PROLONGATION OF THIOPENTAL ANAESTHESIA WITH HYDROXYZINE, SA 97, THIETHYLPERAZINE, AND THIORIDAZINE*

ALLEN B. DOBKIN, M.D., JACOB S. ISRAEL, M.D., AND V. GUY CRISWICK, B.S.†

HYDROXYZINE (Atarax®), Vistaril®), thiethylperazine (GS 95, Torecan®), and thioridazine (Mellaril®) have applications in clinical anaesthesia, which are now being tested, because they are believed to have efficacy in producing neurosedation, and in reducing postoperative nausea and vomiting.^{1,2} SA 97 (N-*p*-chloro-benzylhydriyl-N'-methyl-homopiperazine dihydrochloride) has also been recommended particularly for its antihistaminic properties for management of asthmatic patients.³ It is a diphenylmethane derivative similar to hydroxyzine.

This report describes tests that were made to determine whether these drugs prolong anaesthesia with thiopental.

METHOD

Experiments were carried out four times with each of the drugs using ten mongrel dogs weighing 12 to 26 kg. (mean 19.6 kg.). In every experiment, each dog received 20 mg./kg. of thiopental sodium intravenously in a 2 per cent solution, followed immediately, in alternate experiments, by intravenous injection of the drug under test. This is the same technique as has been used previously for such evaluations.⁴ The dose selected for each drug was based on information provided by the pharmaceutical manufacturer and was adjusted so that severe cardiorespiratory depression would not occur when it was administered intravenously following thiopental sodium.

RESULTS

A summary of the data from the experiments is shown in Table I. Statistical analyses were applied to determine whether the differences observed were significant.

In the dose tested, each drug caused prolongation of thiopental sleep and recovery. Thioridazine doubled the sleep time; SA 97 and thiethylperazine increased the sleep time by approximately 50 per cent. The effect of hydroxyzine was less predictable than that of the other three drugs, but nevertheless the sleep time was prolonged in most of the animals.

DISCUSSION

Although there is considerable individual variation in the effect of sedative, narcotic analgesic, and antihistaminic drugs on the duration of thiopental sleep (Table II), there are few such drugs that do not cause sufficient prolongation to be significant to the anaesthetist.⁴⁻⁷ Whenever these drugs are indicated and used

*From the Anesthesia Research Laboratory, Department of Anesthesiology, Upstate Medical Center, Syracuse, New York.

†Medical student research assistant.

TABLE I
THE EFFECT OF SOME SEDATIVES ON THIOPENTAL NARCOSIS IN DOGS

	Dose (mg./kg.)	Recovery time (minutes)					
		Head up		Difference (%)	Significance <i>P</i>	Legs up	
		Mean*	S.D.			Mean*	S.D.
Thiopental alone +hydroxyzine	20 5	30 43	±17 ±23	+44	>0.05, <0.10	44 60	±25 ±31
Thiopental alone +SA 97	20 5	26 40	±10 ±16	+50	<0.01	36 51	±12 ±18
Thiopental alone +thiethylperazine	20 0.5	23 37	±7 ±15	+60	<0.01	31 44	±10 ±17
Thiopental alone +thioridazine	20 0.5	20 42	±10 ±16	+107	<0.001	31 50	±11 ±14

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

TABLE II

Drug	Generic name	Dose (mg./kg.)	% change in duration of thiopental sleep
Atarax } Vistaril }	Hydroxyzine	5	(+44)*
Benadryl } Dramamine }	Diphenhydramine	5	+63
Gravol }	Dimenhydrinate	5	(+28)
Histadyl }	Thenylpyramine	1	(+25)
Librium }	Methaminodiazepoxide	2 5	+208
Marazine } Marzine }	Cyclizine	5	+49
SA 97 }		5	+50
Tigan }	Trimethobenzamide	10	0
Compazine } Stemetil }	Prochlorperazine	0 5	(+29)
Dartal }	Thiopropazate	0 5	(+17)
Largactil } Thorazine }	Chlorpromazine	1	+112
Largon }	Propiomazine	2 5	+112
Mellaril }	Thioridazine	0 5	+107
Mornidine }	Pipamazine	0 25	(+46)
Nozinan }	Levomepromazine	0 5	+74
Pacatal }	Mepazine	2	0
Panectyl } Temaril }	Trimeprazine	0 25	+48
Permitil }			
Prolixin }	Fluphenazine	0 4	+60
Trancin }			
Phenergan }	Promethazine	5	+138
Sparine }	Promazine	2	+134
Stelazine }	Trifluoperazine	0 1	(+20)
Tacaryl }	Methdilazine	0 5	(+50)
Timovan }	Prothipendyl	1	+118
Torecan }	Thiethylperazine	0 5	+60
Trilafon }	Perphenazine	0 5	+20
Vesprin }	Triflupromazine	0 5	+108
Demerol }	Meperidine	2	+28
Leritine }	Anileridine	1	+37
Levodromoran }	Levorphanol	0 05	+31
Morphine }		0 02	0
Nisentil }	Alphaprodine	1	+51
Numorphan }	Oxymorphone	0 05	+45
Pipadone }	Dipipanone	0 5	+82

*Figures in brackets indicate that the response noted is not as predictable as the rest

in the immediate anaesthetic period, it is wise to observe the patient closely, especially when respiratory depression already exists, or is likely to occur, because the prolongation of anaesthetic sleep increases the risk of airway obstruction and pulmonary complications.⁸ In clinical use, many of these drugs often make the patient too drowsy or too dizzy to allow early ambulation, as well as increasing the likelihood of circulatory depression when they assume the erect posture.^{9,10}

Hydroxyzine does increase the duration of thiopental sleep, but the effect is not consistent in the dog. However, prolonged drowsiness is seen in healthy humans when it is given intravenously.¹⁰ SA 97, a diphenylmethane derivative which is similar in structure to hydroxyzine (Fig. 1), caused consistent prolongation of thiopental sleep and may also cause drowsiness in humans.¹⁰

FIGURE 1. Diphenylmethane derivatives.

FIGURE 2. Phenothiazine derivatives.

Thiethylperazine, and thioridazine are phenothiazine derivatives (Fig. 2) having a similar chemical structure. Both caused rather marked prolongation of thiopental sleep in dogs, but do not appear to cause marked drowsiness in man when used alone.¹⁰ However, such an effect should be expected when any phenothiazine derivative is given during or shortly after an anaesthetic.

SUMMARY AND CONCLUSIONS

Four series of crossover experiments were carried out with mongrel dogs to determine whether hydroxyzine and SA 97 (diphenylmethane derivatives) and thiethylperazine and thioridazine (phenothiazine derivatives) prolong sleep induced by thiopental. It was found that hydroxyzine caused prolongation of thiopental sleep, but this effect was not consistent, whereas the other three drugs invariably delayed recovery from thiopental.

When these drugs are used in association with clinical anaesthesia, the slower awakening should be kept in mind in order to avoid the possibility of airway obstruction and pulmonary complications, which often result from delayed return of consciousness.

ACKNOWLEDGMENT

This study was supported by grants-in-aid from Roerig & Co. (Atarax®), Sandoz Pharmaceuticals (Torecan® and Mellaril®) and Abbott Laboratories (SA 97).

RÉSUMÉ

Nous avons pratiqué quatre séries d'expériences croisées sur des chiens bâtards pour établir si l'hydroxyzine et le SA 97 (dérivés du diphenylméthane), le thiethylpérazine et la thioridazine (dérivés de la phénothiazine) prolongent le sommeil

provoqué par le pentothal. Nous avons observé que l'hydroxyzine prolonge le sommeil produit par le pentothal, mais son effet n'est pas constant, alors que les trois autres produits invariablement retardent de façon marquée le réveil à la suite de l'anesthésie au pentothal.

Si, au cours de l'anesthésie clinique, l'on fait usage de ces produits, on doit garder à l'esprit la possibilité d'un réveil tardif, d'obstruction respiratoire et de complications pulmonaires, rançons d'un retour tardif à la conscience.

REFERENCES

1. BIZARRI, D.; LATTEI, F. S.; SCHMOOKLER, A.; FIERRO, F. E.; GIUFFRIDA, J.; & BERGER, H. C. Preanesthetic Medication with Intravenous Hydroxyzine. *Anesth. & Analg.* 40: 378 (1961).
2. SANDOZ LABORATORY REPORT. 1960.
3. ABBOTT LABORATORY REPORT. 1960.
4. DOBKIN, A. B. Potentiation of Thiopental Anaesthesia: With Tigan®, Panectyl®, Benadryl®, Gravol®, Marzine®, Histadyl®, Librium®, and Haloperidol (R 1625). *Canad. Anaesth. Soc. J.* 8: 265 (1961).
5. ——— Prolongation of Thiopental-Induced Sleep in Dogs by Narcotic Analgesics. *Anesthesiology* 22: 291 (1961).
6. ——— Potentiation of Thiopental Anaesthesia. Comparison of Promethazine, Chlorpromazine, Perphenazine, Fluphenazine, Thiopropazate, Pipamazine and Triflupromazine. *Brit. J. Anaesth.* 32: 424 (1960).
7. ——— Potentiation of Thiopental Anesthesia by Derivatives and Analogues of Phenothiazine. *Anesthesiology* 21: 292 (1960).
8. LEADING ARTICLE. Post-anaesthetic Respiratory Insufficiency. *Lancet* 1: 34 (1961).
9. DOBKIN, A. B. & CRISWICK, V. G. Circulatory Response to Tilt with Some Anti-emetic and Sedative Drugs. *Canad. Anaesth. Soc. J.* 8: 387 (1961).
10. DOBKIN, A. B.; ROBIDOUX, H. J., JR.; & ISRAEL, J. S. Circulatory Response to Tilt with Hydroxyzine (Atarax, Vistaril) Thiethylperazine maleate (GS 95, Torecan), SA 97 and Perphenazine (Trilafon). *Anesth. & Analg.* (in press).