenothiazines and their analogues on potentiation of thiopental narcosis which is one of the important effects of these drugs when used in conjunction with anesthesia.[3, 4]

METHOD

Crossover experiments were carried out four times at weekly intervals with each drug. Ten mongrel dogs of comparable age and size (11 to 17.2 kg., mean 14.9 kg.) were used. The technique employed was the same as has been reported previously.[5, 6] In every experiment each dog received 20 mg./kg. of thiopental intravenously in a 2 per cent solution, injected at the approximate rate of 150 mg. per minute, and was followed at alternate experiments by the injection of the test drug. The selection of the dose of each drug was based on previous clinical and laboratory trials to determine a dose level which would *not* cause severe cardiovascular or respiratory depression when administered immediately after thiopental.

RESULTS

A summary of the data from each of the nine series of experiments are shown in the table. All data were analyzed statistically for standard deviation and standard error of the mean, and the Fisher *t* test was applied to determine the probability of significance of the differences that were observed.

Promazine (Sparine), propriomazine (WY 1359) and prothipendyl (AY 56031, D 206) caused the greatest prolongation of thiopental narcosis. The dose level selected for each of these phenothiazines more than doubled the duration of hypnosis by thiopental. A lesser, but significant prolongation of hypnosis was observed with levomepromazine (Nozinan), Imipramine (Tofranil) and methdilazine (MJ 5022). Little or no significant prolongation was observed with mepazine (Pacatal), proclorperazine (Stemetil, Compazine) and with trifluoperazine (Stelazine).

In figure 1, the effect of these drugs in prolongation of thiopental narcosis is shown together with results of similar tests of some other phenothiazines that have been studied.[6]

DISCUSSION

The potentiation of thiopental hypnosis by promazine, propriomazine and prothipendyl are much the same as that found with chlorpromazine, promethazine and trifluopromazine. Most of the reported effects of promazine are similar to that of chlorpromazine, except that promazine is about half as potent.[2]

Mepazine (Pacatal) lacks hypnotic properties in the dose level which provides a satisfactory antiemetic and neurosedative effect, and depression of myocardial irritability. Potentiation of hypnosis in man occurs only when mepazine is administered intravenously in a large dose (50 to 100 mg.), sufficient to cause also a marked hypotension.[2, 7-11]

Propriomazine (WY 1359). Reports of the use of this drug in clinical practice have not as yet appeared, but the chemical structure and pharmacological properties of propriomazine are similar to that of promethazine. The acute toxicity of these two drugs is said to be the same, whereas the antihistaminic, antisecretory and circulatory (hypotensive) effects are claimed to be less, and the hypnotic effect is thought to be greater than that of promethazine.[12]

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TABLE 1

SUMMARY OF DATA SHOWING THE EFFECT OF PHENOTHIAZINE DERIVATIVES ON THIOPENTAL NARCOSIS IN DOGS

Drugs Tested	Dose mg./kg.	Recovery Time (minutes) Head Up Mean*	S.D.	% Diff.	Significance	Recovery Time (minutes) Legs Up Mean*	S.D.	% Diff.	Significance
Thiopental alone	20	37	14			48	15		
+Promazine	2	87	28	+134	$p = .001$	108	30	+128	$p = .001$
Thiopental alone	20	56	13			62	11		
+ Mepazine	2	56	12	0	None	64	14	0	None
Thiopental alone	20	46	24			55	26		
+ Propriomazine	2.5	97	26	+112	.001	124	50	+126	.001
Thiopental alone	20	46	17			59	17		
+ Levomepromazine	0.5	80	23	+74	.001	130	49	+120	.001
Thiopental alone	20	34	13		$.05 < p$	40	13		$0.1 < p$
+ Proclorperazine	0.5	44	20	+29	< 0.1	48	20	+20	< 0.2
Thiopental alone	20	49	19			61	26		$0.1 < p$
+ Trifluoperazine	0.1	59	68	+20	0.5	77	70	+38	< 0.2
Thiopental alone	20	49	22			61	25		
+ Imipramine	5	74	29	+56	.005	91	34	+50	.005
Thiopental alone	20	44	26		$.05 < p$	56	30		$.05 < p$
+ Methdilazine	0.5	66	35	+50	$< .025$	84	49	+50	$< .025$
Thiopental alone	20	43	23			62	26		
+ Prothipendyl	1.0	94	39	+118	.001	124	50	+100	.001

* Each mean time represents 20 administrations of thiopental alone and with the test drug.

Levomepromazine (Nozinan) has a variety of properties which have been found useful in preanestheic medication and for supplementing general anesthesia. These actions include suppression of apprehension, salivary secretions, nausea and vomiting, and a potent antihistaminic activity. This drug also has analgesic activity. These effects may be enhanced by its combined use with hypnotics.[13-18]

Proclorperazine (Stemetil, Compazine) has been the subject of several reports which show that it is an effective antiemetic and neurosedative.[19-21] However, it is not effective in potentiating thiopental hypnosis, and it is not as satisfactory for allaying preoperative apprehension, even at a dose level which causes hypotension.[18]

Trifluoperazine (Stelazine) is the most potent phenothiazine derivative yet developed for clinical use as a tranquillizer. Although it is about ten times as potent as chlorpromazine in this respect, it is less effective as a hypnotic, its potentiating effect on thiopental narcosis is only slight and is inconsistent, and its short term clinical use is accompanied by a high incidence of restlessness, insomnia, jitteriness and a variety of motor disturbances which resemble extrapyramidal nervous system dysfunction.[22-25]

Imipramine (*G 22355*) is the iminodibenzyl analogue of promazine.[26] It is being used at the present time for the treatment of mental depression.[27, 28, 29] On the basis of this usage, the drug was initially tested for analeptic properties. However, it was immediately evident that imipramine acted like a sedative hypnotic, although it does not reduce motor function or cause general inhibition of activity

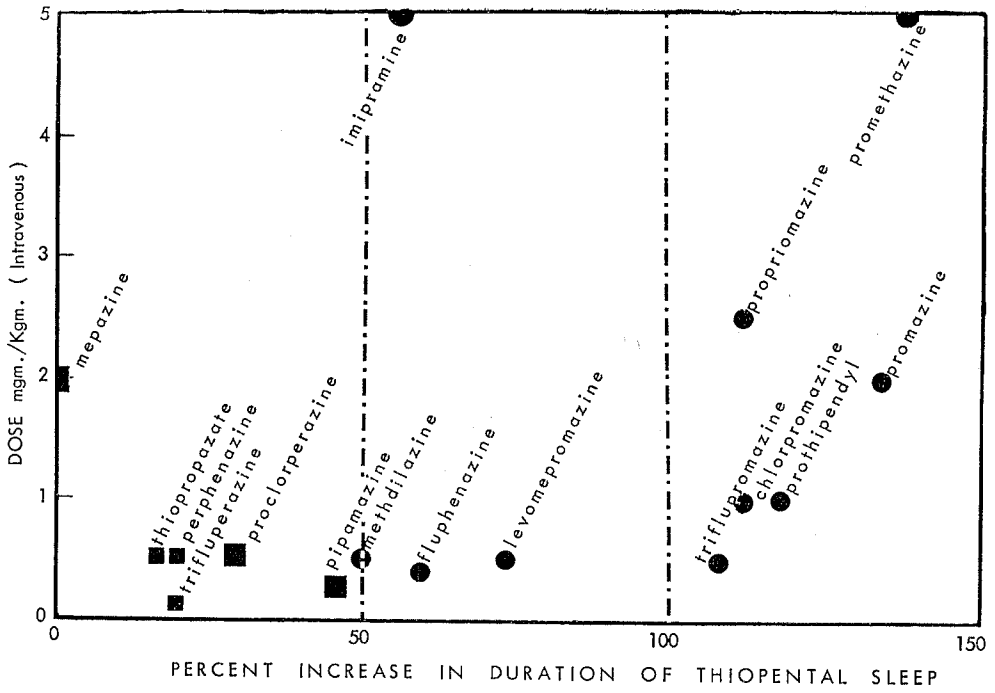

FIG. 1. Comparative hypnotic potency of derivatives and analogues of phenothiazine as measured by prolongation of thiopental sleep in dogs. Observe that these drugs may be divided into three groups: according to the response to a "therapeutic dose"—those that more than double thiopental sleep, those that cause moderate prolongation, and those that have little or no effect.

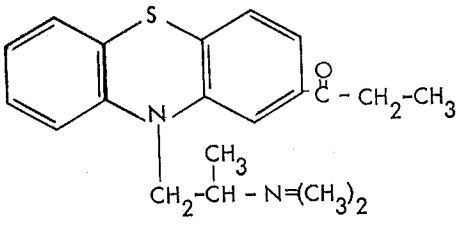

FIG. 2. Structural formula of propriomazine.

as is seen with the derivatives of chlorpromazine.[30, 31] In the present study, it was found to cause about 50 per cent increase in the hypnotic action of thiopental.

Methdilazine (MJ 5022). Clinical reports on the use of this agent have not as yet appeared. In pharmacological studies by Mead Johnson Research Laboratories, this phenothiazine derivative was found to have an acute toxicity similar to that of promethazine, but it had long-acting antihistaminic properties which were twice as great as promethazine. On the basis of this study, methdilazine caused about one half as much potentiation of thiopental hypnosis as promethazine when it was used in one tenth the dosage.

Prothipendyl (AY 56031, D 206). Extensive animal screening tests of this drug by

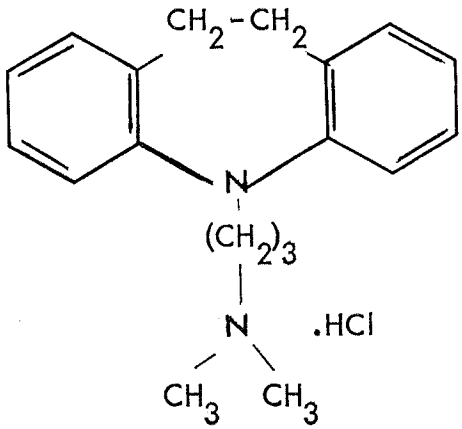

FIG. 3. Structural formula of Imipramine (G 22355).

the Ayerst Research Laboratories, and one clinical report, indicate that this drug is similar to chlorpromazine and promazine in most respects.[32] Its antiemetic effect is of the same order as that of chlorpromazine. Its antihistaminic properties are potent, and similar to that of promethazine. Its effect on thiopental hypnosis is of the same order as that of chlorpromazine.

Mepazine appears to be a useful neurosedative for use in anesthesia if a hypnotic effect is not desired. Proclorperazine and trifluoperazine have undesirable effects which reduce their usefulness as preanesthetic sedatives. The others tested are all useful hypnotic sedatives which are worthy of use for preanaesthetic sedation: levomepromazine, where a potent antihistaminic, analgesic and hypnotic effect are desired; methdilazine, propriomazine and prothipendyl when a potent antihistaminic and hypnotic effect are desired; imipramine for the patient with severe mental depression; and promazine for a potent hypnotic effect—especially in alcoholic patients.

Summary

Several derivatives and analogues of phenothiazine were studied to determine whether they prolong thiopental narcosis in dogs, using a standard crossover method. In the therapeutic dose that was tested, promazine, propriomazine and prothipendyl more than doubled the hypnotic effect of thiopental. Levomepromazine, imipramine and methdilazine also caused a consistent prolongation of thiopental hypnosis in excess of 50 per cent. Mepazine, proclorperazine and trifluoperazine had little or no effect on thiopental hypnosis.

I am indebted to Mr. S. Meakin, Mr. B. St. Germaine and Mr. R. Welgan for their helpful technical assistance during these experiments.

The following pharmaceutical firms kindly supplied drugs for testing and grants-in-aid in support of this work: Ayerst, McKenna and Harrison, Ltd., Montreal; Geigy Pharmaceuticals, Montreal; Mead Johnson, Toronto; Poulenc, Limited, Montreal; Smith, Kline & French, Montreal; John Wyeth and Brother, Limited, Walkerville, Ontario.

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RESEARCH AS EDUCATION Experience in research before formal training is completed is almost prerequisite for any similar productive work afterward. In addition its sharpens one's judgment of the work of others, makes one appreciative of difficulties involved, makes clinical observation more discerning, provides lessons in team work and fosters respect for persistent routine. (*Johnson, V.: The Value of Participation in Research as a Component in the Education of Doctors for the Medical, Graduate and Postgraduate Student, Brit. Med. J. 2: 332 (Sept. 5) 1959.*)

POSTOPERATIVE PAROTITIS Evaluation of 93 cases of acute, noncontagious parotitis, 68 occurring postoperatively, showed no definite relation to the type or duration of anesthesia. The condition is due to an ascending infection from the mouth, with nutritional, general and oral dehydration frequently contributing factors. (*Branson, B., Kugel, A., and Stafford, C.: Re-Emergence of Postoperative Parotitis, West. J. Surg. 67: 38 (Jan.–Feb.) 1959.*)

ANESTHESIA IN NEWBORN For the surgical correction of congenital diaphragmatic hernia in the newborn, cyclopropane is recommended as the anesthetic agent of choice, administered through an endotracheal tube using a closed system adapted for infants. Marked positive pressure is to be avoided because of the danger of rupturing a bleb in the functioning lung. The surgeon should never request the anesthetist to provide increased positive pressure to expand the collapsed affected lung. (*Meeker, I., and Nichols, J.: Congenital Diaphragmatic Hernia in Newborn, West. J. Surg. 67: 42 (Jan.–Feb.) 1959.*)

LARYNGOSCOPE A laryngoscope consisting of a handle, blade, light and lens system suitable for intubating small animals such as rats and mice is described. The light is transmitted by means of a prism lens, thus making it possible to focus the light where is it needed. (*Roberts, J. B.: An Easily Constructed Laryngoscope for Intubation of Small Animals, J. Physiol. 143: 32 (Sept. 23) 1958.*)