POTENTIATION OF THIOPENTAL ANAESTHESIA: WITH TIGAN®, PANECTYL®, BENADRYL®, GRAVOL®, MARZINE®, HISTADYL®, LIBRIUM®, AND HALOPERIDOL (R 1625)*

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PREVIOUS STUDIES have shown that a therapeutic dose of most of the phenothiazines markedly prolongs thiopental anaesthesia, whereas a similar effect with narcotic analgesics is less pronounced.^{1, 2} Two new anti-emetics, trimethobenzamide (Tigan®)³ and haloperidol (R 1625),⁴ and a new neurosedative, methaminodiazepoxide (Librium®),⁵ were studied together with several commonly used antihistaminic drugs to determine also what effect they might have on thiopental narcosis.

METHOD

Crossover experiments were carried out four times at weekly intervals with each drug, using ten mongrel dogs of comparable age and size (13.2 kg. to 20.9 kg., mean 17.5 kg.). 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 min., and was followed at alternate experiments by the injection of the test drug. The dose selected for each drug was based on clinical experience or on information provided by the pharmaceutical manufacturer, and was adjusted so that severe cardiorespiratory depression would not occur when administered intravenously after thiopental.

RESULTS

Data from the experiments on each drug are summarized in Table I. The data from each series of cross-over experiments were analysed statistically to determine the probability of significance of the differences that were observed.

Trimethobenzamide (Tigan®) had no effect on thiopental narcosis. Thenylpyramine (Histadyl®) appeared to cause prolongation, but the effect was inconsistent, and the differences observed were not statistically significant. Dimenhydrinate (Gravol®, Dramamine®) caused only slight prolongation. Trimeprazine (Panectyl®), diphenhydramine (Benadryl®), cyclizine (Marzine®), and haloperidol (R 1625) caused moderate prolongation, whereas methaminodiazepoxide (Librium®) caused very marked prolongation.

No untoward effects were observed with any of these drugs except with haloperidol, which caused a disturbance of gait after recovery from anaesthesia. This effect was indicative of an extrapyramidal disturbance, which was observed also when this drug was administered to humans.

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TABLE I
THE EFFECT OF SOME ANTI-EMETICS AND SEDATIVES ON THIOPENTAL NARCOSIS IN DOGS

	Dose mg./kg.	Recovery time (minutes)			Recovery time (minutes)				
		Mean*	Head up S.D.	Percentage diff.	Significance	Mean*	Legs up S.D.	Percentage diff.	Significance
Thiopental alone	20	55	23	-4	p = 0.5	73	32	-11	p = 0.4
+ Trimethobenzamide	10	53	22			65	25		
Thiopental alone	20	44	11	+48	.001	53	9	+36	.001
+ Trimeprazine	25	65	15			72	14		
Thiopental alone	20	51	23	+63	.005	60	19	+62	.001
+ Diphenhydramine	5	83	34			97	29		
Thiopental alone	20	39	12	+28	.025	47	9	+19	.005
+ Dimenhydrinate	5	50	16			58	11		
Thiopental alone	20	35	9	+49	.001	43	9	+44	.001
+ Cyclizine	5	52	12			62	12		
Thiopental alone	20	43	17	+25	0.1	51	19	+20	0.2
+ Thienylpyramine	1	54	20			61	21		
Thiopental alone	20	47	18	+208	.001	56	17	+225	.001
+ Methaminodiazepoxide	2.5	145	39			182	40		
Thiopental alone	20	42	13	+33	.001	54	15	+41	.005
+ Haloperidol	0.5	63	21			76	25		

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

DISCUSSION

According to these studies, the anti-emetic effect of trimethobenzamide will not be accompanied by any alteration in the hypnotic effect of thiopental, even if it is administered during anaesthesia.³ On the other hand, the antihistaminic drugs all prolonged thiopental sleep.⁴ If cyclizine is given during anaesthesia in order to prevent postoperative vomiting, it may reasonably be expected to prolong anaesthetic sleep considerably. If trimeprazine, diphenhydramine, or dimenhydrinate are administered parenterally during anaesthesia for a sedative or antihistaminic effect they may also significantly prolong sleep. Thenylpyramine HCL (Histadyl®), having the following structural formula,

may be used parenterally during anaesthesia to treat acute urticaria due to drug allergy.⁵ It would probably not prolong anaesthetic sleep if used in the dosage recommended.

Methaminodiazepoxide HCL (Librium®) has a structural formula as follows:

This compound was recently introduced mainly for the treatment of acute agitation and aggressive behaviour. The taming action of this drug is similar to chlorpromazine, and its muscle relaxing properties are greater than that of meprobamate. These effects occur apparently at a dose level which does not produce hypnosis. However, the present study indicates that when it is administered with thiopental, a very marked hypnotic effect is evident. This must be borne in mind when a patient who has been taking this drug must be given an anaesthetic.⁶

Haloperidol (R 1625) has the structural formula shown below.

This compound is one of a group of butyrophenones which have been under clinical trial as a psychosedative and an anti-emetic. Its psychic effect in man is not unlike chlorpromazine at a relatively low dose level which does not cause drowsiness. Unfortunately, it causes a high incidence of extrapyramidal nervous system disturbances which are very disturbing to the patient.⁷ At the dose level tested, it causes moderate prolongation of thiopental sleep.

SUMMARY AND CONCLUSIONS

A standardized cross-over experiment was used on dogs with three recently introduced drugs—Tigan (anti-emetic), Librium (neurosedative), and Haloperidol (psychosedative and anti-emetic)—to determine whether they affect the duration of thiopental narcosis. These were compared with some antihistaminic and anti-emetic drugs (Panectyl, Benadryl, Gravol, Marzine, and Histadyl). The dose selected for each drug was based on clinical experience and was adjusted if necessary so that severe cardiorespiratory depression would not occur when they were administered after thiopental.

Tigan had no effect on thiopental narcosis. Histadyl caused only slight prolongation. Librium caused very marked prolongation. The other drugs caused slight to moderate prolongation of thiopental narcosis.

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RÉSUMÉ

Nous avons employé, chez des chiens qui avaient absorbé récemment du Tigan (antiémétique), du Librium (neurosédatif) et de l'Haloperidol (sédatif psychique et antiémétique), une circulation croisée ordinaire pour étudier si ces médicaments modifient la durée de l'anesthésie au pentothal. Nous avons comparé les effets de ces médicaments avec ceux de certains antihistaminiques et antiémétiques (Panectyl, Benadryl, Gravol, Marzine et Histadyl). L'expérience clinique a servi de base pour déterminer la dose de ces médicaments et nous ajustions les doses de façon à éviter une dépression sérieuse du système cardiorespiratoire lorsqu'ils étaient injectés après une dose de thiopental.

Le Tigan n'a pas semblé avoir d'effet sur l'anesthésie au thiopental. L'Histadyl n'a prolongé que légèrement la durée de l'anesthésie. Le Librium l'a prolongée considérablement. Les autres médicaments ont causé une prolongation plus ou moins longue de l'anesthésie au thiopental.

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