EFFECT OF OXPRENOLOL ON ADRENALINE-EVOKED VENTRICULAR ARRHYTHMIAS IN DOGS ANAESTHETIZED WITH HALOTHANE IN OXYGEN

BY

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SUMMARY

The effect of oxprenolol (CIBA 39,089-Ba), a recently introduced adrenergic beta-receptor antagonist, on adrenaline-evoked ventricular arrhythmias was studied in atropinized dogs anaesthetized with halothane in oxygen. The anti-arrhythmic activity of oxprenolol was due to specific blockade of beta-receptors. The block produced was surmountable in nature and larger doses of adrenaline re-evoked ventricular arrhythmias. Its potency was very similar to that of propranolol. However, in contrast to propranolol, oxprenolol administration following electrical defibrillation of the heart did not precipitate cardiocirculatory collapse. In this respect oxprenolol may have important therapeutic advantages over propranolol.

In recent years, adrenergic beta-receptor antagonists are being used increasingly in the management of a wide variety of cardiac diseases. The danger of inducing or aggravating heart failure by these drugs remains a matter of concern (Stephen, 1966). The depressant action of propranolol on myocardial contractility sometimes leads to serious complications, with fatal outcome in isolated cases (Fleckenstein et al., 1964; Vogel, 1965; Lüthy and Hegglin, 1966; Scheu, 1966). Sharma (1967) showed that in dogs under halothane anaesthesia, administration of propranolol following electrical defibrillation of the heart resulted in severe cardiocirculatory collapse. This risk undoubtedly remains an important drawback to the use of propranolol.

Oxprenolol (Trasicor, CIBA 39,089-Ba) is a recently introduced specific beta-receptor antagonist. In clinical trials, this drug has been reported to produce a negative chronotropic effect similar to that of propranolol, but with significantly less marked depression of myocardial contractility (Grandjean and Rivier, 1966, 1968). It was, therefore, considered desirable to study the effect of oxprenolol on (a) halothane-adrenaline-induced ventricular arrhythmias and (b) heart rate and blood pressure following electrical defibrillation of the heart. This study shows that oxprenolol has anti-arrhythmic activity fairly similar to that of propranolol, but exhibits a significantly less negative inotropic activity.

METHODS

The experiments were performed on seventeen mongrel dogs of either sex, weighing 8-20 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 arterial 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 injection of drugs, using an indwelling 24-gauge needle. Electrocardiograms (lead II) were recorded on a Galileo direct writing electrocardiograph. Drugs used were oxprenolol hydrochloride [1-isopropyl-amino-2-hydroxy-3- (o-allyloxy) phenoxy propane hydrochloride], and adrenaline hydrochloride. Figure 1 shows the chemical structures of oxprenolol and propranolol. The

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drug solutions were prepared fresh in 0.9 per cent sodium chloride solution, the dosages refer to the weight of salts.

\[
\text{OXPRENOLOL} \\
\begin{array}{c}
\text{CH}_3 \\
\text{O} \\
\text{O-CH}_2\text{CH=CH}_2
\end{array}
\]

\[
\text{PROPRANOLOL} \\
\begin{array}{c}
\text{CH}_3 \\
\text{O} \\
\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2
\end{array}
\]

**FIG. 1**  
Chemical structure of oxprenolol and propranolol.

Production of ventricular arrhythmias with adrenaline.

Adrenaline challenges were started after a 30-min period of equilibration on about 1 per cent halothane. Starting with 1 \(\mu\)g/kg the dose of adrenaline was gradually increased until ventricular arrhythmia resulted. Three control runs of arrhythmia were recorded at 5-min intervals, and then the test drug was administered intravenously over a 5-min period. The adrenaline challenge was repeated 15 min after the injection of the test drug to allow the intrinsic sympathomimetic activity to subside. If the adrenaline-evoked arrhythmia was not prevented, a second dose of the 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.

Production of ventricular fibrillation with adrenaline and electrical defibrillation.

Ventricular fibrillation was produced in six dogs by intravenous injection of 5 \(\mu\)g/kg of adrenaline during halothane anaesthesia. As soon as ventricular fibrillation developed a left thoracotomy was performed, pulmonary ventilation being maintained artificially, and the arrhythmia terminated by one or more applications of electric shocks to the heart (50 cycles a.c., 150 V; 0.15 sec duration). A Bircher cardiac defibrillator was used for this purpose. In all the six experiments, normal sinus rhythm returned following successful application of electric shock. The chest was closed in layers, the pneumothorax reduced and spontaneous respiration was restored. The effect of oxprenolol 0.3 mg/kg injected as above on the arterial pressure and heart rate was then studied.

**RESULTS**

Adrenaline-evoked ventricular arrhythmias during halothane anaesthesia.

The mean dose of adrenaline required to produce ventricular arrhythmia in each experiment varied between 2 and 3 \(\mu\)g/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.

No tachyphylaxis developed to adrenaline for 4 hours when a 5-min time cycle was used. Longer periods were not studied.

Effect of oxprenolol on adrenaline-evoked ventricular arrhythmias.

In three dogs, oxprenolol 0.2 mg/kg produced a decrease in sinus rate (mean 13, range 8–16 beats/min). There was no change in the arterial pressure. The threshold of adrenaline-evoked ventricular arrhythmias was increased from 2.34 (SD 0.60) to 4.00 (SD 1.41) \(\mu\)g/kg. This effect was, however, not significant (P>0.05). The increase in sinus rate produced by adrenaline was reduced but not prevented by oxprenolol 0.2 mg/kg. It was completely prevented by 0.3 mg/kg of oxprenolol. A typical experiment is illustrated in figure 2.

A: Heart rate under halothane anaesthesia 150 beats/min.
B: 15 sec after intravenous injection of adrenaline 3 µg/kg. Heart rate increased to 176 beats/min (nodal tachycardia) and followed by ventricular extrasystoles, a short run of ventricular tachycardia and ventricular bigeminy.
C: Heart rate 150 beats/min.
D: 15 min after intravenous injection of oxprenolol 0.2 mg/kg. Heart rate 136 beats/min.
E: 15 sec after injection of adrenaline 3 µg/kg. Heart rate increased to 144 beats/min but without ventricular arrhythmia.
F: 15 sec after injection of adrenaline 6 µg/kg. Heart rate increased to 150 beats/min (nodal tachycardia) followed by ventricular bigeminy.
G: Heart rate 140 beats/min.
H: 15 min after injection of a second dose (0.1 mg/kg) of oxprenolol. Heart rate now 132 beats/min.
I: 15 sec after injection of adrenaline 6 µg/kg. No increase in heart rate and no ventricular arrhythmia. Note that the drug has blocked both the increase in heart rate and the ventricular arrhythmia induced by adrenaline.
J: 15 sec after adrenaline 9 µg/kg. No increase in heart rate and no arrhythmia.
K: 15 sec after adrenaline 12 µg/kg. Heart rate increased to 150 beats/min but no arrhythmia.
L: 15 sec after adrenaline 15 µg/kg. Nodal tachycardia at 152 beats/min followed by multifocal ventricular tachycardia.
In another eight dogs, oxprenolol 0.3 mg/kg was injected intravenously as a single dose. This produced a definite decrease in sinus rate (mean 27.5, range 18-38 beats/min). There was a definite fall in arterial pressure (mean 12, range 8-20 mm Hg). This was short-lived and the pressure returned to the pre-injection level within 7-15 min. The adrenaline dose needed to evoke ventricular arrhythmias was increased from 2.44 (SD 0.54) to 8.37 (SD 3.61) µg/kg. This increase was significant (P<0.05). The increase in heart rate produced by adrenaline was also completely prevented. Larger doses of adrenaline first increased the rate of sinus rhythm and then ventricular arrhythmia resulted. A typical experiment is illustrated in figure 3.

**Effect of oxprenolol following electrical defibrillation.**

In all six dogs, intravenous injection of adrenaline 5 µg/kg resulted in ventricular fibrillation. Electrical shock applied to the heart through a left thoracotomy wound, restored sinus rhythm. In four dogs, only one application of electric shock was sufficient; in one dog two applications were needed and in another, three applications.

![Figure 3](image-url)

**FIG. 3**

Effect of oxprenolol on adrenaline-evoked ventricular arrhythmias in dogs under halothane anaesthesia. Lead II. Adr. = Adrenaline. Time base = 1 sec.

A: Heart rate under halothane anaesthesia 140 beats/min.
B: 14 sec after intravenous injection of adrenaline 2 µg/kg. Nodal tachycardia at 188 beats/min followed by ventricular bigeminy.
C: Heart rate 140 beats/min 3 min after adrenaline injection.
D: 15 min after intravenous injection of oxprenolol 0.3 mg/kg. Heart rate now 120 beats/min.
E: 14 sec after injection of adrenaline 2 µg/kg. No increase in heart rate and no ventricular arrhythmia developed. Note that oxprenolol has blocked both the increase in heart rate and the arrhythmia induced by adrenaline.
F: 14 sec after injection of adrenaline 4 µg/kg. No increase in heart rate and no arrhythmia.
G: 14 sec after injection of adrenaline 6 µg/kg. Nodal tachycardia at 130 beats/min developed but without ventricular arrhythmia.
H: 14 sec after injection of adrenaline 8 µg/kg. Nodal tachycardia at 150 beats/min and followed by ventricular bigeminy.
were needed before sinus rhythm was restored. In all these experiments, arterial pressure remained somewhat below the control level (mean reduction 18, range 15-24 mm Hg). Injection of oxprenolol 0.3 mg/kg intravenously produced a further fall in blood pressure (mean 35, range 30-42 mm Hg). This fall in arterial pressure was short-lived, and almost returned to the pre-injection level within 20-30 minutes.

**DISCUSSION**

In the present study, oxprenolol 0.2 mg/kg prevented the development of ventricular arrhythmias evoked by 2-3 μg/kg of adrenaline. The increase in heart rate produced by adrenaline was reduced but not prevented. This showed that beta-receptor blockade was incomplete. Oxprenolol 0.3 mg/kg prevented both the ventricular arrhythmia and the increase in sinus rate produced by adrenaline. The blockade produced by oxprenolol was surmountable in type, and larger doses of adrenaline re-evoked ventricular arrhythmias in all the experiments. An increase in sinus rate (a normal function of beta-receptors) always preceded the development of ventricular arrhythmia when larger doses of adrenaline were used. This showed that beta-receptor blockade produced by oxprenolol is specific, and is competitive in nature. A similar mechanism of action has been demonstrated with propranolol (Sharma, 1966). The two drugs are apparently equipotent in their anti-arrhythmic activity.

Sharma (1967) showed that in dogs under halothane anaesthesia, propranolol administration following electrical defibrillation of the heart, precipitated acute cardiovacular failure with fatal outcome in two of ten experiments. Oxprenolol produced a somewhat greater fall in arterial pressure, but it was much less marked as compared to that seen after propranolol administration. Thus the fall in arterial pressure produced by oxprenolol was short-lived (the pre-injection levels were reached in 20-30 min), whereas the fall in arterial pressure produced by propranolol was persistent (the pre-injection levels were not reached even after 2-3 hours). The slight transient fall in arterial pressure seen after intravenous injection of oxprenolol in normal dogs under halothane anaesthesia shows that it has some intrinsic sympathomimetic activity, i.e. transient stimulation of beta-receptors precedes this blockade. The fall in blood pressure may thus be due to transient stimulation of beta-receptors in the blood vessels. Propranolol is devoid of any such activity. Again, Levy and Richards (1966) showed that propranolol has an intrinsic depressant effect on the myocardium, which is unrelated to its beta-receptor blocking potency, and is possibly related to its chemical structure (naphthyl nucleus). Thus, it is possible that the cardiovacular collapse seen after propranolol may be due to its direct depressant effect on myocardial contractility, and is unrelated to the beta-receptor blockade. Propranolol is known to produce a significant reduction in cardiac output in man (Hamer and Sowton, 1965; Paley, McDonald and Peters, 1965; Harris et al., 1966; Grandjean and Rivier, 1968), and in animals (Black and Rollett, 1965; Nakano and Kusakari, 1965). Oxprenolol produces only a minor reduction in cardiac output in man (Grandjean and Rivier, 1968). The data presented in this study supports such a possibility. The differences in the effects of oxprenolol and propranolol may thus be due to an intrinsic sympathomimetic activity of oxprenolol and to a lesser depression of myocardial contractility with oxprenolol as compared with propranolol.

These results show that oxprenolol, like propranolol, is a potent adrenergic beta-receptor antagonist, but differs from the latter in that its direct depressant action on myocardium is much less marked. In this respect oxprenolol would have important therapeutic advantages over propranolol. With oxprenolol it may be possible to derive the benefit of complete beta-receptor blockade, with a comparatively lower risk of precipitating or aggravating heart failure.

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**REFERENCES**


L’EFFET D’OXPRENOLOL SUR LES ARRHYTHMIES VENTRICULAIRES CAUSES PAR ADRENALINE, CHEZ LE CHIEN ANESTHESIE A L’HALOTHANE DANS OXYGENE

SUMMARY


DIE WIRKUNG VON OXYPRENOLOL AUF ADRENALIN-INDUZIERTE VENTRIKULARE ARRHYTHMIEN BEI MIT HALOTHAN UND SAUERSTOFF ANÄSTHESIERTEN HUNDEN

ZUSAMMENFASSUNG