SELECTIVE ADRENERGIC BETA-RECEPTOR BLOCKADE IN THE PREVENTION OF ADRENALINE-EVOKED VENTRICULAR ARRHYTHMIAS IN DOGS ANAESTHETIZED WITH HALOTHANE IN OXYGEN

BY

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SUMMARY

The effect of selective beta-receptor blockade on adrenaline-evoked ventricular arrhythmias was studied in atropinized dogs anaesthetized with halothane in oxygen. Cardiac beta-receptors were selectively blocked with ICI 50172, while the peripheral vascular beta-receptors were selectively blocked with H 35/25. ICI 50172 prevented adrenaline-evoked ventricular arrhythmias and the increase in sinus rate produced by adrenaline. The blockade produced was surmountable, larger doses of adrenaline increasing the rate of sinus rhythm and then ventricular arrhythmias followed. In contrast H 35/25 showed only a weak anti-arrhythmic activity. This action appears to be non-specific, since the increase in sinus rate caused by adrenaline was only partially prevented by H 35/25. The results are in agreement with the concept that ICI 50172 blocks excitatory beta-receptors, while H 35/25 blocks inhibitory beta-receptors.

Adrenergic beta-receptor blocking agents, viz. dichloroisoproterenol, pronethalol, propranolol, MJ 1999 and INPEA, have been used successfully in the management of adrenaline-evoked ventricular arrhythmias in the dog, cat and in man (Schull, Berry and Villarheal, 1961; Moran et al., 1962; Murray, McKnight and Davis, 1963; Hess and Hampton, 1964; Johnstone, 1964; Lucchesi, 1964; Payne and Senfield, 1964; Somani and Lum, 1965; Hellewell and Potts, 1965; Sharma, 1966, 1967a, b). All these drugs block the cardiac, peripheral vascular, uterine and bronchial beta-receptors simultaneously.

Some recently synthesized drugs, e.g. H 35/25 and butoxamine, are reported to block selectively the peripheral vascular and uterine beta-receptors when given in doses which have little or no effect on cardiac beta-receptors (Levy, 1966, 1967). This indicates that beta-receptors are complex, and are divisible into subgroups. Dunlop and Shanks (1968) studied a new compound ICI 50172, 4-(2-hydroxy-3-isopropylaminopropoxy) acetic acid hydrochloride. In contrast to propranolol which blocks beta-receptors in all the tissues simultaneously, ICI 50172 selectively blocked beta-receptors in the myocardium when administered in doses which had little effect on peripheral vascular and bronchial beta-receptors.

In the present study, the effect of selective blockade of beta-receptors by ICI 50172 and H 35/25 on the adrenaline-evoked ventricular arrhythmias was studied in dogs anaesthetized with halothane in oxygen.

METHODS

The experiments were performed on 16 mongrel dogs of either sex (weight 6–19 kg). The trachea was intubated under thiopentone anaesthesia (15 mg/kg i.v.) and anaesthesia was maintained with halothane in oxygen, using a semiclosed rebreathing circuit with a to-and-fro soda-lime absorber. Halothane was vaporized in a Fluotec Mark II halothane vaporizer (set to deliver 1 per cent) which was incorporated in the circuit. The fresh gas flow rate was 800–1000 ml/min. Ventilation was spontaneous. Atropine sulphate 0.01 mg/kg was injected intravenously to prevent excessive bronchial secretions.

Mean blood pressure was recorded from the cannulated right common carotid artery using a mercury float manometer. The right femoral vein was exposed to permit direct intravenous injections of drugs, using an indwelling 24-gauge

A: Heart rate during stable halothane anaesthesia 152 beats/min.
B: 12 sec after intravenous injection of adrenaline 3 µg/kg. Heart rate increased to 158 beats/min followed by a short run of ventricular tachycardia and finally ventricular bigeminy.
C: 3 min after adrenaline. Heart rate again 152 beats/min.
D–F: 15, 16 and 21 min respectively after ICI 50172 0.3 mg/kg. Heart rate decreased to 114 beats/min (excerpt D). Fourteen sec after adrenaline 3 µg/kg, heart rate is 125 beats/min but there is no arrhythmia (excerpt E). Twelve sec after adrenaline 4.5 µg/kg, heart rate increased to 150 beats/min and followed by multifocal ventricular extrasystoles, ventricular tachycardia and finally ventricular bigeminy resulted (excerpt F).
G: 26 min after ICI 50172. Heart rate 118 beats/min.
H–J: 15, 16 and 21 min respectively after second dose of ICI 50172 0.3 mg/kg. Heart rate now 108 beats/min (excerpt H). 14 sec after adrenaline 4.5 µg/kg, heart rate increased to 122 beats/min without ventricular arrhythmia (excerpt I). 12 sec after adrenaline 6 µg/kg, heart rate increased to 146 beats/min followed by ventricular tachycardia and ventricular bigeminy (excerpt J).
K: 27 min after second dose of ICI 50172. Heart rate now 108 beats/min.
L–N: 15, 16 and 21 min respectively after third dose of ICI 50172 0.3 mg/kg, heart rate 108 beats/min (excerpt L). 15 sec after adrenaline 6 µg/kg, no increase in heart rate or development of ventricular arrhythmia (excerpt M). 12 sec after adrenaline 9 µg/kg, heart rate increased to 166 beats/min and followed by ventricular bigeminy (excerpt N).
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Production of ventricular arrhythmias with adrenaline.

Adrenaline challenges were started after a 30-min period of stabilization on about 1 per cent halothane. Starting with 1 μg/kg the dose of adrenaline was gradually increased until ventricular tachycardia was produced. Three control runs of arrhythmia were recorded at 5-min intervals, and then the test-drug was administered intravenously slowly over a period of 5 min. The adrenaline challenge was repeated 15 min after the injection of test-drugs to allow the intrinsic sympathomimetic activity to subside. If the adrenaline-evoked ventricular arrhythmia was not prevented, a second dose of test-drug was injected as above and the adrenaline challenge repeated. If the arrhythmia was prevented by the test-drug, the dose of adrenaline was gradually increased until it again produced ventricular arrhythmia.

Student's t test was used to evaluate the significance of the results obtained.

RESULTS

Adrenaline-evoked ventricular arrhythmias during halothane anaesthesia.

The mean dose of adrenaline required to produce ventricular arrhythmia varied between 2 and 3 μg/kg. Adrenaline first increased the rate of sinus rhythm, and this was followed by ventricular extrasystoles, ventricular bigeminy and ventricular tachycardia. The effect of a single dose of adrenaline passed off within 3 min. Therefore, adrenaline challenges were repeated at 5-min intervals.

Effect of ICI 50172 on adrenaline-evoked ventricular arrhythmias.

In three dogs, 0.3 mg/kg was injected intravenously. The drug produced a transient fall in mean arterial pressure (mean 7.0, range 4–12 mm Hg), which lasted for 5–10 min. The rate of sinus rhythm was decreased (mean 21, range 18–30 beats/min). The threshold of adrenaline-evoked ventricular arrhythmia was increased from 2.40 (SD 0.54) to 6.80 (SD 3.24) μg/kg. This apparent increase in threshold was not statistically significant (P>0.05). The increase in sinus rate produced by adrenaline was reduced but not blocked by ICI 50172 0.3 mg/kg; it was completely blocked by 0.9 mg/kg. Larger doses of adrenaline broke through this block, and an increase in sinus rate always preceded the development of ventricular arrhythmias. A typical experiment is illustrated in figure 1. In this experiment, 0.3 mg/kg blocked the arrhythmia produced by adrenaline 3 μg/kg, but the increase in sinus rate produced by adrenaline was only partially blocked. A total dose of 0.9 mg/kg of ICI 50172 prevented both the ventricular arrhythmia and the increase in sinus rate produced by adrenaline (excerpt M). A larger dose of adrenaline increased the sinus rate and then produced ventricular bigeminy (excerpt N).

In five other dogs, ICI 50172 0.9 mg/kg was injected intravenously as a single dose. This was followed by a fall in mean arterial pressure (mean 15.8, range 10–22 mm Hg), which almost returned to the baseline within 10–15 min. There was also a definite decrease in heart rate (mean 32.6, range 22–46 beats/min). The mean dose of adrenaline causing ventricular arrhythmia was increased from 2.40 (SD 0.49) to 9.60 (SD 1.36) μg/kg. This increase in threshold is highly significant (P<0.001). The increase in sinus rate was also blocked. Larger doses of adrenaline first caused an increase in sinus rate and then ventricular arrhythmia followed. A typical experiment is illustrated in figure 2. In this experiment 0.9 mg/kg increased the arrhythmia-evoking dose of adrenaline from 2 μg/kg to 6 μg/kg (excerpts B and C).

Effect of H 35/25 on adrenaline-evoked ventricular arrhythmia.

In three dogs, 5 mg/kg injected intravenously produced a fall in mean arterial pressure (mean 13.0, range 8–20 mm Hg), which lasted for less than 10 min. There was also some decrease in heart rate (mean 18, range 12–32 beats/min). Adrenaline challenge caused an increase in sinus rate and ventricular arrhythmia. The effect of

A: Heart rate under halothane anaesthesia 146 beats/min.
B: 14 sec after injection of adrenaline 2 µg/kg, heart rate increased to 186 beats/min with paroxysms of ventricular tachycardia.
C: 3 min after adrenaline, heat rate again 146 beats/min.
D–H: 15, 16, 21, 26 and 31 min respectively after ICI 50172 0.9 mg/kg, heart rate now 124 beats/min (excerpt D). 15 sec after adrenaline 2 µg/kg, no increase in heart rate and no ventricular arrhythmia (excerpt E). 15 sec after adrenaline 4 µg/kg, heart rate increased to 126 beats/min but no ventricular arrhythmia followed (excerpt F). 15 sec after adrenaline 6 µg/kg, heart rate increased to 152 beats/min and followed by multifocal ventricular extrasystoles and a short run of ventricular tachycardia (excerpt G). 15 sec after adrenaline 8 µg/kg, heart rate increased to 168 beats/min with development of ventricular tachycardia (excerpt H).

adrenaline on sinus rate and the ventricular arrhythmia evoked by it was not prevented even with a total dose of 15 mg/kg of H 35/25. However, the severity of the arrhythmia caused by adrenaline was reduced. Before the drug, adrenaline always evoked ventricular tachycardia but, after injection of H 35/25, adrenaline caused only ventricular extrasystoles and ventricular bigeminy. A typical experiment is illustrated in figure 3. In this experiment, adrenaline 3 µg/kg was followed by ventricular tachycardia (excerpt B). The effect of this dose of adrenaline was reduced but not prevented by a total dose of 15 mg/kg of H 35/25. Adrenaline now produced a smaller increase in heart rate and ventricular bigeminy (excerpt K).

In a further five dogs, 15 mg/kg of H 35/25 was injected intravenously as a single dose. The drug produced a fall in mean arterial pressure (mean 23.4, range 18–34 mm Hg), and a definite decrease in heart rate (mean 34, range 25–42 beats/min). The mean dose of adrenaline required

A: Heart rate under halothane anaesthesia 162 beats/min.
B: 12 sec after intravenous injection of 3 μg/kg of adrenaline. Ventricular tachycardia resulted.
C: 3 min after adrenaline, heart rate 166 beats/min.
D–E: 15 and 16 min respectively after H 35/25 5 mg/kg, heart rate now 144 beats/min (excerpt D). 12 sec after adrenaline 3 μg/kg, ventricular extrasystoles, ventricular bigeminy and finally ventricular tachycardia followed (excerpt E).
F: 21 min after H 35/25, heart rate 150 beats/min.
G–H: 15 and 16 min respectively after second dose of H 35/25 5 mg/kg, heart rate now 144 beats/min (excerpt G). 12 sec after adrenaline 3 μg/kg, heart rate increased to 150 beats/min, followed by ventricular bigeminy and later ventricular extrasystoles (excerpt H).
I: 21 min after second dose of H 35/25, heart rate 148 beats/min.
J–K: 15 and 16 min respectively after third dose of H 35/25 5 mg/kg, heart rate now 144 beats/min (excerpt J). 12 sec after adrenaline 3 μg/kg, heart rate increased to 150 beats/min, followed by ventricular bigeminy and later ventricular extrasystoles.

Note that even in a total dose of 15 mg/kg, H 35/25 did not completely prevent the increase in heart rate caused by adrenaline 3 μg/kg. The severity of the ventricular arrhythmias was, however, reduced.
to evoke ventricular arrhythmia was increased from 2.60 (SD 0.55) to 3.90 (SD 1.32) \( \mu g/kg \). This increase in threshold is not statistically significant (P>0.05). The increase in heart rate produced by adrenaline was reduced but not blocked by H 35/25. A typical experiment is illustrated in figure 4. In this experiment, H 35/25 15 mg/kg injected intravenously increased the arrhythmia-evoking dose of adrenaline from 2 \( \mu g/kg \) to 3 \( \mu g/kg \) (excerpts B and F). The increase in heart rate produced by adrenaline was reduced but not blocked (excerpt F).

The results of all the experiments performed with ICI 50172 and H 35/25 are summarized in table I. Note that a significant increase in threshold of adrenaline-evoked ventricular arrhythmia was only produced by 0.9 mg/kg of ICI 50172.

![Figure 4](image_url)

**FIG. 4**


A: Heart rate under halothane anaesthesia 174 beats/min.
B: 12 sec after intravenous injection of adrenaline 2 \( \mu g/kg \), ventricular bigeminy resulted.
C: 3 min after adrenaline, heart rate 176 beats/min.
D–F: 15, 16 and 21 min respectively after H 35/25 15 mg/kg, heart rate now 120 beats/min (excerpt D). 15 sec after adrenaline 2 \( \mu g/kg \), heart rate increased to 138 beats/min but no ventricular arrhythmia. Note that increase in heart rate caused by adrenaline 2 \( \mu g/kg \) has been only partially prevented by H 35/25 15 mg/kg (excerpt E). 12 sec after adrenaline 3 \( \mu g/kg \), heart rate increased to 142 beats/min and ventricular bigeminy and later ventricular extrasystoles resulted (excerpt F).

**TABLE I**

*The arrhythmia was not prevented but its severity was reduced. Before the drug, adrenaline produced ventricular tachycardia, while after the drug it produced only ventricular bigeminy and ventricular extrasystoles.*
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DISCUSSION
In this study, ICI 50172, a drug which has been shown by Dunlop and Shanks (1968) to have a selective blocking action on the cardiac beta-receptors, antagonized adrenaline-evoked ventricular arrhythmias in dogs under halothane anaesthesia. This blockade appears to be surmountable, because larger doses of adrenaline were able to re-evoke ventricular arrhythmias. An increase in the rate of sinus rhythm (a beta-receptor effect) always preceded the development of ventricular arrhythmias. In contrast, H 35/25, a drug which has been shown by Levy (1967) to block the peripheral vascular beta-receptors selectively, failed to prevent adrenaline-evoked ventricular arrhythmias. When the dose of H 35/25 was increased to 15 mg/kg a slight but statistically insignificant increase in the threshold of adrenaline-evoked ventricular arrhythmia was seen. This weak anti-arrhythmic activity appears to be non-specific, since the increase in sinus rate produced by adrenaline was only partially blocked by H 35/25. Also, Levy (1967) showed that this drug reduced the positive inotropic action of catecholamines as well as that of calcium chloride. This indicates that its action upon the heart is non-specific.

Ahlquist (1948) demonstrated that excitatory responses elicited by catecholamines result from activation of alpha-receptors whilst the inhibitory responses resulted from activation of beta-receptors. The one exception to this hypothesis was the positive inotropic and positive chronotropic responses to catecholamines, which are excitatory, but have been categorized as beta-receptor effect. Levy (1967) showed that H 35/25 has a selective blocking action on the peripheral vascular beta-receptors, which is an inhibitory beta-receptor effect. Dunlop and Shanks (1968) showed that ICI 50172 selectively blocked the cardiac responses to catecholamines, which is excitatory beta-receptor effect. It has been suggested that beta-receptors may be divided into two subgroups, namely excitatory and inhibitory (Levy, 1967; Dunlop and Shanks, 1968).

The selective blockade by ICI 50172 of the cardiac beta-receptors may offer a distinct advantage over classical beta-receptor antagonists (dichloroisoproterenol, pronethalol, propranolol, MJ 1999, INPEA, etc.), which block beta-receptors in all the tissues simultaneously. Blockade of bronchial beta-receptors is known to reduce ventilatory function in asthmatic patients, and an acute attack of asthma may be precipitated (McNeill, 1964; McNeill and Ingram, 1966; Stephen, 1966). Dunlop and Shanks (1968) showed that ICI 50172 does not block bronchial beta-receptors. Thus, in clinical practice ICI 50172 is unlikely to precipitate asthma. Also, the pressor response to adrenaline was not potentiated by ICI 50172 (Dunlop and Shanks, 1968). It may be safer to use this drug in hypertensive patients.

In the present study, ICI 50172 has been shown to increase the threshold of adrenaline-evoked ventricular arrhythmias. The effect produced by 0.3 mg/kg was not statistically significant. Thus the action of ICI 50172 is weaker than that of propranolol, which undoubtedly is the most potent beta-receptor antagonist currently available. Sharma (1966, 1967a) showed that specific blockade of beta-receptors was responsible for the anti-arrhythmic activity of classical beta-receptor antagonists. The results obtained by producing a selective blockade of cardiac beta-receptors with ICI 50172, adds further support to this view.

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