ICI 50,172* DURING HALOTHANE ANAESTHESIA IN SURGICAL PATIENTS

BY

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SUMMARY

ICI 50,172 is a cardioselective beta-adrenergic receptor blocker. A dose of 20 mg was given intravenously to each of 75 atropinized patients lightly anaesthetized with halothane in oxygen. Adrenergic overactivity of the heart was present in each patient before the drug was administered. The drug blocked the chronotropic, inotropic and dysrhythmic reactions of the heart to the adrenergic stimuli provoked by surgery under halothane anaesthesia. It did not influence dromotropic activity. It is concluded that ICI 50,172 is superior to propranolol in anaesthetized patients because of its cardioselectivity and its lack of analgesic action.

ICI 50,172 is the code number of a beta-adrenergic receptor antagonist. Its chemical formula is:

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C_{14}H_{22}N_2O_3
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CH_3CO-NH
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\[
O-CH\_CH\_NH-CH\_CH_3
\]

\[
OH
\]

4-(2-hydroxy-3 isopropyloninopropoxy) acetanilide

A pharmacological study (Dunlop and Shanks, 1968) shows that it blocks the effects of catecholamines on the hearts of anaesthetized dogs. Its potency is approximately one-quarter that of propranolol. Unlike propranolol, it has little effect on the beta-adrenergic receptors of the bronchi or the peripheral arteries. It is devoid of analgesic action—it does not block the conductivity of sensory nerve fibres. It has a sympathomimetic influence on the hearts of catecholamine-depleted animals.

Cardiovascular studies by conventional means in men with good cardiac function during erect exercise show that an intravenous dose of 5 mg causes a 16 per cent decrease (mean of 10 subjects) in the heart rate with no changes in the blood pressure or cardiac output, because of a reciprocal increase in the stroke volume following the injection of the drug (Gibson and Sowton, 1968). Similar studies in patients with ischaemic heart disease reveal negative chronotropic and possibly positive inotropic effects after a similar dose. The latter reaction is thought to be a therapeutic advantage over propranolol (Sowton et al., 1968).

The purpose of the present study was to determine the ability of ICI 50,172 to protect the human heart from some of the adrenergic stimuli reflexly or directly provoked by general surgical procedures in anaesthetized patients. The positive chronotropic and inotropic reactions of the heart to such stimuli in normovolaemic patients raise the blood pressure, increase the peripheral blood flow, and cause excessive bleeding from incised tissues (Johnstone and Horsfall, 1966). Ventricular and atrioventricular dysrhythmias may also occur when the sensitivity of the heart to catecholamines is increased by drugs such as halothane or atropine, by an excess of carbon dioxide, or by diseases such as thyrotoxicosis or phaeochromocytoma.

Some of the surgical procedures which reflexly cause sympathetic overactivity of the heart of an anaesthetized patient are: swabbing of the female perineum with tincture of iodine; the insertion of a cystoscope into a male with urethral obstruction; incision of the skin; dilatation of the anal sphincter; operations involving the pelvic floor.

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* Code number, property of Imperial Chemical Industries Limited. The drug has now been named Eraldin.
surgical interventions on the periosteum and the tissues of the skeletal joints; and the intraperitoneal insufflation of carbon dioxide gas for endoscopic purposes. Cardiac hyperactivity may be precipitated in anaesthetized patients by the topical application or the hypodermic injection of adrenaline or other beta-adrenergic agonists.

**METHOD**

Seventy-five patients in whom signs of cardiac overactivity occurred during surgical operations under general anaesthesia were selected for study. Their ages ranged from 18 to 50 years and each had clinically normal cardiovascular and respiratory systems. They came to the hospital for surgery involving one or more of the above-mentioned surgically adrenergic procedures. The dysrhythmic reactions of their hearts to an excess of carbon dioxide and the effect of ICI 50,172 thereon were studied in 12 of them whose peritoneal cavities were distended with carbon dioxide to facilitate laparoscopy. The effects of subcutaneous injections of adrenaline solution 1/200,000 were observed in 9 patients, the injections being given for haemostatic purposes.

A standard method of pre-operative sedation and anaesthesia was used in all patients. Each was given haloperidol 5 mg with pethidine 50 mg intramuscularly 1 hour before the induction of anaesthesia. Anaesthesia was induced with an intravenous injection of propanidid 250 mg mixed with atropine 0.5 mg. Anaesthesia was maintained with halothane in oxygen from a circle system (Boyle Mark 3) fed by a Fluotec vaporizer situated outside the circuit. A face-mask and an oropharyngeal airway were used in all patients. The dose of halothane used for the maintenance of anaesthesia was 3 per cent in an oxygen flow of 1 l./min after 5 minutes with a similar concentration in an oxygen flow of 5 l./min into the circuit. Spontaneous respiration was maintained in all patients at a minute volume between 6 and 10 l./min as shown by a Wright respirometer. A soda-lime absorber was in the circuit.

The chronotropic, dromotropic and dysrhythmic activities of the patients' hearts were displayed continuously and registered periodically by electrocardiography. Changes in the inotropic activity of the heart were observed indirectly by digital plethysmography, phonocardiography and conventional sphygmomanometry, using the devices previously described (Horsfall, 1968; Johnstone and Barron, 1968). Permanent records were made immediately before the initial surgical incision and at 1-minute intervals for 15 minutes thereafter. A 20-mg dose of ICI 50,172 was given intravenously to each patient 3 minutes after cardiac hyperactivity became evident.

**RESULTS**

**Sinus tachycardia.**

Sinus tachycardia was present in 50 patients after the operations started. The range of sinus rates was 115–155 beats/min (mean 123); 5 minutes after the injection of ICI 50,172 the range was 70–105 beats/min (mean 89). The atrioventricular conduction times were unchanged.

**Ventricular and atrioventricular dysrhythmias.**

Prior to the injection of ICI 50,172 ventricular dysrhythmias were present in 21 patients and supraventricular dysrhythmias in 4. The ventricular variety consisted of 5 patients with multifocal ventricular tachycardia, 13 with bigeminy, and 3 with isolated ventricular extrasystoles.

The intraperitoneal insufflation of carbon dioxide was followed by the appearance of bigeminy in 3 patients and by multifocal ventricular tachycardia in 1. The subcutaneous injection of adrenaline caused bigeminy in 3 patients, ventricular tachycardia in 1, and supraventricular tachycardia in 1.

The 20 mg dose of ICI 50,172 restored sinus rhythms in all patients within 1 minute after injection (figs. 1 and 2).

A  
B  

![Fig. 1](image)


A. Halothane anaesthesia, 3 minutes after the subcutaneous infiltration of adrenaline. Blood pressure 120 mm Hg systolic.

B. 2 minutes after ICI 50,172 20 mg i.v. Blood pressure 120 mm Hg systolic.

Recorder speed 25 mm/sec.

A. Halothane anaesthesia during the intraperitoneal insufflation of carbon dioxide. Blood pressure 90 mm Hg systolic.

B. 2 minutes after ICI 50,172 20 mg i.v. Blood pressure 110 mm Hg systolic.

Recorder speed 25 mm/sec.

Systolic blood pressure.

Following the induction of halothane anaesthesia and immediately before the initial surgical incision the range of systolic blood pressures was 80–125 mm Hg (mean 103); 2 minutes after the onset of surgical stimuli the range was 85–155 mm Hg (mean 121). Injection of ICI 50,172 did not alter the blood pressures of 23 patients, 4 patients showed increases, and the remainder decreases which in no case exceeded that which existed prior to the onset of surgery. The range of blood pressures 5 minutes after the injection of ICI 50,172 was 80–115 mm Hg (mean 102).

Volme-pulse (digital).

Fifty patients with regular sinus rhythms were studied. The amplitudes of the pulse waves immediately before surgical stimulation were from 15 to 35 mm (mean 23); 2 minutes after the surgical stimulation the range was 16–36 mm (mean 29); 5 minutes after the injection of ICI 50,172 the range was 15–26 (mean 19). The ICI 50,172 was followed by increases in the amplitudes of the pulse waves in 11 patients, 9 were unchanged, and the remainder decreased. The decreases occurred in the patients in whom increases appeared after the onset of surgery (fig. 3).

Venous occlusion plethysmograms.

Ten patients with regular sinus rhythms and in whom plethysmographic evidence of increases in digital blood flow followed the onset of surgery were selected for study. The responses to surgery and to ICI 50,172 are illustrated in figure 4. Immediately before the initial surgical incision the displacement of the baselines of the plethysmograms of the 10 patients during 5-second periods of occlusion of the venous outflow ranged from 12 to 26 mm (mean 17). During surgery the range was 17–34 mm (mean 22). After ICI 50,172 the range was 11–24 mm (mean 16).

Phonocardiograms.

Ten anaesthetized patients who provided phonocardiographic evidence of increases in the
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Male, 42 years. Haemorrhoidectomy. Blood pressure 130/70 mm Hg. Serial venous-occlusion plethysmograms.
A. Halothane anaesthesia. Blood pressure 110 mm Hg systolic. Baseline displacement in 5 sec is 12 mm.
B. Anal sphincter dilated. Blood pressure 145 mm Hg systolic. Baseline displacement is 23 mm.
C. 2 minutes after ICI 50,172 20 mg i.v. Blood pressure 120 mm Hg systolic. Baseline displacement is 16 mm.

Recorder speed 12.5 mm/sec.

intensity and frequency of the heart sounds and decreases in the duration of systole—the time interval between the first and second heart sounds—after the onset of surgery were selected for study. The increases in the frequency and intensity of the heart sounds and the decrease in the duration of systole provoked reflexly by surgery in each patient were completely reversed by ICI 50,172 (fig. 5). Prior to the onset of surgery the duration of systole in the 10 patients ranged from 0.30 to 0.38 sec (mean 0.346). During surgery it was 0.28–0.32 sec (mean 0.312). After ICI 50,172 it was 0.32–0.36 sec (mean 0.348).

DISCUSSION

These results indicate that ICI 50,172 consistently blocks the sympathetic overactivity of the heart that is caused by surgical stimuli, by subcutaneous injections of adrenaline solutions, or by excesses of carbon dioxide in atropinized patients lightly anaesthetized with halothane. In these circumstances the drug has a negative chronotropic action on the sinus node, the atrioventricular node, and on the tertiary pacemakers of the ventricles. The irritability of the ventricular pacemakers is completely suppressed by ICI 50,172.

The 20-mg dose reduced the mean sinus rate of 50 atropinized and anaesthetized patients from 123 to 89 beats/min, i.e. a 28 per cent reduction in the activity of the adrenergically stimulated sino-atrial pacemakers. The effect lasted for approximately 30 minutes. The negative chronotropic and the anti-arrhythmic actions of the drug were not associated with electrocardiographic evidence of a negative dromotropic action on the cardiac conduction tissue as is seen with the anti-arrhythmic drugs that are analgesic (Johnstone...
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and Barron, 1968). It may therefore be concluded that the anti-arrhythmic action of ICI 50,172 is due to a competitive blockade of the beta-adrenergic receptors and is unrelated to an impairment of conductivity in the Purkinje tissue. No obvious evidence of a positive chronotropic reaction to the drug was observed in any patient.

The plethysmographic studies indicate that ICI 50,172 has a negative inotropic action on the hearts of anaesthetized patients when administered in the circumstances described above. It is believed that changes in the amplitude of the volume pulse in a finger and in the rate of its swelling in response to the occlusion of its venous outflow in patients anaesthetized with halothane, are due to changes in the stroke-volume and output of the heart because the reflex vasoconstrictive reaction of the alpha blood vessels to trauma and hypotension is blocked by halothane (Johnstone 1967; Johnstone and Barron, 1968). Changes in the amplitude of the pulse wave reflect changes in the stroke volume of the heart. Changes in the rate of finger swelling reflect changes in cardiac output.

Venous occlusion plethysmography showed considerable decreases in the peripheral blood flow immediately after the injection of ICI 50,172. No doubt this was partly due to the decreases in the heart rates. The decrease in the blood pressure, the diminution in the intensity of the heart sounds, the increase in the duration of systole, and the decrease in the amplitude of the volume pulse in most patients, together indicate a decrease in the contractile force of a heart that is under adrenergic stimulation when the drug is administered. The negative inotropism of the drug did not exceed the positive inotropism provoked by the adrenergic stimuli. This effect is in keeping with a blockade of the beta-adrenergic receptors and means that the drug does not directly depress the myocardium.

Moderate increases in the amplitude of the volume pulse followed the administration of ICI 50,172 in 11 patients. This may be due to a sympathomimetic action on the heart causing an increase in its stroke volume. A more likely explanation is that the increase in the stroke volume is secondary to a longer diastolic filling time.

ICI 50,172 is at least a suitable alternative to propranolol (Inderal) for the control of adrenergic overactivity in the hearts of anaesthetized patients. In some respects it may be superior to the latter. Its sympathomimetic action, as shown in the pharmacological experiments by Dunlop and Shanks (1968), and its lack of analgesic activity, indicate the absence of a directly depressant or "quinidine-like" action on the healthy myocardium. The fact that it fails to block the effects of catecholamines on the bronchi suggests that it may be the beta-blocker of choice for use in patients prone to bronchial asthma (Macdonald and McNeill, 1968). In anaesthetic practice it is advisable to administer the drug with a small dose of atropine (0.5 mg intravenously) to avoid the possibility of vagal arrest of the heart: the negative chronotropism of ICI 50,172, like that of other beta-adrenergic blockers, may suddenly expose the unprotected heart to severe vagal inhibition because of the relative increase in vagal tone precipitated by the sudden blockade of the sympathetic innervation.

Halothane in clinical doses is the only anaesthetic agent that has been studied in conjunction with beta-adrenergic blockade imposed by ICI 50,172 or other drugs of this type. Most of the other inhalational and intravenous anaesthetic drugs are regarded as being "catecholamine dependent" and may therefore be unsuitable for use with beta-blockers. The myocardial depressant effect of the volatile ethers is largely offset by spontaneous activation of the sympathetic nervous system, a reaction which may be protective (Brewster, Isaacs and Anderson, 1953).

ACKNOWLEDGEMENT

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REFERENCES


ICI 50,172 DURING HALOTHANE ANAESTHESIA


ICI 50,172 PENDANT L’ANESTHESIE PAR L’HALOTHANE CHEZ DES MALADES CHIRURGICAUX

SOMMAIRE


BOOK REVIEW


The difficulties that are encountered in attempting to unravel the mysteries of foetal physiology in the human are obvious though some progress has been made in recent years and, as the author points out, some investigations are occasionally performed by nature herself. However, the field of comparative foetal physiology is rapidly expanding. This book has therefore been written to gather together all the information that is now known concerning the main features of the development of the foetus and newborn.

The contents cover four topics of foetal and neonatal physiology: the placenta, foetal circulation, labour, and the mechanisms concerned with physiological adjustment following birth. Six chapters cover aspects of placental function including the comparative anatomy, oxygen transfer, the relation to foetal growth, maternal and myometrial blood flow in the umbilical circulation. The foetal circulation, including the pulmonary circulation in the foetus and newborn, and blood-gas tensions are admirably dealt with in the following three chapters. The effects of labour and delivery, the establishment of pulmonary respiration and birth asphyxia, resuscitation and brain damage are described in three chapters which lucidly set out the problems encountered by the foetus in attaining a separate existence. Finally, the last five chapters are concerned with the changes in circulation after birth, the control of the circulation and breathing in the newborn, oxygen consumption and temperature regulation in the newborn, energy metabolism in the foetus and after birth and other aspects of developmental physiology.

Throughout the whole book one is conscious of the tremendous contribution that the author has made personally to the understanding of the problems involved. Not only is the experimental work reviewed critically and with authority but the areas of future work are clearly delineated. Much of what is written has intense practical application to all those concerned with the care of the newborn, and is relevant in particular to those anaesthetists who are involved in the labour ward with parturient women and the resuscitation of the newborn and those who are connected with neonatal surgery and intensive care.

This masterful dissertation must rank as a classic textbook in this field and will certainly advance the general knowledge of the many complex physiological mechanisms of the foetus and newborn.

Gordon H. Bush