EFFECT OF PROPIOMAZINE, PERPHENAZINE, PROMETHAZINE AND PROMAZINE ON ADRENALINE-INDUCED VENTRICULAR ARRHYTHMIAS DURING NITROUS OXIDE-HALOTHANE ANAESTHESIA IN THE DOG

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SUMMARY

Ventricular tachycardia was produced in the dog by intravenous injection of 2–3 μg/kg of adrenaline during nitrous oxide-halothane anaesthesia. On a weight basis, propiomazine was found to be as effective as perphenazine in preventing the arrhythmias. Promethazine and promazine showed similar effects in much higher doses. The protection provided by all these drugs could be surmounted by doses of adrenaline of 4–6 μg/kg. Propiomazine did not produce any action on blood pressure whereas the other drugs tested produced a prolonged fall in pressure in all the experiments. Since the clinical dose of propiomazine is 2–4 times that of perphenazine, it is possible that the former may prove superior to the latter in clinical trials.

The occurrence of adrenaline-induced ventricular arrhythmias under halothane anaesthesia in the dog and in man is well documented (Raventós, 1956; Hall and Norris, 1958; Millar, Gilbert and Brindle, 1958; Johnstone and Nisbet, 1961; Andersen and Johansen, 1963). Raventós (1956) reported that chlorpromazine did not completely prevent these arrhythmias in the dog. Recently, perphenazine has been found to be an effective antagonist in the dog and in man (Dobkin and Purkin, 1959; Rollason, 1964). This drug, however, may cause falls in blood pressure and preoperative restlessness has been reported by Dundee and associates (1965). These workers reported that the newer phenothiazine derivative, propiomazine, has a lesser tendency to cause these undesirable side effects. This drug is also claimed to be a more effective sedative than promethazine (Lipson and Parker, 1965).

A study was, therefore, undertaken to investigate the effectiveness of propiomazine in adrenaline-induced arrhythmias in the dog during nitrous oxide-halothane anaesthesia, and to compare its action with that of perphenazine, promethazine and promazine. These drugs are commonly used in pre-anaesthetic medication.

METHODS

The experiments were performed on 28 mongrel dogs of both sexes weighing between 9 and 24 kg. The trachea was intubated, after giving intravenous thiopentone sodium 15 mg/kg, and anaesthesia was maintained with a mixture of 50 per cent nitrous oxide and oxygen, in a non-rebreathing circuit with Ruben valve. The respiration was spontaneous. When anaesthesia was established, atropine sulphate 0.01 mg/kg was injected intravenously.

Blood pressure was measured with a mercury manometer in the cannulated right common carotid artery. The right femoral vein was exposed to give direct intravenous injection of drugs. Electrocardiograms lead II were recorded with a Galileo direct-writing electrocardiograph. Fifteen minutes were allowed after the operative procedure to let the arterial pressure and heart rate reach a stable level.

The drugs used were propiomazine hydrochloride, perphenazine hydrochloride, promethazine hydrochloride and promazine hydrochloride. All the drug solutions were prepared fresh (1 per cent w/v in 0.9 per cent sodium chloride) on the day of each experiment.

Production of ventricular arrhythmias.

Halothane was administered from a Fluotec Mark II vaporizer in a concentration of 1 per cent in all the experiments. This produced a gradual
fall in arterial pressure which reached a stable level in 10–15 minutes. Adrenaline hydrochloride (2–3 \( \mu g/kg \)) was then injected intravenously (0.01 per cent solution, injected in 10 seconds). This produced ventricular tachycardia, usually multifocal, in all the experiments. The effect of adrenaline completely disappeared within 3 minutes.

The test drugs were then injected intravenously slowly over a period of 5 minutes (under identical ventilatory conditions), and the injection of adrenaline was repeated after another 5 minutes. If the arrhythmia was not completely prevented, another dose of the test drug was given, and the injection of adrenaline repeated. When the arrhythmia was completely prevented, the dose of adrenaline was increased (4–6 \( \mu g/kg \)) to see if this protection was surmountable or not.

**RESULTS**

*Propiomazine hydrochloride.*

In two experiments, 0.05 mg/kg provided incomplete protection against halothane-adrenaline arrhythmias. Ventricular extrasystoles or ventricular bigeminy was invariably seen at the height of the pressor response. A second dose of 0.05 mg/kg completely prevented the arrhythmia.

A single dose of propiomazine 0.1 mg/kg prevented ventricular arrhythmia in each of five experiments. Injection of a larger dose of adrenaline (4–6 \( \mu g/kg \)) produced ventricular extrasystoles or ventricular bigeminy in all the experiments. Propiomazine produced no effect on arterial pressure in any of these experiments.

A typical experiment is illustrated in figure 1. Injection of adrenaline 3 \( \mu g/kg \) during nitrous oxide-halothane anaesthesia produced multifocal...
Illustrating the prevention of adrenaline-induced ventricular tachycardia by perphenazine during nitrous oxide-halothane anaesthesia. Lead II. Chart speed = 25 mm/sec.

A: Heart rate during nitrous oxide-oxygen-halothane anaesthesia is 144 beats/min.
B, C: These two strips are continuous. Adrenaline 3 μg/kg injected intravenously produced multifocal ventricular tachycardia.
D: Before perphenazine administration, the heart rate is 144 beats/min.
E: After the injection of perphenazine 0.1 mg/kg, the heart rate is 132 beats/min.
F: Intravenous injection of 3 μg/kg of adrenaline 5 min after perphenazine administration increased the heart rate to 138 beats/min but did not produce ventricular arrhythmia.
G: A larger dose of adrenaline (6 μg/kg) produced slow rate ventricular arrhythmia.

ventricular tachycardia (strips B and C). Promethazine 0.1 mg/kg injected intravenously prevented the development of this arrhythmia (strip F). A larger dose of adrenaline (6 μg/kg) produced a few ventricular extrasystoles and ventricular bigeminy and trigeminy (strip G).

**Perphenazine hydrochloride.**

In two experiments, 0.05 mg/kg provided incomplete protection against adrenaline-induced ventricular arrhythmias. A second dose of 0.05 mg/kg prevented the arrhythmia in both the experiments.

A single dose of 0.1 mg/kg was also effective in each of five experiments. Perphenazine produced a prolonged fall in arterial pressure in all the experiments (mean 23.8 mm Hg, range 18–32).

A typical experiment is illustrated in figure 2.

Adrenaline 3 μg/kg injected intravenously produced multifocal ventricular tachycardia (strips B and C). Perphenazine 0.1 mg/kg injected intravenously prevented this arrhythmia (strip F). A larger dose of adrenaline (6 μg/kg) produced only slow rate ventricular arrhythmia (strip G).

**Promethazine hydrochloride.**

In two experiments, 2.5 mg/kg provided incomplete protection against adrenaline-induced ventricular arrhythmias. Ventricular extrasystoles were seen in both the experiments. A second dose of promethazine 0.5 mg/kg prevented the development of this arrhythmia.

In another five experiments, a single dose of 3 mg/kg prevented the development of adrenaline-induced ventricular arrhythmias. There was a prolonged fall in blood pressure following pro-
EFFECT OF PROPIOMAZINE, ETC., ON VENTRICULAR ARRHYTHMIAS

Promazine administration in all the experiments (mean 29.5 mm Hg, range 20–44).

A typical experiment is illustrated in figure 3. Intravenous injection of adrenaline 2 μg/kg during nitrous oxide-oxygen-halothane anaesthesia produced multifocal ventricular tachycardia. Promethazine 2.5 mg/kg injected intravenously reduced the severity of the arrhythmia (strip D). Adrenaline injection now produced ventricular bigeminy. An additional dose of 0.5 mg/kg of promethazine prevented the development of this arrhythmia (strip E). A larger dose of adrenaline (4 μg/kg) produced ventricular tachycardia (strip F).

Promazine hydrochloride.

In two experiments, 2 mg/kg reduced the severity of the ventricular arrhythmia evoked by adrenaline injection. An additional dose of 0.5 mg/kg prevented the development of the arrhythmia.

In another five experiments, a single dose of 2.5 mg/kg of promazine prevented the development of ventricular tachycardia. There was a prolonged fall in blood pressure following promazine administration in all the experiments (mean 17 mm Hg, range 12–20).

A typical experiment is illustrated in figure 4. Adrenaline injection 3 μg/kg produced multifocal ventricular tachycardia (strips B and C). Promazine 2.5 mg/kg prevented the development of this arrhythmia (strip F). A larger dose of adrenaline (6 μg/kg) produced a transient run of ventricular tachycardia (strip G).

The results obtained in all the experiments in this study are presented in table I.
FIG. 4
Illustrating the prevention of adrenaline-induced ventricular tachycardia by promazine during nitrous oxide-oxygen-halothane anaesthesia. Lead II. Chart speed = 25 mm/sec.
A: Heart rate during nitrous oxide-halothane anaesthesia is 125 beats/min.
B, C: These two strips are continuous. Adrenaline 3 \( \mu g/kg \) injected intravenously produced ventricular tachycardia of multifocal origin.
D: Heart rate before the administration of promazine is 116 beats/min.
E: Following the intravenous injection of promazine 2.5 mg/kg, the heart rate is 102 beats/min.
F: This strip was recorded 5 min after the administration of promazine. Adrenaline 3 \( \mu g/kg \) produced no ventricular arrhythmia. The heart rate was increased to 184 beats/min.
G: A large dose of adrenaline (6 \( \mu g/kg \)) injected intravenously increased the heart rate to 192 beats/min and produced a short run of ventricular tachycardia.

TABLE I
Comparative effectiveness of intravenously injected propiomazine, promethazine, perphenazine and promazine in ventricular arrhythmias induced by adrenaline during nitrous oxide-halothane anaesthesia in the dog.

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of expts.</th>
<th>Dose (mg/kg)</th>
<th>Effect on ventricular arrhythmia</th>
<th>Effect on arterial pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propiomazine</td>
<td>2</td>
<td>0.05</td>
<td>Incomplete protection*</td>
<td>None</td>
</tr>
<tr>
<td>Propiomazine</td>
<td>5</td>
<td>0.1</td>
<td>Protection†</td>
<td>None</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>2</td>
<td>0.05</td>
<td>Incomplete protection</td>
<td>Fall</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>5</td>
<td>0.1</td>
<td>Protection</td>
<td>Fall</td>
</tr>
<tr>
<td>Promethazine</td>
<td>2</td>
<td>2.5</td>
<td>Incomplete protection</td>
<td>Fall</td>
</tr>
<tr>
<td>Promethazine</td>
<td>5</td>
<td>3.0</td>
<td>Protection</td>
<td>Fall</td>
</tr>
<tr>
<td>Promazine</td>
<td>2</td>
<td>2.0</td>
<td>Incomplete protection</td>
<td>Fall</td>
</tr>
<tr>
<td>Promazine</td>
<td>5</td>
<td>2.5</td>
<td>Protection</td>
<td>Fall</td>
</tr>
</tbody>
</table>

*Incomplete protection indicates that adrenaline produced ventricular extrasystoles or ventricular bigeminy or trigeminy.
†Protection indicates that normal sinus rhythm was not disturbed by adrenaline injection.
DISCUSSION

In spontaneously ventilating dogs, intravenous injection of adrenaline 2-3 μg/kg during nitrous oxide-oxygen-halothane anaesthesia produced multifocal ventricular tachycardia in all the experiments. Propiomazine hydrochloride 0.1 mg/kg prevented the development of this arrhythmia. On a weight basis, propiomazine was as potent as perphenazine hydrochloride but was much more potent than promethazine hydrochloride and promazine hydrochloride. After administration of these drugs, injection of large doses of adrenaline 4-6 μg/kg produced only slow rate ventricular arrhythmia or ventricular extrasystoles. This showed that the protection provided by these drugs can be surmounted.

One distinct advantage of propiomazine over the other drugs studied was that it did not affect the arterial pressure. Since hypotension is a very frequent and troublesome side effect of phenothiazine derivatives (Dundee et al., 1965), this lack of hypotensive effect in the case of propiomazine is an important advance. It is suggested that propiomazine merits controlled clinical trial to ascertain its value in preventing arrhythmias during anaesthesia.

The clinical dose of propiomazine (20–40 mg) is 2-4 times that of perphenazine (10 mg), and on this basis it is possible that propiomazine may in practice prove superior to perphenazine.

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REFERENCES


ZUSAMMENFASSUNG