NEUROLEPTANALGESICS: 1. EFFECT OF DROPERIDOL, FENTANYL, INNOVAR, BENZQUINAMIDE, AND PENTAZOCINE ON THE DURATION OF THIOPENTAL-INDUCED SLEEP IN DOGS*

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MOST NEUROSEDATIVES and analgesic sedatives are devoid of a hypnotic effect, so that it is desirable to use some form of supplementary anaesthesia to put the patient to sleep when one wishes to use neuroleptanalgesic drugs.^{1,2} The object of this study was to determine whether Innovar and its ingredients droperidol and fentanyl, benzquinamide and pentazocine, alter the duration of thiopental-induced sleep. Previous tests of the same kind have been performed in our laboratory on a wide variety of sedative and analgesic drugs, so that we have a sound basis for comparing these new agents with sedatives and analgesics with which we are familiar.³⁻⁸

METHOD

Crossover experiments were performed four times at weekly intervals with each compound, using 10 mongrel dogs of comparable age and size (13.2 to 24.8 kg., mean 20.9 kg.). Prior to each test, the dogs were weighed after a 12-hour fast. In every experiment, each dog received 20 mg./kg. thiopental in a 2 per cent solution, injected intravenously in a forepaw vein at the approximate rate of 150 mg. per minute. This was followed immediately, in alternate experiments, by injection of the test drug. The dose selected for the test drug was based on the therapeutic range of usefulness. Immediately after injection, the dog was placed on the floor of the laboratory and allowed to recover without being disturbed or stimulated. The recovery time of each animal was recorded as the time which elapsed from the beginning of the injection until the dog lifted its head, and then until it attempted and was able to stand on all four paws without collapsing. As soon as a dog recovered, it was removed from the room so that it would not disturb the remaining dogs.

RESULTS

A summary of the data from each of the five series of crossover experiments is shown in Table I. All data were analysed statistically for standard deviation, standard error of the mean (S.E.), and the Fisher *t* test was applied to determine the probability of significance of the differences that were observed.

Droperidol produced a significant extension of the thiopental-induced sleep-time, and full recovery to ambulation was at least twice as long as that caused by thiopental alone. Fentanyl prolonged thiopental-induced sleep by approximately 75 per cent while recovery to ambulation was delayed in excess of 50 per cent.

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TABLE I

EFFECT OF SOME NEUROLEPTANALGESICS ON THIOPIENTAL NARCOSIS IN DOGS

Dose (mg./kg.)	Recovery time (min.)				Recovery time (min.)			
	Head up				Legs up			
	Mean*	S.E.	Difference (%)	Significance <i>p</i>	Mean*	S.E.	Difference (%)	Significance <i>p</i>
Thiopental alone	20.4	4.5	+170	<0.001	26.9	5.1	+121	<0.001
+ Droperidol	55.2	7.0			60.8	7.3		
Thiopental alone	23.6	4.8	+77	<0.001	31.0	5.5	+56	<0.001
+ Fentanyl	41.8	6.2			48.4	6.1		
Thiopental alone	21.6	4.6	+138	<0.001	29.0	5.3	+95	<0.001
+ Innovar	51.0	6.8			56.5	7.0		
Thiopental alone	19.4	4.4	+24	>0.1	27.4	5.1	+21	>0.05
+ Benzquinamide	24.0	4.8			33.1	5.6		
Thiopental alone	22.7	1.8	+70	<0.001	30.5	2.5	+46	<0.001
+ Pentazocine	38.5	3.8			44.5	3.8		

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

†0.25 mg droperidol + 0.005 mg fentanyl/kg.

When the combination of droperidol and fentanyl was used in one-half the doses employed in the individual drug tests, an intermediate effect was observed which was closer to that produced by the droperidol, indicating that its potentiating effect is dominant.

Benzquinamide had virtually no effect on the duration of thiopental-induced sleep whereas pentazocine had an effect which was similar to that of fentanyl.

Diarrhoea occurred in six dogs after the first time they received droperidol with thiopental and in four dogs after the second such test. One dog had diarrhoea after the first test with Innovar-thiopental and five dogs developed this symptom after the second test. The diarrhoea usually began the day after the test. Two dogs became apnoeic after each of the tests with fentanyl-thiopental. This was treated by compressing the thorax manually until spontaneous respiration began (usually in 3 to 5 minutes). No untoward effects were observed during or after the tests with pentazocine or with thiopental alone. Most of the dogs appeared to be hyperventilating for a brief period after the injections of benzquinamide.

Aside from the above side-effects, all the dogs recovered fully within 24 hours of each test and all dogs survived the entire series of tests.

DISCUSSION

The response of the dogs to the drugs was much as was expected from clinical experience and the known pharmacological activity of these drugs.

In the case of the simultaneous administration of thiopental with Innovar, it would seem wise to avoid use of the combination of droperidol and fentanyl after induction has been accomplished if supplementary anaesthesia is required, and the choice should be made between adding fentanyl if more analgesia is required or more thiopental if more hypnosis is necessary. Since fentanyl is an extremely potent respiratory depressant, it is important to be prepared to augment pulmonary ventilation whenever its use is elected.

Although benzquinamide has been shown to have neuroleptic properties similar to that of chlorpromazine, it is devoid of any hypnotic effects. Since it has no analgesic properties either, its use should be considered only for premedication rather than as an agent for use during anaesthesia.

Pentazocine combined with thiopental produced a period of smooth anaesthesia without evidence of severe respiratory depression, and recovery was quiet and uneventful, indicating that this combination would probably be quite satisfactory for clinical anaesthesia.

SUMMARY AND CONCLUSIONS

A standardized crossover experiment was employed to determine the effect of combining some new neuroleptic and analgesic drugs with thiopental on the duration of thiopental-induced sleep in dogs. The dose selected for each of the drugs was within the therapeutic effective dose range of their primary action, and was unlikely to produce severe cardiorespiratory depression. Droperidol prolonged thiopental-induced sleep and delayed full recovery by more than twice

the time for thiopental alone. Fentanyl and pentazocine had approximately the same effect, causing a 50 per cent to 75 per cent delay in recovery. The effect with Innovar was less than that of droperidol, but was much more than that with fentanyl, indicating a dominant action of droperidol in the mixture with respect to the hypnotic effect. Benzquinamide had virtually no effect on the duration of thiopental-induced sleep.

A few side-effects of significance were observed: droperidol and Innovar commonly caused diarrhoea the day after the test, and fentanyl caused a brief period of apnoea during the test in a few dogs.

From these experiments, we concluded that if Innovar is used for anaesthesia with thiopental, no more should be given after anaesthesia is fully induced, and maintenance requirements should be restricted to supplementary doses of either fentanyl (for analgesia) or thiopental (for hypnosis). When fentanyl is used, one should always be prepared to augment pulmonary ventilation because apnoea is likely to occur shortly after its injection. Benzquinamide has no hypnotic or analgesic properties which would warrant its use during anaesthesia, whereas pentazocine appears quite useful in both these respects and has no apparent side-effects.

RÉSUMÉ

Les auteurs se sont servi d'une méthode standardisée à double contrôle pour déterminer l'effet de quelques nouveaux neuroleptanalgésiques sur la durée du sommeil produit par le thiopental chez des chiens. La dose choisie pour chaque médicament était en deçà de la posologie ordinaire et ne devait donc pas produire de dépression cardio-respiratoire importante. En comparaison avec les cas au thiopental seul, le dropéridol a doublé la durée de la période d'anesthésie et celle du retour à la conscience. Le fentanyl et le pentazocine ont sensiblement eu le même effet, allongeant la période de réveil de 50 à 75 pour cent. L'effet de l'Innovar était plus faible que celui du dropéridol mais beaucoup plus puissant que celui du fentanyl; ces faits mettent en lumière l'action prépondérante du dropéridol dans son association avec le thiopental quant à l'effet hypnotique. Le benzquinamide n'a eu pratiquement aucun effet sur la durée du sommeil produit par le thiopental.

On a observé quelques effets secondaires importants: le dropéridol et l'Innovar causaient ordinairement de la diarrhée le lendemain de l'épreuve, et le fentanyl a produit de brèves périodes d'apnée durant l'expérience chez quelques animaux.

A la suite de ces expériences on peut conclure que si l'Innovar est employé avec du thiopental on ne devrait pas en ajouter après que l'anesthésie est vraiment commencée, et les doses d'entretien doivent être réservées à des quantités supplémentaires soit de fentanyl (pour l'analgesie) soit de thiopental (pour l'hypnose). Quand on emploie le fentanyl on devrait toujours être prêt à assister la ventilation du malade parce que l'apnée peut survenir peu après l'injection du médicament. Le benzquinamide n'a aucun effet tant hypnotique qu'analgesique justifiant son emploi en anesthésie. Pour ce qui est du pentazocine, il semble assez efficace à ce double rôle et n'a aucun effet secondaire apparent.

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