HAEMODYNAMIC EFFECTS OF BETA-RECEPTOR BLOCKING DRUGS DURING NITROUS OXIDE/HALOTHANE ANAESTHESIA

BY

G. W. STEPHEN, I. T. DAVIE AND D. B. SCOTT

SUMMARY

Oxprenolol 2 mg, alprenolol 5 mg or practolol 15 mg was given intravenously to three groups of six patients receiving general anaesthesia with nitrous oxide, oxygen and halothane 1 per cent. Only one drug was administered to each patient. The effects on cardiac output, mean arterial blood pressure, heart rate and central venous pressure were measured. All three drugs caused marked falls in cardiac output and heart rate with sustained rises in central venous pressure. The clinical implications of these effects are discussed.

In recent years there has been considerable interest in drugs causing blockade of beta-adrenergic receptors. In anaesthesia the main indications for their use are the control of cardiac arrhythmias (Payne and Senfield, 1964; Johnstone, 1966, 1968, 1969) and the management of phaeochromocytoma (Robertson, 1965; De Blasi, 1966). They have been shown to be effective against arrhythmias induced by injected catecholamines (Katz, 1969) and have been recommended as an adjunct to hypotensive anaesthesia (Hewitt, Lord and Thornton, 1967). In medical practice they are used in angina pectoris, hypertension and thyrotoxicosis. As a result, patients receiving them may sometimes require anaesthesia and surgery.

Propanolol was the first beta-blocking drug to gain wide clinical use. However, it is presently being superseded by other drugs said to be more cardioselective and having less negative inotropic effect on the myocardium as a result of an intrinsic sympathomimetic effect. Three such drugs are practolol, oxprenolol and alprenolol. The present study investigated the central haemodynamic effects of these drugs during nitrous oxide/halothane anaesthesia.

METHODS

Eighteen female patients were studied, aged 22-25 years. All were about to undergo minor gynaecological surgery and all gave permission for the investigation. None had clinical evidence of cardiopulmonary disease.

Anaesthesia was induced with thiopentone 400-500 mg intravenously, 1 hour after premedication with atropine 0.6 mg intramuscularly. Anaesthesia was maintained using nitrous oxide and oxygen (3:1 l./min in a closed system with carbon dioxide absorption) to which halothane 1 per cent was added. Ventilation was spontaneous on all occasions. A central venous catheter was passed percutaneously through a cubital vein using the Seldinger technique.

Cardiac output was measured using the indocyanine green dye dilution technique with a Waters XE302 earpiece and densitometer. Changes in cardiac output were monitored with a Sanborn cardiac output computer No. 130. Calibration of the dye curves was achieved by passing the patient’s blood, containing known amounts of dye, through the jaws of the earpiece using the glass blood chamber removed from a Waters cuvette. The area beneath each curve was calculated by the method of Williams, O’Donovan and Wood (1966). Electrocardiography was continuous and the heart rate displayed by a Sanborn cardiocountochometer 350-3400A. Arterial blood pressure was measured by standard sphygmomanometry, the mean pressure being calculated as the diastolic pressure plus one-third of the pulse pressure. Central venous pressure was measured with a Sanborn 267 AC pressure transducer, the zero
reference point being taken as 5 cm below the manubrium sterni. Once the position of the catheter tip in a central vein was confirmed by the pressure tracing, electrical damping was used to reduce the respiratory swing. All electrical measurements were recorded simultaneously on a Sanborn 7700 six-channel recorder.

Four recordings of cardiac output were made at 2-minute intervals in the control period. One of the three test drugs was given intravenously over a period of 2 minutes in the doses of oxprenolol 2 mg, alprenolol 5 mg and practolol 15 mg. Each drug was given to a total of six patients. Five minutes from the beginning of the injections and after three further intervals of 5 minutes, all the measurements were repeated. Measurements were thus recorded on eight occasions, four in the control period and four in the postinjection period. Statistical analysis by the Student’s t test was performed on the data obtained.

| Table I |

Cardiac output, heart rate, mean arterial pressure and central venous pressure before and after injection of oxprenolol, alprenolol or practolol expressed as mean values (+ SD). Each drug was given to six patients. The mean maximal change in individual patients without regard to time is given and compared with mean control values. Statistical significance relates to the comparison.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cardiac output (l/min)</th>
<th>Mean (n=24)</th>
<th>Minutes</th>
<th>Mean (n=6)</th>
<th>Mean maximal change in individual patients</th>
<th>Significance</th>
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<td>4.87</td>
<td>4.94</td>
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<td>4.84</td>
<td>4.77</td>
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<th>Minutes</th>
<th>Mean (n=6)</th>
<th>Mean maximal change in individual patients</th>
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<td>(±14)</td>
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<td>(±6)</td>
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<th>Minutes</th>
<th>Mean (n=6)</th>
<th>Mean maximal change in individual patients</th>
<th>Significance</th>
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<td>4.7</td>
<td>4.7</td>
<td>4.6</td>
<td>(±1.1)</td>
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Haemodynamic measurements before and after intravenous oxprenolol, alprenolol and practolol (six subjects in each group) expressed as mean values both in absolute terms and as percentages, with the control value immediately pre-injection being taken as 100 per cent.

**Fig. 1**
Cardiac output values in individual patients before and after intravenous oxprenolol, alprenolol and practolol.
HAEMODYNAMIC EFFECTS OF BETA-RECEPTOR BLOCKING DRUGS

Diagrammatic representation of the change in cardiac output following injection of oxprenolol, alprenolol and practolol. The mean control value is compared with the lowest output measured after injection.

ence between the control values and the maximum change observed in each case. It will be seen that in only two cases was no fall in cardiac output seen.

It is appreciated that the earpiece method for dye-dilution measurement of cardiac output is open to criticism, especially in regard to the calibration and expression of results in absolute terms. However, as output was measured sequentially in individual patients, it is felt that the changes observed are valid. Two serious objections to the earpiece, namely, poor circulation through the ear and changes in posture, did not apply in our patients.

The changes observed were statistically significant (P<0.02) and there appeared to be little difference between the three drugs tested.

Heart rate. This fell by about 12 per cent after injection of the beta-blocking drugs and showed no tendency to return to control values during the 20 minutes of observation. The reduction was highly significant (P<0.001). It will be seen that the fall in heart rate was less than the fall in cardiac output (25 per cent) and therefore there was also a fall in stroke volume.

Mean arterial pressure. Following injection of the beta-blocking agents there was a small (10 per cent) but definite decrease in arterial pressure which, however, was recovering towards the control value by the end of 20 minutes. In view of the fact that cardiac output remained low, recovery of the arterial pressure indicated an increase in peripheral resistance.

Central venous pressure. All three drugs caused a rise in central venous pressure which was still elevated after 20 minutes. Occurring concomitantly with the reduction in cardiac output, it must be assumed that the drugs had a negative inotropic effect on the myocardium.

DISCUSSION

Drugs used to revert cardiac arrhythmias can be divided into at least four groups (Vaughan-Williams, 1970).

(a) Quinidine-like drugs which include most of the local anaesthetics. These cause a decrease in the maximal rate of depolarization of myocardial cells, and also a lengthening of the effective refractory period (Bigger and Mandel, 1970).

(b) Beta-adrenergic receptor blockers. These protect the myocardium from the effects of catecholamines. The position is complicated by the fact that many of these drugs are also local anaesthetics. Propranolol is quite a powerful local anaesthetic and in vitro at least it possesses definite quinidine-like actions. The newer agents practolol, alprenolol and oxprenolol have little or no local anaesthetic action and are also more specific to the myocardium in regard to the beta-blockade they produce. Thus they have two major advantages over propranolol in that they have much less negative inotropic effect (Jewitt, 1970) and they do not provoke bronchoconstriction. Macdonald and McNeil (1968) found that propranolol could cause serious bronchoconstriction in asthmatic patients.

(c) Antithyroid drugs, e.g. amiodarone, which prolong the action potential of myocardial cells, increasing the refractory period.

(d) Other drugs, e.g. diphenylhydantoin, which are thought to act primarily in the central nervous system and reduce the output of sympathetic impulses from the hypothalamus.

During anaesthesia, most cardiac arrhythmias can be terminated by correction of hypercarbia and hypoxia and only rarely are drugs indicated. The agents most frequently used in these circumstances are lignocaine (Hitchcock and Keown, 1958; Weiss, 1960) and the beta-blocking drugs (Johnstone, 1970).
Because of its marked negative inotropism and tendency to cause bronchoconstriction, propranolol is no longer acceptable. The newer drugs investigated in the present study have been shown to be without marked negative inotropic effect in conscious subjects (Jewitt, 1970; Grandjean and Rivier, 1968; Forsberg and Johnsson, 1967). Under general anaesthesia, however, there is apparently a well marked negative inotropic effect as indicated by the fall in cardiac output (which was greater than the fall in heart rate) and the rise in central venous pressure. This effect has been previously described in animal experiments performed under halothane anaesthesia (Norman and Atkinson, 1970; Strong et al., 1971). The difference between the conscious and the general anaesthetic states in regard to the circulation depends largely on the sympathetic-parasympathetic balance. With potent anaesthetic agents, direct depression of the myocardium and peripheral vasodilatation are counterbalanced by an increase in sympathetic activity mediated both through direct sympathetic nervous discharge to the myocardium and by release of catecholamines into the circulation. (The effects of hypercarbia are probably due to this latter mechanism.) Thus a patient may compensate and maintain normal haemodynamic parameters. When, however, the sympathetic drive is removed by beta-blockade, the purely depressive effects of the anaesthesia (especially marked with halothane) becomes apparent.

One problem in investigating beta-blocking drugs is deciding upon equipotent dosage. This can be done by attempting to titrate isoprenaline reversal using the heart rate as the index of isoprenaline effect. However, this considerably increases the length of time required to study a patient. We therefore were guided both by the manufacturer’s advice and by the dosage used in clinical reports from other workers. In the dosage used in the present study, no difference between the effects of the three drugs could be shown. It may be concluded that beta-blockade can, during halothane anaesthesia, cause a fall in cardiac output which may be as large as 40 per cent in an individual patient. The generalized use of these drugs for all cases developing arrhythmias is inadvisable and they should probably be restricted to cases where excessive amounts of circulating catecholamines are unavoidable, e.g. phaeochromocytoma, or where adrenaline is injected by the surgeon. Unfortunately, those cases who might benefit most from reversion of a cardiac arrhythmia, e.g. patients undergoing cardiac surgery or those with pre-existing heart disease, are, generally speaking, those least able to tolerate such reductions in cardiac output.

Patients who have received beta-blocking drugs respond less readily to isoprenaline and this may be of importance during and following cardiac surgery when isoprenaline is commonly employed.

ACKNOWLEDGEMENTS

We are grateful to Professor R. J. Kellar for allowing us to study patients under his care and to his junior staff for their very considerable co-operation. We would also like to thank Miss Edith McLachlan for her excellent technical help, Dr D. A. Richards of Ciba Laboratories for advice and the supply of oxprenolol (Trasicor) and Dr I. Slessor of Astra Chemicals Ltd for his help and the supply of alprenolol (Aptin). This work was supported by a grant from the British Heart Foundation.

REFERENCES


EFFETS HEMODYNAMIC DES MEDICATIONS BETA-BLOQUANTES AU COURS D'ANESTHESIES AU PROTOXYDE D'AZOTE/HALOTHANE

SOMMAIRE
On a administré par voie intraveineuse 2 mg d'oxprenolol, 5 mg d'alprenolol ou 15 mg de practolol à trois séries de six malades soumis à une anesthésie générale comportant l'administration du mélange suivant : protoxyde d'azote, oxygène et halothane à un pour cent. Chaque malade a reçu un seul des médicaments précités. Les effets de ceux-ci sur le débit cardiaque, la pression artérielle moyenne, la fréquence cardiaque et la pression veineuse centrale ont été enregistrés. Les trois médicaments ont entraîné une chute marquée du débit et de la fréquence cardiaques avec une augmentation soutenue de la pression veineuse centrale. Les implications cliniques de ces effets font l'objet d'une discussion.

HAMODYNAMISCHE WIRKUNGEN VON BETA-REZEP TOREN-BLOCKERN UNTER LACHGAS-HALOTHAN-NARKOSE

ZUSAMMENFASSUNG

EFECTOS HEMODINAMICOS DE MEDICAMENTOS BLOQUEADORES DE RECEPTORES BETA DURANTE LA ANESTESIA OXIDO NITROSO/HALOTANO

RESUMEN
Fue administrado por vía intravenosa oxprenolol 2 mg, alprenolol 5 mg o practolol 15 mg a tres grupos de seis pacientes recibiendo anestesia general con óxido nitroso, oxigeno y halotano al 1 por ciento. Solamente fue administrado un medicamento a cada paciente. Fueron medidas los efectos sobre el rendimiento cardíaco, presión sanguínea arterial media, frecuencia cardíaca y presión venosa central. Los tres medicamentos causaron acusadas reducciones en el rendimiento cardíaco y frecuencia cardíaca con elevaciones sostenidas de la presión venosa central. Son discutidas las implicaciones clínicas de estos efectos.

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PRIMARY FELLOWSHIP EXAMINATION
The last occasion on which Anatomy and Pathology will be accepted is May, 1971. As and from that date the subjects of the Primary Examination will be Physiology, Pharmacology, Physics, Clinical Measurement and Clinical Chemistry.