OXPRENOLOL AND THE CIRCULATION DURING ANAESTHESIA IN THE DOG: INFLUENCE OF INTRINSIC SYMPATHOMIMETIC ACTIVITY

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SUMMARY
Oxprenolol is a non-selective adrenergic beta-receptor antagonist displaying beta-mimetic activity. To test the hypothesis that beta-mimetic activity could minimize the response of the circulation to adrenergic beta-receptor blockade, cumulative dose-response curves to oxprenolol 0.1–1.6 mg kg⁻¹ were obtained in seven anaesthetized dogs. Anaesthesia was maintained with 0.5% halothane supplementing nitrous oxide 66% in oxygen, under moderately hypocapnic IPPV. Oxprenolol, up to 0.4 mg kg⁻¹ i.v., caused modest increases in heart rate, LV dP/dt max and cardiac output. With the largest dose (1.6 mg kg⁻¹), significant increases in heart rate (+19%), LV dP/dt max (+13%) and cardiac output (+27%) were observed while arterial pressure remained unchanged and systemic vascular resistance decreased (-18%).

There are two categories of indication for the i.v. administration of adrenergic beta-receptor antagonists either immediately before or during anaesthesia and surgery. First, prophylaxis against the effect on the cardiovascular system of spontaneously exaggerated sympathetic activity (phaeochromocytoma, hyperthyroidism, subarachnoid haemorrhage). Second, prevention or treatment of disturbances of the circulation caused by anaesthetic or surgical manoeuvre (bronchoscopy, laryngoscopy, tracheal intubation, deliberately induced hypotension or hypothermia, administration of catecholamines, dental surgery, surgery of the posterior fossa, vascular surgery, thoracic surgery).

Propranolol, which is not selective for cardiac or other adrenergic beta-receptors, is commonly used in these circumstances. It causes dose-dependent depression of myocardial performance in man and in experimental animals although not at the doses usually required to produce clinically effective adrenergic beta-receptor blockade (Meier, 1973). Increases in systemic vascular resistance are observed after i.v. propranolol (Foex and Prys-Roberts, 1974; Prys-Roberts et al., 1976; Horan et al., 1977a) and may be attributed to blockade of beta-receptors subserving active vasodilatation in the skeletal muscle vascular bed. Sympathetic activation can then exert only an unopposed alpha-receptor mediated vasoconstrictor effect. This increases the left ventricular afterload and may contribute to a decrease in cardiac output.

Oxprenolol is equipotent with propranolol and similarly lacks selectivity for the various subgroups of beta-receptors. The two drugs share the property of membrane stabilization, but differ in that oxprenolol displays significant beta-mimetic activity whereas propranolol is totally devoid of this property (Nayler and Chang, 1973). Some therapeutic advantages might be conferred to oxprenolol by its partial agonist properties. Thus, we have studied the effects on the circulation of oxprenolol, administered in logarithmically increasing doses, in dogs, during steady state anaesthesia using nitrous oxide in oxygen supplemented by halothane. Dogs chronically implanted with blood-flow and pressure-measuring transducers were used as a preparation shown to be stable during prolonged anaesthesia (Roberts, 1974). Animal experiments were preferred to human studies because of the very high total doses of oxprenolol, the effects of which could not be adequately predicted.

MATERIALS AND METHODS
Left thoracotomy was performed in seven healthy dogs (mean weight 14.6 kg) under sterile conditions in order to implant a cuff electromagnetic flow transducer (type 230 SE Laboratories) around the root of the aorta, a miniature
Konigsberg (type Pi9) pressure transducer into the cavity of the left ventricle and p.v.c. catheters into the main pulmonary artery and left atrium. The ends of the leads and catheters were brought through all the layers of the chest wall except the skin and placed in a dorsal subcutaneous pocket. The details of this technique have been reported previously (Roberts et al., 1976). The animals were allowed to recover for 7-10 days before being studied.

On the day of study, anaesthesia was induced in the (unpremedicated) dogs with thiopentone sodium 15mg kg\(^{-1}\) i.v. After tracheal intubation, anaesthesia was maintained with nitrous oxide 66% in oxygen supplemented by 0.5% halothane. Ventilation was controlled, tidal volume (50 ml kg\(^{-1}\)) and rate (12 b.p.m.) remaining constant. An Oxford-Penlon ventilator was used with a partial rebreathing circle system. Fresh gas flow was adjusted so that the end-tidal carbon dioxide concentration as indicated by a calibrated infra-red analyser, was maintained in the range 3.5-4%. Body temperature was measured with an oesophageal thermistor probe connected to a digital thermometer and maintained between 36 and 37 °C by under-table electrothermal heating. Lactated Ringer's solution 4ml kg\(^{-1}\) h\(^{-1}\) was infused i.v. to maintain fluid balance.

The following haemodynamic variables were recorded. The electrocardiogram (e.c.g.) was obtained from standard limb leads. Aortic pressure and left atrial pressures were measured using Statham P23 De strain gauge transducers. Left ventricular pressure was measured with a Konigsberg miniature pressure transducer. Aortic blood flow was measured with an electromagnetic flow transducer. These variables were recorded on an eight-channel ink-jet recorder (Mingograph 81) together with the electronically derived variables LVdP/dt, aortic blood acceleration and stroke volume. Details of the techniques used have been reported (Roberts et al., 1976).

Blood-gas analyses were performed using calibrated standard electrodes (Radiometer, Copenhagen) connected to amplifiers described previously by Hahn (1969, 1971). Arterial and mixed venous blood was sampled anaerobically and stored in iced water. Elapsed time and temperature corrections were derived from the tables of Kelman and Nunn (1966). A blood-gas difference of 4% was applied to all \(P_{O_2}\) measurements (Prys-Roberts, 1968).

Data analysis was carried out on an ICL 1906A computer according to programs written by one of the authors (M. J. B.). In order to process the data, haemodynamic variables had to be transferred to computer punch cards.

**Experimental programme**

After a steady state of anaesthesia had been established, haemodynamic variables and blood-gas tensions were measured. A dose–response study of the chronotropic and inotropic effects of isoprenaline was performed. The haemodynamic effects of increasing the inspired halothane concentration were noted (the results will be reported later). Nitrous oxide in oxygen in halothane anaesthesia was recommenced and all variables were measured once a steady state had been achieved for at least 30 min. Oxprenolol was administered i.v. at 15-min intervals in such increments as to achieve the cumulative doses of 0.1, 0.2, 0.4, 0.8 and 1.6 mg kg\(^{-1}\). Haemodynamic recordings were always taken 15 min after each incremental dose. Fifteen minutes after the last dose of oxprenolol blood-gases were analysed and haemodynamic measurements repeated. A second dose–response study of the chronotropic and inotropic effects of isoprenaline was carried out at the end of each experiment.

**RESULTS**

Some haemodynamic effects of the increases in the dose of oxprenolol are shown on figures 1 and 2.

**Circulatory indices**

Heart rate increased progressively as the dose of oxprenolol was increased such that it was 3% above control after 0.1 mg kg\(^{-1}\) and 19% faster after oxprenolol 1.6 mg kg\(^{-1}\). The values after oxprenolol 0.4 and 1.6 mg kg\(^{-1}\) were significantly different from control \((P<0.05)\).

Stroke volume remained unchanged during the administration of oxprenolol.

Cardiac output increased progressively with increases in drug dosage, reaching a maximum of 27% greater than control after oxprenolol 1.6 mg kg\(^{-1}\), at which point the increase in cardiac output was statistically significant \((P<0.05)\).

Mean arterial pressure altered little throughout the study. Although statistically significant, the increases observed at the doses oxprenolol
0.2 mg kg\(^{-1}\) and 0.4 mg kg\(^{-1}\) were small (respectively +3% and +6%).

Systemic vascular resistance remained unchanged up to the dose of oxprenolol 0.8 mg kg\(^{-1}\) at which it decreased by 7%. After oxprenolol 1.6 mg kg\(^{-1}\) the reduction of systemic vascular resistance was large (−18%; \(P<0.001\)).

Left ventricular end-diastolic pressure did not vary by more than ±1 mm Hg from control at any stage.

Left ventricular performance. \(LVdP/dt_{\text{max}}\) was 5% greater than control value after the smallest dose and increased progressively to 13% above the control value. At the first two and at the last two doses, the increases were statistically significant (\(P<0.05\)). Maximum aortic blood acceleration was not significantly altered at any stage. Peak left ventricular power was essentially unchanged throughout this dose–response study.

The external work of the left heart increased...
progressively by, respectively, 4%, 9%, 15% \((P<0.05)\), 16% \((P<0.05)\) and 28% \((P<0.05)\) after each of the successive doses of oxprenolol.

**Isoprenaline dose–response curves**

These indicated that a 30-fold shift to the right had been obtained for the chronotropic response of the heart, and a 25-fold shift to the right had been obtained for the inotropic response of the heart after the cumulative dose of oxprenolol 1.6 mg kg\(^{-1}\).

**Blood-gas analyses**

These were performed before the administration of the first dose of oxprenolol and 15 min after the last dose of oxprenolol. The control values for arterial blood-gas tensions were \(P_{aO_2}\), 28.3 kPa (SD 3.7), \(P_{aCO_2}\), 3.6 kPa (1.1), pH\(\text{a}\) 7.48 unit (0.01). After oxprenolol, the respective values were \(P_{aO_2}\), 28.5 kPa (4.1), \(P_{aCO_2}\), 3.7 kPa (0.8), pH\(\text{a}\) 7.46 unit (0.01). The differences from control did not reach statistical significance. The control values for mixed venous blood-gas tensions were \(P_{vO_2}\), 6.9 kPa (1.1), \(P_{vCO_2}\), 4.7 kPa (1.1), pH\(\text{v}\) 7.44 unit (0.01). After oxprenolol the respective values were \(P_{vO_2}\), 7.4 kPa (1.5), \(P_{vCO_2}\), 4.7 kPa (1.1), pH\(\text{v}\) 7.42 unit (0.01). The differences from control were not significant.
DISCUSSION

Some adrenergic beta-receptor blockers behave as partial agonists and exhibit intrinsic sympathomimetic activity (ISA). Bilski, Robertson and Wale (1979) have shown that in catecholamine-depleted rats, ISA is not a uniform parameter and may be dissociated from \(\beta\)-adrenoceptor blockade. Practolol, for example, exerts intrinsic betamimetic activity at all \(\beta\)-adrenoceptor blocking doses. Pindolol, acebutol and oxprenolol preferentially block \(\beta\)-adrenoceptors at low doses and exhibit ISA at higher doses. In the study, carried out under conditions more closely related to clinical anaesthesia and in the absence of catecholamine depletion, even the low doses of oxprenolol caused small increases in heart rate, LV \(dP/dt\) max and cardiac output. At greater doses, oxprenolol further increased heart rate and cardiac output while systemic vascular resistance decreased. Enhancement of the performance of the heart as a pump was most marked after administration of the cumulative dose of 1.6 mg kg\(^{-1}\). This large dose had caused a 30-fold shift to the right of the chronotropic dose–response curve to isoprenaline, accompanied by a 25-fold shift to the right of the inotropic dose–response curve to isoprenaline.

With such a high degree of \(\beta\)-adrenoceptor blockade, increase in heart rate and enhancement of LV \(dP/dt\) max may have been a result of the increase of heart rate. The reduction of peripheral vascular resistance suggests the development of \(\beta_2\)-adrenoceptor-mediated vasodilatation in the vasculature of the skeletal muscle. Thus, the partial agonist characteristics of oxprenolol appear to be present at both \(\beta_1\) and \(\beta_2\) adrenoceptors. Peripheral vasodilatation may have contributed to the increase of cardiac output at a time left ventricular end-diastolic pressure was unchanged and contractility was only moderately increased. However, the largest contribution to the increased cardiac output is likely to have been the increase in heart rate.

The effects on the circulation of the highest doses of oxprenolol may not be of clinical significance. However, the effects of the lower doses are more immediately relevant. Cumulative doses of 0.1, 0.2 and 0.4 mg kg\(^{-1}\) caused modest increases in heart rate and LV \(dP/dt\) max accompanied by small but not significant increases in cardiac output. Vascular resistance was unchanged over this range of doses. This is at variance with the 13% increase observed under halothane anaesthesia (Foëx and Ryder, 1981). The difference may be attributed to the anaesthetic technique. Normocarbia and 1% halothane in oxygen were used in the previous study of oxprenolol (Foëx and Ryder, 1981), while mild hypocarbia, and 0.5% halothane in nitrous oxide in oxygen were used in the present study. With the latter technique, vascular resistance was fairly high before administration of oxprenolol. Blockade of the \(\beta_2\)-receptors and beta-mimetic activity appear to have cancelled out. Only at the greatest doses did vasodilatation occur. These effects of oxprenolol are totally different from those of another non-selective \(\beta\) adrenoceptor blocker, propranolol. Under nitrous oxide in oxygen anaesthesia supplemented by halothane (Prys-Roberts et al., 1976), enflurane anaesthesia (Horan et al., 1977a) and isoflurane anaesthesia (Horan et al., 1977b), propranolol 0.3 mg kg\(^{-1}\) i.v. has been shown to cause decreases in heart rate (−7% to −17%), LV \(dP/dt\) max (−15% to −24%) and cardiac output (−8% to −26%). After propranolol, systemic vascular resistance increased (+9% to +33%). The increase in vascular resistance after the administration of propranolol may have contributed to the observed decreases in cardiac output. The differences between oxprenolol, causing mild enhancement of the circulation, and propranolol, causing moderate depression of the circulation, seem to indicate that intrinsic sympathomimetic activity contributes, under anaesthesia, to minimize the effects of \(\beta\)-adrenoceptor blockade. Since propranolol and oxprenolol are equipotent \(\beta\)-adrenoceptor agents (Brunner et al., 1970) the differences in the responses to their administration cannot be ascribed to a lesser degree of \(\beta\)-adrenoceptor blockade. Since propranolol and oxprenolol are equipotent \(\beta\)-adrenoceptor agents (Brunett et al., 1970) the differences in the responses to their administration cannot be ascribed to a lesser degree of \(\beta\)-adrenoceptor blockade with oxprenolol. In the absence of any significant changes of arterial pressure, differences between oxprenolol and propranolol cannot be attributed to altered baroreceptor reflexes. Thus, intrinsic sympathomimetic activity, a known characteristic of oxprenolol (Barrett, 1970; Meier, 1970; Nayler, 1970; Wale et al., 1979) appears to be an important determinant of its haemodynamic effects.

The aim of adrenergic beta-receptor blockade during anaesthesia is to prevent the effects on the myocardium of sympathetic overactivity without causing cardiovascular depression. This may be
achieved by the administration of oxprenolol without causing any impairment of cardiac performance even with a very high cumulative dose. In the case of ischaemic heart disease, it may be argued that the small increase in heart rate and contractility may increase oxygen demand. However, these increases, with cumulative doses of oxprenolol of up to 0.4 mg kg$^{-1}$ are very small by comparison with the effects of sympathetic overactivity observed in clinical practice (Prys-Roberts, Meloche and Foex, 1971) or in experimental studies (Slogoff et al., 1977) and are unlikely to cause significant imbalance between myocardial oxygen demand and supply.

The difference between the effects of practolol (Prys-Roberts et al., 1976) and metoprolol (Burt and Foex, 1979) had suggested that intrinsic sympathomimetic activity may be important to minimize the interaction between cardioselective $\beta$-adrenoceptor blockade and anaesthesia. The lack of adverse interaction between oxprenolol and anaesthesia with nitrous oxide supplemented by halothane over a very wide range of doses suggests that partial agonists may be safer to use during anaesthesia than pure $\beta$-adrenoceptor antagonists.

ACKNOWLEDGEMENTS

We are grateful to Mr W. A. Ryder and the Technical Staff of the Nuffield Department of Anaesthetics for their assistance. This work has been supported by CIBA-GEIGY (Horsham, England).

REFERENCES


OXPRENOLOL ET LA CIRCULATION PENDANT L'ANESTHESIE D'UN CHIEN: INFLUENCE DE L'ACTIVITE SYMPATHOMIMETIQUE INTRINSEQUE

RESUME
L'oxprenolol est un antagoniste bêta-récepteur adrénergique non sélectif présentant une activité bêta-mimétique. Pour tester l'hypothèse qui veut que l'on peut minimiser la réaction de la circulation au blocage bêta-récepteur adrénergique par l'activité bêta-mimétique, on a obtenu sur sept chiens anesthésies des courbes cumulatives dose/réaction à l'oxprenolol (0,1-1,6 mg kg⁻¹). On a entretenu l'anesthésie avec 0,5% d'halothane comme complément du protoxyde d'azote 66% dans de l'oxygène, sous ventilation au moyen de respirateurs à pression positive intermittente modérément hypokapnique. Jusqu'à 0,4 mg kg⁻¹, administré par voie intraveineuse, l'oxprenolol n'a causé qu'une modeste augmentation de la fréquence cardiaque, de la dP/dr max, ventriculaire gauche, et du débit cardiaque. Avec la dose la plus forte (1,6 mg kg⁻¹), on a observé une augmentation significative de la fréquence cardiaque (+19%), de la dP/dr max, ventriculaire gauche (+13%) et du débit cardiaque (+27%), alors que la pression artérielle demeurait inchangée et que la résistance systémique vasculaire diminuait (-18%).

OXPRENOLOL UND DIE ZIRKULATION WAHREND NARKOSE BEIM HUND: EINFLUSS VON INNERLICHER SYMPATHOMIMETISCHER AKTIVITAT

ZUSAMMENFASSUNG
Oxprenolol ist ein nicht-selektives adrenergisches Betarezeptor-Gegenmittel mit betamimetischer Aktivität. Um die Hypothese zu prüfen, dass die betamimetische Aktivität die Reaktion der Zirkulation auf eine adrenergische Betarezeptorenblockierung minimalisieren könnte, wurden kumulative Dosisreaktionskurven nach Oxprenolol 0,1-1,6 mg kg⁻¹ bei sieben narkotisierten Hunden festgehalten. Die Narkose wurde mit 0,5% Halothan als Ergänzung von 66% Stickoxyd in Sauerstoff aufrecht erhalten, unter mässigem hypokapnischem IPPV. Dosen bis zu 0,4 mg kg⁻¹ Oxprenolol intravenös bewirkten geringe Anstiege der Herzfrequenz, von LV dP/dr max sowie des Herzminutenvolumens. Bei der grössten Dosis (1,6 mg kg⁻¹) kam es zu bedeutenden Anstiegen der Herzfrequenz (+19%), LV dP/dr max (+13%) und des Herzminutenvolumens (+27%), während der arterielle Druck unverändert blieb und sich der systemische Gefäßwiderstand senkte (-18%).

EL OXPRENOLOL Y LA CIRCULACION DURANTE LA ANESTESIA DEL PERRO: INFLUENCIA DE LA ACTIVIDAD SIMPATOMIMETICA INTRINSECA

SUMARIO
El oxprenolol es un antagonista adrenérgico no selectivo de carácter betareceptor que presenta una actividad beta-mimética. Con el fin de verificar la hipótesis de que la actividad betamimética reduciría a un mínimo la respuesta circulatoria al bloqueo adrenérgico beta-receptor, se obtuvieron curvas acumulativas de dosis contra respuesta sobre el oxprenolol (0,1-1,6 mg kg⁻¹) correspondientes a siete perros anestesiados. La anestesia se mantuvo con halotano al 0,5% como suplemento al óxido nitroso (66%) en oxígeno. La administración intravenosa de 0,4 mg kg⁻¹ de oxprenolol produjo modestos incrementos del ritmo cardíaco, LV dP/dr max y de la producción cardíaca. Con la mayor dosis (1,6 mg kg⁻¹) se observaron incrementos significativos del ritmo cardíaco (+19%), LV dP/dr max (+13%) y de la producción cardíaca (+27%) al tiempo que la presión arterial permaneció invariable y la resistencia sistémica vascular disminuyó (-18%).