PROPANIDID AND METHOHEXITONE: THEIR COMPARATIVE POTENCY AND NARCOTIC ACTION

BY
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SUMMARY
The paper presents a method of study designed to establish the narcotic potency ratio between the two agents methohexitone and propanidid. Comparisons were made through a range of five doses of each drug such that the smallest dose failed to produce narcosis in 50 per cent of subjects and the largest resulted in over 50 per cent still unresponsive after 6 minutes. By plotting curves relating dose to arousal times a reasonably accurate means of deriving a potency ratio is achieved. The results show methohexitone to be 5.2 times as potent as propanidid in all doses used. Equipotent doses of each drug produce the same duration of anaesthesia. No attempt was made to evaluate final recovery times.

Dundee and Clarke (1964), Goldman and Kennedy (1964), Howells and colleagues (1964), Harnik (1964) and Swerdlow (1965) have recently reported on the use of the new non-barbiturate intravenous narcotic, propanidid (Epontol). Propanidid—a phenoxyl oxyacetic acid (eugenol) derivative—is characterized by its short duration of action, and it seemed appropriate to compare its narcotic potency and duration of action with the barbiturate methohexitone.

METHOD
Two hundred and eighty patients of both sexes between the ages of 16 and 60 years destined for relatively minor in-patient surgery formed the basis of the study. All patients were normotensive and had no clinically detectable pulmonary, cardiovascular or neurological lesion. They were given atropine sulphate 0.6 mg as the sole premedicant and were randomly allotted to one of ten drug and dose groups. The smallest number of patients which could be expected to yield meaningful results was allotted to the groups receiving the smallest and largest doses because these dose ranges were not expected to be of great clinical interest. This permitted the inclusion of a larger number of subjects in the clinically useful dose groups and the determination of a potency ratio in these groups with a higher degree of precision.

In this study, narcosis was defined as occurring when the patient failed to continue a voluntary count-up and also failed to respond to the command "open your eyes", repeated every 10 seconds. The narcosis was thus measured as auditory unresponsiveness and was considered to have ended when the patient responded to this command. Timings began when half the drug had been given.

The doses of the two anaesthetic agents used were determined in a preliminary uncontrolled trial designed to assess the doses of each drug required to maintain narcosis in 50 per cent of the patients for 1, 3 and 4 minutes. The drugs were administered intravenously at a constant rate as follows: propanidid 50 mg/sec.; methohexitone 10 mg/sec.

Potency was defined in terms of the doses of each drug required to keep 50 per cent of the patients unresponsive for 1, 3, and 4 minutes. These doses and their 95 per cent confidence limits were calculated by the Spearman-Kärber method (Finney, 1952).

RESULTS
Figures 1 and 2 display the results of the study. The percentage of patients receiving each dose of methohexitone and propanidid remaining unresponsive is plotted against the time after the anaesthetic injection. In figure 3, the family of log
Dose-response curves for both drugs are plotted in terms of the percentage of patients unresponsive at 1 to 6 minutes after injection. The parallelism of the curves is striking and it would appear that the five doses of propanidid used (2.25, 3.9, 5.0, 7.5 and 11.25 mg/kg) correspond closely in narcotic potency with those of methohexitone (0.47, 0.78, 1.0, 1.5 and 2.25 mg/kg). Table I shows the calculated doses of each drug required to keep 50 per cent of the patients unresponsive for 1, 3 and 4 minutes together with the 95 per cent confidence limits. The potency ratios do not vary significantly with the duration of the narcosis.

### Table I

<table>
<thead>
<tr>
<th></th>
<th>1 minute</th>
<th>3 minutes</th>
<th>4 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propanidid</td>
<td>3.5 (2.8-4.4)</td>
<td>6.8 (6.2-7.5)</td>
<td>9.9 (8.7-10.7)</td>
</tr>
<tr>
<td>Methohexitone</td>
<td>0.64 (0.51-0.79)</td>
<td>1.31 (1.21-1.43)</td>
<td>1.65 (1.50-1.82)</td>
</tr>
<tr>
<td>Potency ratio</td>
<td>Methohexitone/Propanidid</td>
<td>5.5 (3.7-8.6)</td>
<td>5.2 (4.3-6.2)</td>
</tr>
</tbody>
</table>

**Fig. 1**

Duration of unresponsiveness from methohexitone.

**Fig. 2**

Duration of unresponsiveness from propanidid.
PROPANIDID AND METHOHEXITONE: COMPARATIVE POTENCY

Fig. 3

Family of log dose-response curves for methohexitone and propanidid. The percentage of subjects unresponsive 1, 2, 3, 4, 5, and 6 minutes after the midpoint of drug injection is plotted against the dose given.

It may be concluded that methohexitone is 5.2 times more potent than propanidid and with equipotent doses of each drug, the duration of anaesthesia does not differ significantly.

DISCUSSION

All reported work on propanidid has referred to the short duration of its narcotic action and testimony is given about the quicker "final" ("street fitness", "full ambulation", etc.) recovery time as compared with thiopentone and, more appropriately, methohexitone. It is remarkable, however, that only Dundee and Clarke (1964) have attempted to relate comparisons of recovery on a basis of equipotent dose administration. When comparing phenomena of any kind it is essential to establish a common reference frame upon which basis related variables may be assessed.

With this need in mind, the present study was arranged to establish the common denominator based on narcotic action of the two anaesthetic agents. While we were also able to estimate the duration of anaesthesia for the two drugs using equipotent doses, no attempt was made to assess the time taken for the patient to reach the point of complete recovery to normal. Our previous experience in this field (Green et al., 1963) highlighted the difficulties in distinguishing differences in recovery between agents when small doses in the clinical range were used, and in future studies we shall be using comparatively high doses.

The fast rate of detoxication of propanidid (50 per cent of induction dose in 20 minutes) compared with barbiturate (20 per cent per hour) is probably bringing postanaesthetic recovery into a realm where psychic and metabolic responses to anaesthesia and surgery are influences on a patient's demeanour that outlast the survival of narcotic molecules within the body. That is to say, any comprehensive assessment of recovery may be more of a test of a subject's ability to withstand stress than of the residual effects of drug action. Nevertheless, a definitive study of recovery to normal between methohexitone and propanidid based on equipotent dosage is still outstanding in order to establish firmly the clinical impression that propanidid clearance is much quicker than methohexitone.

ACKNOWLEDGEMENT

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REFERENCES


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PUISANCE COMPARATIVE ET ACTION
NARCOTIQUE

SOMMAIRE
Cette article presente une methode d'etude permettant d'établir le rapport de puissance narcotique des 2 agents propanidide et methohexitol. Des comparaisons ont été effectuées en utilisant une série de 5 doses de chacun d’eux, telles que la plus petite de ces doses ne produisait pas de narcose chez plus de 50% des patients, et que la plus grande la provoquait chez plus de 50% des patients chez qui on n’avait pas obtenu de réponse après 6 minutes. En établissant une courbe portant la dose en fonction du temps nécessaire pour obtenir une réponse, on obtient un moyen correct de dériver les rapports de puissance. Les résultats montrent que la méthohexitone est 5,2 fois plus puissante que la propanidine à toutes les doses utilisées.

Des doses de même puissance de chaque agent produisent une anesthésie de même durée. Les auteurs n’ont pas essayé d’évaluer le temps final de récupération.

PROPANIDID UND METHOHEXITONE:
VERGLEICH IHRENL WIRKUNGSSTÄRKE UND
IHRES NARKOTISCHEN EFFEKTES

ZUSAMMENFASSUNG

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