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# Clinical Studies on the Hypnotic Properties of Propazone (5,5-Di-n-propyl-2,4-oxazolidinedione).

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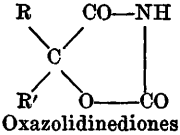
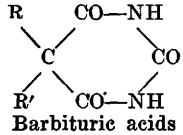
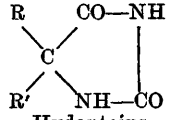
A series of new chemical compounds 5,5-dialkyl-2,4-oxazolidinediones have recently been shown by Stoughton[1] to have hypnotic and anesthetic properties. These are structurally related to the barbituric acids and to the hydantoins and have chemical and physical properties very similar to them.



Oxazolidinediones



Barbituric acids



Hydantoins

Oxazolidinediones are mostly low-melting solids very slightly soluble in water, but on account of the acidic nature of the hydrogen on the nitrogen, they form stable water-soluble sodium and calcium salts, the solutions of which are stable to boiling. As yet, only 2 types of these oxazolidinediones have been studied pharmacologically. In the first, R is methyl, while R′ consists of different alkyl radicals. In the second type, both R and R′ are identical alkyl groups.

All of these substances, when given intravenously to animals, produce a certain degree of anesthesia which is usually of very short duration. Although the different members of these and other types of oxazolidinediones are being investigated further by Stoughton, the di-n-propyl-, to which we have given the tentative name "Propazone", differed so greatly in its effects on animals that it was chosen as the first to be studied more carefully in order to determine if it was suitable for clinical trial. A detailed report of the chemical properties of "Propazone" and its pharmacological actions can be found in the papers by Stoughton[1] and Stoughton and Baxter.[2] This may be briefly summarized as follows:

When dogs were given a sufficient amount of Propazone to produce a state of complete surgical anesthesia (125-175 mg per kg) the anesthesia lasted for about half an hour. During the next 15

[1] Stoughton, submitted for publication.

[2] Stoughton and Baxter, *J. Pharm. and Exp. Therap.*, 1940, **69**, 304.

to 20 hours, the animal remained in a state of deep hypnosis, from which it could not be completely aroused, although reacting to painful stimuli. This was followed by a period of lighter hypnosis, of about the same duration, during which time the animal remained asleep but could be aroused sufficiently to take food and water, although unable to stand and walk about. There was practically no effect on blood pressure or respiration if the drug was slowly injected. No change in the electrocardiogram was observed. Dogs were given intravenously 8 or 10 doses of Propazone, varying in size from 25-250 mg per kg, at intervals varying from 5 days to 2 weeks. Although these animals were completely anesthetized by most of these injections, they all recovered and showed no visible signs of injury or any pathological changes in the blood or urine. They were killed after various intervals and sections made of several tissues but no pathological changes were found.

The smoothness with which anesthesia could be produced, the very prolonged period of hypnosis which followed and the absence of side effects seemed to justify a clinical trial of this substance.

A group of psychiatric patients was chosen for study. All of them were in good physical condition and their behavior was such that modification by the drug could be readily recognized.

As there is practically no latent period before the onset of action of Propazone, the intravenous route of administration was chosen. In this way, it was possible to follow very exactly the effects of definite amounts of the drug and to stop its administration at any moment. A 10% solution of Propazone* as the sodium salt was used in these cases. Amounts varying from 12 mg to 100 mg per kg of body weight were given intravenously at speeds varying from 1.2 to 3.3 cc per minute. In all, 22 intravenous injections were made in 11 patients. The blood pressure, pulse rate and respiratory rate were recorded during the injection and for some time afterwards. No significant change in any of these factors was observed when the drug was injected slowly. If it was injected too rapidly, there was a burning sensation in the arm and an increase in the pulse rate as well as a slight fall of blood pressure, but there was no apparent effect on the respiration. Such signs and symptoms passed off at once if the rate of injection was slowed. Two cubic centimeters per minute seemed to be the optimum injection rate as it caused no untoward effects in any case.

It should be pointed out that a definite fall in blood pressure may

* For the early experiments, this substance was prepared in our laboratory, but was later supplied to us through the kindness of the Mallinckrodt Chemical Works.

occur if the drug is injected too rapidly. This was observed when determining the optimum rate of injection. One patient in whom 44 mg per kg of Sodium Propazone was injected intravenously at a slow rate showed no untoward effects whatever. Ten cubic centimeters more of the 10% solution was injected rapidly and the systolic blood pressure fell from 110 to 80 mm of Hg. The blood pressure was immediately restored by the subcutaneous injection of nikethamide (coramine). This same effect is seen after too rapid injection of other hypnotics and should serve to emphasize the need of caution with regard to the rate of injection.

Drooping of the eyelids occurred with doses of about 5-10 mg per kg. After such amounts of the drug, the patients stated that they were not sleepy, but when left alone, were found to have slept more than normally. With doses of approximately 10 to 20 mg per kg, there was pronounced relaxation, although the patients were readily accessible. After such doses, a sleep of 2 to 5 hours followed. Loss of consciousness usually occurred after the injection of 30-50 mg per kg, but the patient could be aroused by mechanical stimuli, as pinching. If left alone, they slept for 8 to 10 hours. Complete anesthesia from which the patient could not be aroused by mechanical stimuli was obtained with doses of 50-100 mg per kg. These patients could be aroused after a few hours and were able to take food 8 or 10 hours later, but they immediately went back to sleep. One patient remained under the influence of the drug for 30 hours. A summary of the results obtained is given in Table I. No figures are given for the duration of anesthesia or hypnosis as it was impossible to observe all the patients continuously after treatment. (See table.)

These patients were followed for several weeks after treatment and showed no ill effects from the administration of Propazone. The urine was examined for sugar, albumin and casts, and showed no pathological changes.

A small group of epileptics who had been receiving luminal daily were given Sodium Propazone by mouth in doses of 1 g twice daily to replace the luminal. In all instances there was a reduction in number and in severity of attacks. One patient was given an intravenous injection during a convulsion. After about 5 cc of the 10% solution were given, she became completely relaxed and talked to the physician.

A patient with marked choreiform movements associated with episodes of crying and noisiness showed definite improvement in behavior when given the drug by mouth.

TABLE I.

| Patient | Wt, kg | No. of inj. | Dosage, mg/kg | Rate of injection, cc/min | Degree of change during or immediately following injection: Blood pressure, mm of Hg | Pulse per min | Respiration per min |
|---|---|---|---|---|---|---|---|
| 1 | 80 | 1 | 100 | 2.0 | 106/60-128/76 | 74-96 | 20-23 |
| 2 | 57 | 2 | 61 | 3.3 | 118/74-80/50 | 110-82 | 18-15 |
| | | | 37 | 1.2 | 120/70-106/70 | 87-96 | 20 |
| 3 | 64 | 1 | 34 | 1.1 | 120/80-117/76 | 78-88 | 18-17 |
| 4 | 47 | 1 | 81 | 1.8 | 88/56-108/70 | 75-86 | 22-18 |
| 5 | 57 | 2 | 100 | 2.1 | 90/58-108/72 | 90-110 | 20-18 |
| | | | 53 | 2.1 | 110/70-106/68 | 86-97 | * |
| 6 | 83 | 7 | 12 | 2.9 | 120/56-116/50 | 84-72 | 18-20 |
| 7 | 64 | 1 | 17 | 3.3 | 104/68-102/62 | 68-72 | * |
| 8 | 65 | 3 | 38 | 2.2 | 116/68-110/66 | 84-69 | 18-17 |
| | | | 19 | 1.9 | 112/70-108/60 | 82-80 | * |
| | | | 31 | 2.3 | 122/74-118/74 | 80-84 | * |
| 9 | 47 | 1 | 21 | 1.2 | 118/70-112/68 | 82-90 | * |
| 10 | 44 | 1 | 42 | 2.3 | 100/66-104/70 | 92 | * |
| 11 | 50 | 2 | 60 | 2.0 | 100/66-104/71 | 88-92 | 20-18 |
| | | | 40 | — | — | — | — |

*Not taken.

*Conclusions.* Propazone (5,5-dipropyl-2,4-oxazolidinedione) has been given intravenously and by mouth to a group of patients. All stages of hypnosis and anesthesia have been produced without ill effects. The absence of side reactions, the striking degree of relaxation which comes on in even the early stages of hypnosis and its long duration of action indicate that this substance might be of therapeutic value. Its use in epilepsy is being investigated.