PROPRANOLOL (INDERAL) DURING HALOTHANE ANAESTHESIA

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SUMMARY

Propranolol (Inderal) is safely compatible with a light plane of halothane anaesthesia in an atropinized patient with a normal cardiovascular system. It prevents the cardiac overactivity and the arrhythmias caused by fear, pain, vagolytic drugs, surgical stimulation and catecholamines. Judging from its effects on the volume-pulse wave, the electrocardiogram, the systolic blood pressure and the pulse-wave velocity, it has been concluded that the combined effects of light halothane anaesthesia and beta-adrenergic blockade with propranolol do not appreciably impair the intrinsic contractility of the healthy myocardium or its ability to respond immediately to an increase in the venous return in atropinized vasodilated patients. The potential risks of beta-adrenergic blockade in anaesthetics have been discussed. The results of this investigation are not applicable to any anaesthetic agent other than halothane.

The increasing use of propranolol (Inderal) by physicians and general practitioners in the treatment of medical diseases means that the anaesthetist will inevitably be confronted with patients who are under the influence of beta-adrenergic blockers should the need for surgical treatment arise. As with the other forms of sympathetic suppression and anti-hypertensive therapy, blockade of the beta-adrenergic receptors will alter the cardiovascular reactions to surgical disease, to surgical operations and to general anaesthesia. It is, therefore, a matter of some urgency that the anaesthetist should be made aware not only of the advantages of beta-adrenergic blockade but also of its risks and the steps which may be taken to avoid them.

Propranolol is the second compound designed specifically to antagonize the actions of catecholamines on the beta-adrenergic receptors of the heart and other viscera (Black, Duncan and Shanks, 1965). Its chemical formula and those of its analogues are illustrated in figure 1.

Propranolol is pharmacologically similar to its predecessor pronethalol (Alderlin) and it is not carcinogenic in mice (Tucker, Alcock and Baker, 1965). Comparative studies of the two compounds in animals show it to be ten times more potent than pronethalol in blocking the inotropic action of isoprenaline on the myocardium (Black et al., 1964).

During the past two years beta-adrenergic blockade with propranolol has been used successfully in the treatment of various diseases of the heart and other viscera. These diseases include angina of effort (Gillam and Prichard, 1965; Keelan, 1965), essential hypertension (Prichard and Gillam, 1964; Richards, 1965), acute myocardial infarction (Snow, 1965), digitalis and quinidine intoxications (Stock, 1966; Wolfson, 1966), paroxysmal tachycardia (Schamroth, 1966; Rowlands, Howitt and Markman, 1965; Harrison Griffin and Fiene, 1965), thyrotoxicosis and anxiety states (Howitt and Rowlands, 1966; Turner, Granville-Grossman and Smart, 1965), and phaeochromocytomas (Robertson, 1965; Prichard and Ross, 1966). Sloman, Robinson and McLean (1965) and Harris (1966) have reported the successful control with propranolol of the ventricular fibrillations and other arrhythmias which may complicate acute or chronic heart disease. It has also been used to alleviate the muscle tremor of Parkinsonism (Owen and Marden, 1965).

Propranolol does not appear to have any undesirable effects which cannot be dissociated from those of catecholamine-antagonism. As would be expected, it will predispose to bronchiolar spasm in patients subject to bronchial asthma (McNeil, 1964). Similarly, sympathetic blockade at any level may precipitate myocardial failure with pul-
PROPRANOLOL (INDERAL) DURING HALOTHANE ANAESTHESIA

CH(OH)₂.CH₂.NH.CH(CH₃)₂

Isoprenaline

HO

HO

Dichloroisoprenaline D.C.I.

CH(OH)₂.CH₂.NH.CH(CH₃)₂

PRONETHALOL ("ALDERLIN")

CH(OH)₂.CH₂.NH.CH(CH₃)₂

PROPRANOLOL ("INDERAL")

Fig. 1

Chemical formulae of propranolol and its analogues.

monary congestion when the function of the failing heart is largely dependent on the stimulating effect of catecholamines released into the circulation under the stresses of incipient circulatory failure (Braunwald, 1965).

COMPATIBILITY OF BETA-ADRENERGIC BLOCKADE WITH SURGERY AND ANAESTHESIA

The available pharmacological and clinical evidence indicates that propranolol insulates the heart from the chronotropic and inotropic effects of catecholamines and that it has no effect on the constrictive action of these substances on the peripheral blood vessels. It may also diminish the cardiac stimulant effect of the usual doses of the common pressor drugs such as ephedrine and methylamphetamine but it will not antagonize the vasoconstrictive action of methoxamine. Catecholamines may be released in the surgical patient by fear, pain, respiratory acidosis, hypovolaemia, general anaesthesia and surgical trauma. It is, therefore, to be expected that the rate of the heart which is under the influence of propranolol will not be increased in the usual way by the stressful stimuli encountered in the surgical patient. Similarly, the tachycardia produced by drugs such as atropine or gallamine will be modified, but their anticholinergic action will not be impaired (fig. 2).

Sympathetic blockade at levels proximal to the beta-adrenergic receptors may cause cardiac arrest in animals with metabolic acidosis (Thrower, Darby and Aldinger, 1961). It seems reasonable to assume that a similar reaction will occur in man and in animals in response to beta-adrenergic blockade induced during a metabolic acidosis produced by renal failure, diabetes mellitus, circulatory failure, general anaesthesia or any other cause (Johnstone and Malhotra, 1962). It is not improbable that the myocardial depressant effects of bacterial toxins, hypoxia, chemical poisons, hypovolaemia and electrolyte depletion will be potentiated by beta-adrenergic blockade. The sudden onset of acute surgical emergencies such as intestinal or urinary obstructions, trauma or haemorrhage in patients under treatment with propranolol may precipitate circulatory collapse more rapidly when the negative inotropic effect of beta-adrenergic blockade is not counteracted by catecholamines such as isoprenaline.

Ether and chloroform cause cardiac arrest in animals when either is administered in the presence of sympathetic blockade at any level, including that of the beta-adrenergic receptors (Brewster, Isaacs and Andersen, 1953; Sekiya and Vaughan-Williams, 1965). Propranolol also causes cardiac collapse when given to dogs anaesthetized with ether or chloroform but has no such action in the presence of halothane (Rouse, 1966). The pharmacological effects of beta-adrenergic blockade during anaesthesia with thiopentone, methoxyflurane, the nitrous oxide-relaxant and various other techniques have not been defined.

Light planes of cyclopropane or halothane anaesthesia appear to be safely compatible with beta-adrenergic blockade with pronethalol in atro-
pinized patients with normal cardiovascular and respiratory systems (Johnstone, 1964a). A preliminary study of propranolol in the treatment of cyclopropane-induced ventricular arrhythmias in atropinized patients showed it to be immediately effective (Johnstone, 1964b). The adult dose was from 2 to 5 mg intravenously. Sensitivity to the drug increases with age, the higher doses being required in patients between the ages of 16 and 35 years (fig. 3).

In view of the limited nature of the available pharmacological evidence concerning the compatibility of beta-adrenergic blockade with the various anaesthetic techniques it was decided to restrict its further use in anaesthetics to selected patients lightly anaesthetized with halothane in oxygen. Some of the reasons for the use of a beta-adrenergic blocker during anaesthesia have already been described (Johnstone, 1964a, b). The same considerations were applied in the investigation of propranolol. Particular attention was paid to its effects on the sinoatrial, the atrioventricular and the ventricular tachycardias which may be provoked by surgical stimulation or by the injection of catecholamines or atropine into patients lightly anaesthetized with halothane. Propranolol 2 to 10 mg has now been administered to 200 patients selected from a total of 2000 patients anaesthetized with halothane during the past 18 months. The remainder of this report is an account of the method used and the results obtained in assessing the effects of propranolol on the heart during halothane anaesthesia.

**METHOD**

The patients to whom propranolol was administered during halothane anaesthesia were aged between 16 and 73 years. All except twelve had
Female, 22 years. Evacuation of the uterus. Blood pressure 130/80 mm Hg. No premedication.
A. Cyclopropane anaesthesia for 15 minutes. Blood pressure 135/80 mm Hg.
B. 1 minute later after atropine 0.5 mg intravenously. Blood pressure 145/90 mm Hg.
C. 1 minute later: propranolol 5 mg intravenously. Blood pressure 140/90 mm Hg.

clinically normal cardiovascular and respiratory systems. The twelve exceptions had clinical and electrocardiographic signs of hypertensive heart disease, old myocardial infarcts, or atrial fibrillation; none of them suffered from congestive heart failure or asthma. Obstetric patients were excluded, as were those with metabolic acidosis, bacterial toxaemia or sepsis, diminished blood volume, or diseases requiring prolonged chemotherapy. The operations included herniorrhaphy, appendicectomy, hysterectomy, prostatectomy, colporrhaphy, thyroidectomy, mastectomy, laminectomy and various orthopaedic, gynaecological and plastic procedures. Upper abdominal and intrathoracic procedures were excluded as mechanical interference with the venous return during these operations often causes fluctuations of cardiovascular activity which are difficult to dissociate from those caused by drugs.

Most patients were premedicated with pethidine 50 mg and either promethazine 50 mg or haloperidol 5 mg intramuscularly 1 hour preoperatively. Anaesthesia was induced with thiopentone 150 to 200 mg intravenously and maintained in a light plane, with halothane in oxygen. Atropine 0.25 to 0.5 mg was usually injected with the thiopentone, except where otherwise stated. The usual indications for endotracheal intubation under suxamethonium paralysis were observed.

“Light” halothane may be described as the dose which maintains anaesthesia with maximal peripheral vasodilatation and a less than 20 per cent decrease in the systolic pressure after the onset of surgery. These conditions are provided by the passage of 30 to 40 ml/min of halothane vapour (1 l./min of oxygen through a Fluotec vaporizer set at 3 or 4 per cent) into a circle or a to-and-fro system with a 2-litre bag and a soda-lime filter. The dose is decreased as the period of anaesthesia increases and is often in the region of 15 ml/min of vapour after 30
minutes. This dose is safely compatible with
tubocurarine 20 mg or gallamine 80 mg for
abdominal relaxation in adults.

Prior to the intravenous injection of propranolol
the dose of halothane was adjusted to ensure that
the blood pressure and the pulse rate of each
patient were not reduced by more than 20 per
cent of their pre-induction levels. The propranolol
was then administered either immediately before
or a few minutes after the initial surgical incision.
An adequate respiratory minute volume was main-
tained by either spontaneous or manually
controlled respiration. The blood volumes were
preserved within normal limits by the intravenous
infusion of the appropriate fluids. Methoxamine
2 to 5 mg intravenously was used to restore
normal blood pressures in each of fifteen patients
in whom moderate degrees of postural hypo-
tension were induced for haemostatic purposes
for 30 to 40 minutes after the injection of prop-
ranolol.

The electrocardiogram and the digital plethys-
mogram were displayed continuously on a two-
channel oscilloscope throughout the period of
anaesthesia in all cases. Paper recordings were
obtained at intervals, the monitoring procedure
being essentially similar to that used in the
investigation of pronethalol (Johnstone, 1964a).
A Piezo electric-crystal transducer was used,
instead of the carbon microphone, for monitoring
the volume pulse wave. This device was more
reliable and consistent in its performance than the
carbon-microphone. It was still possible to
measure the velocity of the pulse wave from the
heart to a finger by feeding the signals from the
electrocardiographic electrodes and the finger
transducer simultaneously into the recorder in
the manner previously described (Johnstone,
1964a). Details of the equipment have been
reported separately (Horsfall and Johnstone,
1964). The effect of propranolol on the latter
parameter was studied in ten anaesthetized
patients as it was considered, like the volume-
pulse amplitude, to be a useful index of changes
in the contractile force of the ventricles in a vaso-
dilated patient.

The systolic blood pressure was measured at
frequent intervals in all patients by brachial cuff
occlusion. The cuff pressure which obliterated
the digital pulse wave was regarded as the systolic
pressure.

 RESULTS

The effects of propranolol on ventricular arrhyth-
mos.

Ventricular arrhythmias appeared in eighteen
patients after the induction of halothane anaes-
thesia. All except one received atropine 0.5 mg
with the induction dose of thiopentone. The
arrhythmias consisted of three instances of
isolated ventricular extrasystoles, twelve of big-
eminy and three of multifocal ventricular beats.
All except one were related to surgical stimulation
of the skin, periosteum, or the pelvic floor during
light anaesthesia. The exception was an elderly
female with atrial fibrillation due to thyrotoxic
heart disease for which a partial thyroidectomy
had been performed three months previously. A
multifocal ventricular arrhythmia occurred during
the induction of anaesthesia with thiopentone—atropine was not given. The ventricular arrhyth-
mia in this patient persisted for several minutes
despite adequate ventilation and a reasonable
depth of anaesthesia. It disappeared within 1
minute after the intravenous injection of prop-
ranolol 2 mg intravenously, with the reap-
pearance of the atrial fibrillation which persisted
throughout the subsequent cystoscopy which
lasted 35 minutes. The ventricular arrhythmias in
the remaining cases were also immediately
abolished by propranolol. A dose of 2 to 3 mg
was effective in the patients who were over 60
years of age and the 5-mg dose was usually
required for immediate effect in the younger
patients. Sinus rhythm persisted throughout the
remainder of the anaesthesia in all cases and no
significant changes were observed in the blood
pressure.

Atropine-induced tachycardia.

Twenty-five patients between the ages of 17
and 55 years were investigated. No vagolytic
drugs were given prior to the induction of anaes-
thesia. Anaesthesia was induced with thiopentone
and maintained with halothane in oxygen. Atro-
pine 1.0 mg was injected intravenously a few
minutes after the start of the surgical operation;
5 minutes later each patient was given propranolol
5 mg intravenously; 15 minutes later this dose was
repeated.
Before injection of atropine the sinus rates of the anaesthetized patients were between 48 and 94 (mean 61) beats/min; and the systolic blood pressures were between 95 and 115 (mean 105) mm Hg. Following atropine the figures rose to 95 to 140 (mean 120) beats/min and 115 to 145 (mean 127) mm Hg respectively. Propranolol reduced the sinus rates in all patients. The slowing usually commenced 1 minute after the injection and was slowly progressive for about 10 minutes. At 15 minutes the range of sinus rates was 60 to 110 (mean 72) beats/min, the faster rates occurring in the younger patients. The systolic pressures usually showed falls which did not exceed 20 mm Hg. The second 5-mg dose of propranolol caused no further changes in the blood pressure and slight decreases in the sinus rates of seven patients, all of whom were between the ages of 17 and 25 years. Precipitous falls in the blood pressure and the pulse rate did not occur in any patient.

The amplitude of the volume-pulse wave was altered characteristically in all patients. All patients showed the usual large increase after the induction of halothane anaesthesia, an increase which sometimes preceded the fall in blood pressure. A further increase often occurred after the incision of the skin (fig. 7). Atropine caused no change, apart from the rate increase, in nineteen patients; all of whom had considerable increases in the pulse rates. Propranolol caused no change in the amplitudes of twelve patients; a slight decrease (mean 14 per cent) in nine; and a small increase in the remainder. The increases occurred in patients whose sinus rates exceeded 120 beats/min after the injection of atropine.

Sensitivity to the hypotensive effect of halothane was increased in all patients after the injection of propranolol. Doses of halothane not usually associated with much hypotensive action in the more robust patients (3 per cent in oxygen 1 l./min into a circle system) caused a slowly progressive decline in the blood pressure and in the amplitude of the volume-pulse. Both changes were promptly reversed by reducing the dose of halothane or by methoxamine 5 mg intravenously.

A similar study was conducted on fifteen patients, using the relaxant gallamine 80 mg instead of atropine. Gallamine caused sinus tachycardia in thirteen patients and atrioventricular nodal tachycardia in two. Three minutes after the injection of propranolol sinus rhythm was present in all patients at rates ranging between 50 and 75 beats/min (fig. 4).

Propranolol in non-atropinized patients.

Propranolol 5 mg was administered to each of twenty-five non-atropinized patients anaesthetized with halothane. Before injection of propranolol the ranges of sinus rates and systolic pressures

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**FIG. 4**

Male, 52 years. Herniorrhaphy. Blood pressure 145/80 mm Hg. Premedication: pethidine 50 mg and promethazine 50 mg.

A. Halothane for 25 minutes and gallamine triethiodide 80 mg. Blood pressure 135/80 mm Hg.

B. 1 minute later: propranolol 5 mg. Blood pressure 120/70 mm Hg.
were 55 to 84 (mean 63), beats/min and 95 to 150 (mean 110) mm Hg respectively. Propranolol reduced the pulse rate and the systolic pressure in all patients, and the amplitude of the volume-pulse in most. The slowing was excessive in nine patients and rates around 40 beats/min were encountered. The bradycardia was regular and of sino-atrial origins in five of these, and irregular with mixed sino- and atrioventricular nodal beats in the remainder. Two of the latter arrhythmias were associated with considerable falls in blood pressure and in the amplitude of the volume-pulse.

Atropine 1.0 mg intravenously abolished the cardiac inhibition and restored the blood pressure and the pulse rates to normal levels in all patients. The range of the pulse rates after the atropine was 60 to 73 (mean 63) beats/min. The amplitude of the volume-pulse wave was also increased but did not always return to its pre-propranolol height. A typical sequence of events is illustrated in figure 5.

**Propranolol and catecholamine infusions during halothane anaesthesia.**

Adrenaline in doses of 0.25 mg to 0.5 mg in a 1/200,000 solution was infiltrated by surgeons into the subcutaneous and the muscle tissues of twenty-one non-atropinized patients anaesthetized with halothane to provide bloodless operating fields. Immediately before or during the infiltration each patient was given propranolol 5 mg mixed with atropine 0.5 mg intravenously.

Ventricular extrasystoles did not occur in any patient after the infiltration of adrenaline. Apart from transient increases in the blood pressure, no significant changes were seen.

Intravenous infusions of noradrenaline solutions 1/125,000 were given to sixteen patients in whom normal or 20 per cent elevations of the normal systolic blood pressure were required for short periods during the operations. Each patient was premedicated using pethidine 50 mg with promethazine 50 mg or haloperidol 5 mg. Anaesthesia was induced with thiopentone (150 to 200 mg) and maintained in a light plane for at least 30 minutes with halothane in oxygen. Propranolol 10 mg mixed with atropine 0.5 mg was then injected intravenously and the noradrenaline infusion started. The drip rate was adjusted to give 32 μg/min of noradrenaline until the desired
level of blood pressure was obtained, usually in 2 to 3 minutes. The drip rate was then reduced and steady levels of systolic pressure were maintained with doses of up to 20 \( \mu \text{g/min} \) for about 20 minutes, or until a total dose of 500 \( \mu \text{g} \) were given.

Sinus rhythms persisted in all patients during the periods of noradrenaline infusion, with minor variations in rate. Ventricular ectopic beats did not occur. The peripheral vasodilatation caused by the halothane, as depicted by the volume-pulse wave, was considerably reduced in all patients by the infusion and reappeared within 2 minutes of stopping it. The typical changes are illustrated in figure 6.

**The adrenergic response to surgery.**

It is well known that the initial surgical incision often causes a brisk rise in the blood pressure, which sometimes exceeds the pre-induction level in a patient lightly anaesthetized with halothane. The increase is usually associated with an increase in the amplitude of the volume-pulse, suggesting that it is due to adrenergic stimulation of the myocardium (fig. 7). The pulse rate also increases and ventricular ectopic beats may appear, especially in atropinized patients. These reactions combine to produce much bleeding from cut tissues, presumably because of the increases in cardiac output and peripheral blood flow.

Relatively large doses of halothane are required to block completely the adrenergic reactions of the heart to surgical stimulation, especially in robust subjects. These doses are considerably greater than those required for narcosis or muscular relaxation, and are potentially dangerous in inexperienced hands when they are administered by controlled respiration.

Propranolol in doses of 3 to 5 mg has now been administered intravenously to eighty patients anaesthetized with halothane for operations in which the need for haemostasis was recognized. The operations included mastectomy, thyroidectomy, vaginal hysterectomy and various orthopaedic and plastic procedures. Only those patients who showed little or no hypotensive response to the halothane were chosen. Propranolol, mixed with atropine 0.25 to 0.5 mg, was injected a few minutes before the initial surgical incision. The usual adrenergic cardiovascular response to the
surgical incision was completely blocked in all cases, the heart rate, systolic pressure and pulse-wave amplitude remaining unchanged. Excellent haemostasis was obtained by combining postural drainage with minimal doses of halothane which usually did not exceed 30 ml/min of vapour. Moderate degrees of hypotension—60 to 70 mm Hg systolic—could be rapidly induced with slightly higher doses of halothane, especially when administered by controlled respiration with the patient in a 15-degree head-up tilt. Reversal of the hypotension was usually achieved by reducing the dose of halothane and tilting to a head-down posture whenever practicable. The return of the blood pressure to normotensive levels was usually slow when the patient was supported in the head-up position. The hypotension in these circumstances was associated with a considerable decrease in the amplitude of the volume-pulse, presumably because of the reduced cardiac stroke-volume from the diminished venous return caused by the pooling of blood in the dependent parts. Methoxamine 2 to 5 mg intravenously caused an immediate increase in the blood pressure and in the amplitude of the volume pulse in all twelve patients to whom it was given for the treatment of postural hypotension during halothane-propranolol anaesthesia. A larger dose of methoxamine caused a further increase in the blood pressure and a progressive decrease in the amplitude of the pulse wave. It would seem that the venous return is expedited by small doses of methoxamine. Larger doses cause widespread vasoconstriction (fig. 8).

The precise duration of action of a single dose of propranolol is difficult to assess accurately in the anaesthetized patient. Judging from the time interval elapsing between injection and the subsequent return of response in the pulse rate to surgical stimuli, it would appear to be in the region of 60 minutes.

Propranolol and the conduction time of the pulse wave during halothane anaesthesia.

The conduction time of the pulse wave was obtained by measuring the time interval between the R wave of the electrocardiogram and the arrival of the pulse wave in the finger as depicted by the crystal-transducer of the plethysmograph. Ten surgical patients between the ages of 26 and 38 years were selected. Their cardiovascular and respiratory systems were normal. Measurements of the pulse wave conduction time were obtained before the induction of anaesthesia, after 30 minutes of halothane anaesthesia and approximately 15 minutes of operative surgery, and again at 5 minute intervals after the intravenous injection of propranolol 5 mg. Five of the patients received atropine 0.5 mg intravenously 5 minutes before the injection of propranolol. The atropine was withheld in the remaining five patients until 5 minutes after the injection of propranolol when the 0.5-mg dose was injected intravenously.

Before induction of anaesthesia, the time interval between the R wave and the digital pulse wave was from 0.14 to 0.18 sec in the ten patients.
Propranolol (Inderal) During Halothane Anaesthesia

During halothane anaesthesia it increased to 0.18 to 0.24 sec. No further change occurred following the injection of propranolol in the atropinised patients. The injection of propranolol caused a further increase in the conduction time to a range of 0.26 to 0.31 sec in the non-atropinized group. The intravenous injection of atropine reduced the conduction time of the latter group to a range of 0.20 to 0.28 sec. The typical sequence of changes is illustrated in fig. 9.

Discussion

The results of this and the other investigations to which reference has been made indicate that propranolol blocks the cardiac overactivity caused by fear, pain, vagolytic drugs, surgical trauma, anaesthesia, respiratory acidosis and catecholamines of either endogenous or exogenous origins. The dose range in atropinized adults anaesthetized with halothane is from 2 to 10 mg according to the age of the patient and the intensity of the adrenergic stimulus. Sensitivity to the drug increases with age, doses of 2 mg being effective in the control of ventricular arrhythmias of anaesthetic origins in the elderly patients. The larger doses are required to control the arrhythmias in young adults particularly when they are caused by exogenous catecholamines. The duration of action of a 5-mg dose appears to be in the region of 60 minutes. Its competitive action on the heart may be overcome by the administration of isoprenaline, as suggested by Mahon (1965).

It would seem that the heart which is under the combined influences of atropine and propranolol is essentially "denervated". Its rate in these circumstances is the intrinsic rate (Jose, 1966) of the sino-atrial node which varies with the age of the patient. The intrinsic rate of patients between the ages of 17 and 45 years in this investigation was between 110 and 80 beats/min respectively. As the age of the patient increased the intrinsic rate during halothane anaesthesia decreased and at 60 years of age was approximately 60 beats/min.

The slow intrinsic heart rate of the elderly patient during halothane anaesthesia combined with propranolol and atropine will not respond to further doses of atropine because the adrenergic drive of the circulating catecholamines has been blocked. This may give the impression in dealing

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**Fig. 9**

Electrocardiogram and volume-pulse wave on a single channel tracing to permit the measurement of the pulse wave velocity. Recorder speed 50 mm/sec.

A. Before induction. Conscious, apprehensive and vasoconstricted. Blood pressure 150/90 mm Hg. Premedication: pethidine 50 mg and promethazine 50 mg.

B. Surgery during halothane anaesthesia. Blood pressure 145 mm Hg systolic. Conduction time 0.21 sec.

C. 3 minutes later: propranolol 5 mg intravenously. Blood pressure 80 mm Hg systolic. Conduction time 0.28 sec.

D. 2 minutes later: atropine 0.5 mg intravenously. Blood pressure 120 mm Hg systolic. Conduction time 0.20 sec.
with the anaesthetized-curarized patient, that the vagolytic effects of atropine have been annulled and that it may be inadvisable to administer cholinergic drugs for the reversal of the somatic effects of a competitive relaxant (Vetten and Kündig, 1965). The intravenous injection of the usual 1-mg dose of atropine with the neostigmine will undoubtedly fail to cause the usual tachycardia in the presence of propranolol. During this investigation a similar dose of atropine with neostigmine 2.5 mg was administered intravenously to twenty-one patients to reverse the effects of gallamine or tubocurarine. The usual increases in the pulse rates did not occur when the atropine was administered within 30 minutes after the propranolol injection. The neostigmine caused minimal slowing of the pulse rate. As the response of the somatic musculature to the neostigmine was satisfactory in all cases it may be concluded that beta-adrenergic blockade with propranolol does not impair the anticholinergic action of atropine on the heart.

Judging from the changes observed in the form of the pulse wave, its velocity, and in the blood pressure, it would seem that the effects of propranolol on the contractile force of the heart during halothane anaesthesia depend on the conditions prevailing at the time of its injection. When the drug is administered in the absence of atropine there usually occurs a decrease in the amplitude and rate of the volume-pulse, a decrease in the blood pressure and a slowing of the pulsewave velocity. These changes are reversed by atropine and may therefore be regarded as being predominantly of vagal origins because of the relative increase in cholinergic activity brought about by the adrenergic blockade.

The administration of propranolol to an atropinized patient after the start of the surgical operation is also followed by decreases in the heart rate, the amplitude of the volume-pulse wave and the blood pressure. The changes in the blood pressure and in the amplitude of the pulse wave do not occur in atropinized patients when the propranolol is administered before the start of the surgical operation. It may be concluded, therefore, that the decrease in cardiodynamics observed in the former circumstances is the result of the insolation of the heart from the adrenergic effects of surgical stimuli.

It is interesting to note that the combined effects of halothane and propranolol on the atropinized heart do not impair its ability to respond immediately to an increase in the venous return brought about by methoxamine. In other words, the intrinsic ability of the myocardium to raise its output in response to an increased venous return is independent of catecholamines and is intact for all practical purposes during halothane anaesthesia in normovolaemic patients. The initial increase in the amplitude of the volume-pulse following the intravenous injection of small doses of methoxamine into atropinized patients rendered hypotensive by the combined effects of the head-up posture, halothane and propranolol, suggests that the initial rise in the blood pressure in response to methoxamine is due to an increase in the stroke-volume of the heart secondary to an increase in the venous return.

Li, Shimosato and Ettsten (1965), using the conventional methods of measuring the cardiac output, stroke volume, ventricular work and the total peripheral resistance in patients during spinal analgesia, observed that methoxamine often raised the cardiac output and stroke-volume by augmenting the venous return. Blinks (1964) has shown that low concentrations of methoxamine block the inotropic and chronotropic effects of catecholamines on the isolated atria of guinea pigs and have no effect on the strength or frequency of spontaneously occurring contractions. In this respect methoxamine appears to be a beta-adrenergic receptor blocker incapable of directly stimulating the myocardium. It is, therefore, apparent that the beta-adrenergic blocking actions of propranolol and methoxamine during halothane anaesthesia do not impair the inherent ability of the heart to increase its output in response to an augmented venous return. As methoxamine is predominantly an alpha-adrenergic receptor agonist it is evident that the sensitivity of the alpha-adrenergic receptors of the peripheral blood vessels in man is unaffected by halothane and propranolol.

Whilst it is clear that a postural hypotension in a patient during halothane-propranolol anaesthesia will respond satisfactorily to treatment with methoxamine, it is also equally clear that a hypotension primarily due to myocardial failure will not. Vetten and Kündig (1965) have reported
the occurrence of bradycardia and hypotension refractory to both atropine and methoxamine during open-heart surgery under nitrous oxide-methoxyflurane anaesthesia in two patients who were treated pre-operatively with pronethalol. Transient improvements in cardiovascular performance were obtained with isoproterenol in both cases.

It should be emphasized that halothane is the only anaesthetic agent which has been shown clinically and experimentally to be safely compatible with the simultaneous induction of beta-adrenergic blockade with small doses of propranolol in patients with normal cardiovascular systems. The effects of halothane anaesthesia on patients previously treated for long periods of time with larger doses of propranolol are not known. Where other anaesthetic agents have been involved, ether and chloroform would appear to be contraindicated in the presence of beta-adrenergic blockade, and vice versa. The position of nitrous oxide and methoxyflurane in relation to beta-adrenergic blockade has not been determined in either man or the experimental animal. Caution should therefore be exercised in the use of beta-adrenergic blockers during anaesthesia with the latter agents until the performance of the heart under their combined effects has been investigated pharmacologically.

A major problem presently confronting anaesthetists is the anaesthetic management of emergency surgical operations in patients previously treated with beta-adrenergic blockers. The complications of acute surgical ailments—hypovolaemia, dehydration, electrolyte depletion, metabolic acidosis, bacterial toxaemias and sepsis—may aggravate a pre-existing heart disease. In these circumstances the survival of the patient may depend on the unimpaired action of catecholamines on the myocardium. It might, therefore, be necessary to increase the supply of circulating catecholamines from exogenous sources in order to overcome the competitive blockade imposed by the propranolol. Before the induction of anaesthesia the blood volume should be adequately restored and atropine administered. The maintenance of myocardial function during anaesthesia may require the continued intravenous infusion of a beta-adrenergic stimulant, e.g. isoprenaline.

The prevention and the control of the cardiac arrhythmias caused by catecholamine injections are the obvious indications for the use of propranolol during general anaesthesia. It is known that the intravenous infusion of adrenaline or noradrenaline solutions into patients anaesthetized with halothane will precipitate ventricular arrhythmias when the dose of either exceeds 10 \( \mu g \) a minute (Andersen and Johansen, 1963). In the present study it has been observed that atropinized patients protected by propranolol in doses up to 10 mg will tolerate noradrenaline in doses up to 32 \( \mu g \) a minute for 20 minutes during halothane anaesthesia without the appearance of cardiac arrhythmias. This dose of noradrenaline increases the blood pressure and constricts the peripheral blood vessels.

The induction and the control of hypotension for haemostatic purposes during halothane anaesthesia is facilitated by propranolol. Propranolol seems to act by preventing the adrenergic response to surgical stimulation especially in robust subjects under halothane anaesthesia. At the moment it would seem desirable to withhold the beta-blocker until surgical anaesthesia has been induced and the response of the blood pressure to the vasodilatation of halothane has been assessed. Halothane will sometimes provide sufficient hypotension and haemostasis. In certain circumstances such as phaeochromocytomas, thyrotoxicosis, hypertension with tachycardia, or pulse irregularities due to digitalis or quinidine, it may be advisable to give the propranolol before the induction of anaesthesia.

In conclusion, it may be stated that the heart of a reasonably fit normovolaemic patient will safely tolerate a moderate depth of halothane anaesthesia in the presence of combined beta-adrenergic and cholinergic blockades with propranolol and atropine respectively. It should be remembered, however, that the heart so treated is insulated from its autonomic protection. Its continued action depends on the intrinsic periodicity of the pacemaker and the inherent contractility of the myocardium, both of which may be directly depressed by drugs and by surgery. Changes in the rate, apart from slowing, will not occur in response to the return of consciousness, blood loss, respiratory acidosis, hypoxia or asphyxia. The cardiac reactions to excessive doses
of anaesthetic or other drugs may be profoundly depressant. Whilst adding to the safety of anaesthesia in a manner not previously possible, blockade of the beta-adrenergic receptors of the heart with propranolol may add to the dangers thereof if it is not applied with care.

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REFERENCES


PROPRANOLOL (INDERAL) DURING HALOTHANE ANAESTHESIA

LE PROPRANOLOL (INDERAL) PENDANT L'ANESTHESIE À L'HALOTHANE

ZUSAMMENFASSUNG
Bei einem Patienten mit normalem Herz-Kreislauf-
System und nach Atropin-Gabe vertritt sich Pro-
pranolol (Inderal) gut mit einer oberflächlichen
Halothan-Narkose. Es verhindert die durch Angst,
Schmerz, vagolytische Arzneimittel, chirurgischen
Reiz und Katecholamine verursachte Überaktivität des
Herzens und Herzrhythmen. Bei Beurteilung der
Wirkung anhand der Auswirkungen auf die Volumen-
pulschwelle, das Elektrokardiogramm, den systolischen
Blutdruck und die Pulswellengeschwindigkeit kann
geschlossen werden, daß die Kombination der Wirk-
ungen einer oberflächlichen Halothan-Narkose und der
beta-adrenergen Blockade durch das Propranolol
die dem gesunden Myokard innenwahrende eigene Kon-
taktilität oder dessen Fahigkeit zu einer sofortigen
Reaktion auf einen Anstieg des venösen Rückflusses
bei Patienten mit Vasodilatation durch Atropin nicht
nennenswert beeinflußt. Die möglichen Gefahren der
wichtigsten Voraussetzungen für die Narkose werden
nochmals angesprochen. Was die neue Narkosemittel
sind nicht anwendbar auf andere Narkosemittel
sondern nur auf das Halothan.

BOOK REVIEW

Emergency Anaesthesia. Edited by H. L. Thornton
and P. F. Knight. Published by Edward Arnold
Price £5 net.
The editors of this volume have successfully collected
information relevant to emergency anaesthesia, to be
undertaken by novices or by experienced anaesthetists
in both poorly and well-equipped hospitals. The book
is well produced, makes interesting reading, and the
problem of multiple authorship (12 writers for 20
chapters) appears to have been largely overcome.
Illustrations are generally excellent; exceptions, to
the reviewers, are the insertion of an intravenous
needle right up to the hub (p. 82), a rather dark and
small epidural tray (p. 147), and in the photograph
illustrating external defibrillation (p. 428) the operator
is not wearing rubber gloves while the anaesthetist
is touching the patient at the moment of electrical
discharge.
Dogma is occasionally obvious: cyclopropane is
contraindicated in diabetes mellitus; analgesic sprays
to the larynx are condemned on grounds of introduc-
ing tracheal infection; and, in regard to atropine, it is
said that its use is mandatory in most cases, that it is
contraindicated in any digitalized patient, and that it
should be given even after injection of pethidine,
chlorpromazine, and promethazine.
There are a few further curiosities: since tubo-
curarine releases histamine, gallamine causes tachy-
cardia, and succinylcholine stimulates autonomic
ganglia, decamethonium is said to be the muscle
relaxant of choice in the patient with a phaeochromo-
cytoma. Just a bit theoretical in an essentially practical
book. And it is safe, in a brief chapter on ophthalmic
emergencies, to induce facial nerve block with ligno-
caine and 1/80,000 adrenaline hydrochloride during
recovery from halothane anaesthesia?
The section on blood transfusion is perhaps the
most helpful, concise, and impressive among those
written for anaesthetists, while fluid and electrolyte
balance is dealt with succinctly and clearly. Deserving
special mention, also, is "Emergency anaesthesia in
the presence of intercurrent disease", a 39-page effort
of much practical merit, written by the two editors.
Partly on account of the illustrations, the chapter
on regional anaesthesia stands out; but it was disap-
pointing to find no reference to axillary brachial
plexus block, and it might have been useful to
emphasize the simplicity of the short (British No. 1
disposable) needle for caudal analgesia.
Neuroleptanalgesics, although perhaps of little value
in emergency anaesthesia, do not receive specific men-
tion. In a generally satisfying chapter on postoperative
anesthetic complications, there is insufficient distinc-
tion made between the atypical (dibucaine resistant)
pseudocholinesterase and the fluoride variant, and no
mention of complete absence of the enzyme (a situa-
tion causing the longest apnoea).
As in other matters, it is considerably easier to
discuss than to write a new book, but this worth-
while effort is likely to survive the foregoing criticisms,
and others might well profit by what have been omitted
(there are a good many spelling or printing errors).
It is easy to visualize a volume of such excellent
general presentation extending into several editions of
even greater practical value, but readers will plead
for no increase, and preferably a reduction, in size
and price. Truth, brevity, and common sense remain
the order of today and tomorrow for survival of the
medical textbook.
R. J. Bailey
R. A. Millar