THE EFFECT OF METHYLPHENIDATE (RITALIN) ON POST-HALOTHANE MUSCULAR SPASTICITY

BY

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SUMMARY

Methylphenidate, a psychomotor stimulant with a weak sympathomimetic action, completely suppresses the muscular spasticity and tremor which may occur during the recovery from halothane anaesthesia. It is suggested that the spasticity is due to the recovery of spinal reflex activity before the upper motor neurones have recovered from the inhibition of anaesthesia and that methylphenidate acts by stimulating the midbrain reticulum. The adrenergic overactivity of the heart which is provoked by methylphenidate is prevented by small doses of a beta-blocking drug and by neostigmine.

Spasticity of some somatic muscles occurs in about 70 per cent of patients during recovery from halothane anaesthesia. It starts in the masseters and causes trismus. It extends to the adductor and flexor muscles of the upper limbs and may involve the nuchal and the extrinsic laryngeal musculature. In the more severe cases the intercostal, abdominal, spinal and lower limb muscles are affected. Coarse tremor or clonus appears spontaneously in about 30 per cent of cases and may be elicited in others by the prepatellar and ankle tests. The tendon reflexes are exaggerated and a positive Babinski sign may be seen during the period of spasticity.

The incidence of the spasticity is unrelated to the duration of anaesthesia. It occurs more frequently after moderately deep anaesthesia. The duration of the spasticity varies directly with the duration of anaesthesia and may persist for 90 minutes after prolonged anaesthesia (Dawkins, 1961). The spasms precede the return of consciousness and may continue for a short time after. Coincidental with the onset of the spasticity the blood vessels of the skin constrict, causing a shut-down of the pulsatile blood flow. This leads to a fall in the skin temperature and we have recorded decreases of 5°C within 10 minutes after the withdrawal of the anaesthetic.

The syndrome is not of serious consequence in the majority of patients and disappears spontaneously. In certain circumstances it may be serious. Trismus may jeopardize the upper air passages in patients with surgical fixation therapy for mandibular, maxillary and facial injuries, especially in those with nasal obstruction. Spasm of the limb muscles may disrupt the results of orthopaedic procedures for fractures and dislocations, and of plastic operations requiring pedicle-grafts, etc. The intense muscular activity creates an increased demand for oxygen which may be difficult to meet in the presence of impaired respiration due to the spasm of the intercostal and abdominal muscles and to partial obstruction of the upper air passages (Moir and Doyle, 1963; Jones and McLaren, 1965). In view of these dangers it was decided to seek a means to control and to prevent the syndrome.

It has been suggested that the syndrome may be related to heat loss during anaesthesia, though the relationship was not considered to be one of cause and effect (Moir and Doyle, 1963). Although one may suspect heat loss to be a factor in prolonged anaesthesia, it seems unlikely as the syndrome frequently occurs after short operations lasting only one or two minutes on fully clothed patients in warm operating theatres. It is the authors' experience that drugs which suppress...
true shivering, for example opiates and phenothiazine derivatives, have little effect on the spasticity. We have also observed the ineffectiveness of many other drugs in the diazepine, barbiturate, anti-Parkinsonian, cyclohexylamine and sympatholytic groups. On account of the failure of the cerebral-depressant and anticonvulsant types of drug it was decided to investigate the effect of a cerebral stimulant. Methylphenidate (Meier, Gross and Tripod, 1954) was chosen. Its beneficial effect on the spasticity was immediately obvious. In view of the fact that it is also a sympathomimetic, a careful watch was maintained on its effect on cardiac behaviour as it was anticipated that halothane anaesthesia might augment this action. Electromyography, digital plethysmography, electrocardiography and systolic blood pressure measurements by conventional sphygmomanometry were used to assess the effects of the drug. A standard premedication, consisting of pethidine 50 mg and haloperidol 5 mg, was given intramuscularly in all adult patients.

METHOD AND RESULTS

Methylphenidate and muscular spasticity.

An initial series of 50 adult patients was selected. Each patient had undergone major abdominal or orthopaedic surgery under halothane anaesthesia and had developed widespread spasticity during recovery. Methylphenidate 20 mg was given intravenously to each patient when the spasticity had persisted for 5 minutes. The presence of muscular spasticity and the effect of methylphenidate thereon were confirmed by electromyograms from the right pectoralis major muscle. Digital plethysmograms, electrocardiograms and systolic blood pressures were recorded simultaneously. Methylphenidate abolished spasticity in every patient within 2 minutes and there was no recurrence. The recovery of consciousness thereafter was uneventful and associated with normal muscular activity in all patients. The typical sequence of events is illustrated in figure 1.

The prophylactic effect of methylphenidate was then studied in 1000 patients anaesthetized with halothane in oxygen combined with relaxants whenever necessary. The ages of the patients ranged from 2 months to 85 years. The operations were mainly gynaecological, urogenital, orthopaedic, abdominal, plastic and maxillofacial. The dose of methylphenidate ranged from 1 to 5 mg in patients between the ages of 2 months and 5 years; 10 mg in those between 5 and 10 years; and 20 mg in the remainder. The drug was given intravenously about 5 minutes before the withdrawal of the anaesthetic. In selected adult cases, as described below, it was combined with a beta-blocking agent (oxprenolol) to determine the effect of the latter on the cardiovascular reaction to methylphenidate. The cardiovascular reaction was recorded by electrocardiography, plethysmography and sphygmomanometry.

Methylphenidate completely prevented the development of spasticity during the recovery from anaesthesia in all except 7 patients. The 7 exceptions were robust young male adults in whom moderate trismus developed during recovery; a satisfactory response was obtained in each of them from an additional dose of 20 mg intravenously.

FIG. 1

Male, 17 years. Amputation of left forearm for ischaemic gangrene.
Premedication: pethidine 50 mg haloperidol 5 mg, and atropine 0.3 mg.
The plethysmograms are from the little finger on the right hand and the electromyograms are from the right pectoralis major muscle.
A. After 55 minutes of halothane-oxygen anaesthesia.
B. Two minutes after the withdrawal of the anaesthetic. Blood pressure 115 mm Hg systolic and no muscular activity.
C. Two minutes later, after methylphenidate 20 mg i.v. Blood pressure 125 mm Hg systolic. Vasoconstriction and muscular quiescence. Patient conscious.
Methylphenidate and cardiovascular behaviour.

Eighty adult patients were studied. Each patient received atropine 0.3 mg intravenously during the induction of anaesthesia which was maintained with halothane-oxygen and additional curare-type relaxants as required. The operations were major and lasted from 40 to 240 minutes. Methylphenidate 20 mg was given intravenously to each patient a few minutes before the end of the operation. The effects of the drug on the electrocardiogram, digital plethysmogram and systolic blood pressure were recorded at frequent intervals for 15 minutes after the injection. Sinus rhythm was present in all patients prior to the injection of methylphenidate, the range being 65–112 (mean 84) beats/min, blood pressures were between 90 and 146 mm Hg systolic (mean 113), and blood loss was negligible in all cases. The patients were divided into four groups, according to the circumstances in which the methylphenidate was administered:

Group 1. Twenty-five patients with spontaneous respiration which was manually assisted from time to time to ensure a minute volume of 8–10 l./min as measured by a Wright respirometer. Methylphenidate caused atrioventricular nodal tachycardia in 4 patients, sinus tachycardia with occasional ventricular ectopics in 2, sinus tachycardia between 95 and 145 (mean 105) beats/min in 15, and the remainder were unaltered. The cardiac dysrhythmias disappeared spontaneously in approximately 10 minutes and the sinus rates became normal after approximately 20 minutes. The plethysmograms showed no evidence of vasoconstriction during the immediate response to methylphenidate; the systolic blood pressures were unchanged in 19 patients, and slightly raised in the remainder, the maximal elevation being 30 mm Hg.

Group 2. Five patients with spontaneous and slightly depressed respiration which caused a mild respiratory acidosis, the range of carbon dioxide tensions of the arterialized venous blood being 47–58 mm Hg. Methylphenidate caused multifocal ventricular tachycardia in 1 patient, bigeminy in 3, and sinus tachycardia with frequent ventricular extrasystoles in 1. Sinus rhythms at normal rates were restored in all patients within 1 minute by the intravenous injection of oxprenolol 1 mg.

Group 3. Twenty-five patients breathing spontaneously at respiratory minute volumes ranging between 5 and 8 l./min as measured by a Wright respirometer. Oxprenolol 1 mg was mixed with the methylphenidate and both drugs were injected intravenously in each patient. The methylphenidate-oxprenolol mixture caused virtually no changes in cardiac behaviour in this group. The range of sinus rates 2 minutes after the injection was 58–94 (mean 81) beats/min. Blood pressures and digital plethysmograms were unaltered.

Group 4. Twenty-five patients who were lightly anaesthetized and fully curarized. Respiration was controlled throughout the operation in each case at an average minute volume of 8 l./min which maintained normal or slightly lowered carbon dioxide tensions in the blood. Neostigmine 2.5 mg with atropine 1.0 mg was given intravenously at the end of the operation, followed 5 minutes later by methylphenidate. Apart from moderate increases in the sinus rates of 2 patients methylphenidate caused no changes in cardiac behaviour in this group.

DISCUSSION

Methylphenidate controls and prevents the muscular spasticity and tremor which may complicate the recovery from halothane anaesthesia. Its mode of action is not understood but it is interesting that it is equally effective in abolishing the tremor and spasticity which may complicate reserpine therapy in schizophrenic patients (Bartlet, 1959). The drug is a psychomotor stimulant with an effect between that of caffeine and amphetamine (Meier, Gross and Tripod, 1954). Methylphenidate has been used hitherto as a non-specific antidote to drug-induced and other forms of narcosis and as a non-specific respiratory stimulant (Gale, 1958; Percheson, Carroll and Screech, 1959; Hoagland, 1965).

The cause of the tremor and the spasticity which may follow halothane anaesthesia is a subject for speculation. The syndrome is reminiscent of decerebrate rigidity and may be related to the return of spinal reflex activity before the upper motor neurones have recovered from the inhibition of anaesthesia (Johnstone, 1968). It has been observed that halothane has a depressant effect on the posteroventrolateral nucleus of the
EFFECT OF METHYLPHENIDATE ON MUSCULAR SPASTICITY

thalamus and depresses the activity of the midbrane reticular area in cats (Davis, Quitmeyer and Collins, 1961). It is not improbable that during recovery from anaesthesia the relatively small amounts of the anaesthetic in the spinal cord are eliminated before the larger amounts are cleared from the brain. This would cause what seems to be a transient upper motor neurone block. Methylphenidate antagonizes the inhibitory effect of reserpine on the brain stem and may have a similar antagonism to subanaesthetic doses of halothane. The drug has no obvious effect on respiratory activity or on the depth of anaesthesia in anaesthetized patients.

The sympathomimetic action of methylphenidate is potentially dangerous in patients anaesthetized with drugs which sensitize the heart to sympathetic stimulants. The hazard is increased by respiratory acidosis. The rapid intravenous injection of 20 mg doses of the drug frequently causes tachycardia and dysrhythmia in patients anaesthetized with halothane. The sympathetic stimulation is of central origin as pharmacological studies on isolated organs failed to reveal any peripheral sympathomimetic action (Meier, Gross and Tripod, 1954). The fact that the intravenous injection of a mixture of a small dose of a beta-blocking drug with a relatively large dose of methylphenidate was not associated with any cardiac reaction supports the central origin of the stimulation as the heart would be protected by the beta-blocker before the methylphenidate reached the vasomotor centre.

The peripheral vasoconstrictive reaction to central sympathetic stimulation was blocked by halothane. The sympathetic stimulation of the heart, although potentially dangerous in the presence of mild hypercapnia, thyrotoxicosis, or in hypertensive patients, does not appear to be severe as it is almost completely suppressed by the increased vagal tonicity caused by neostigmine and also by a small dose of a beta-blocking agent. It is not improbable that methylphenidate should be used with caution in patients under treatment with monoamine oxidase inhibitors and in those requiring vasoconstrictive agents such as ergometrine.

No undesirable psychological reactions to the drug have been encountered in this investigation, though restlessness, excitement and mental confusion have been reported in other studies (Percheson, Carroll and Screech, 1959). The absence of psychotropic side effects in our study may be related to the use of sedative agents before and during anaesthesia, notably nitrazepam and butyrophenones. The sleepiness induced by nitrazepam is not antagonized by methylphenidate. A curious indifference to or unawareness of somatic pain in the immediate postoperative period has been observed in many patients who received methylphenidate during the recovery from anaesthesia. The need for postoperative analgesics was delayed for several hours. The accurate assessment of this effect is difficult. It is complicated by the simultaneous use of other drugs given before or during the anaesthesia and will be investigated and reported separately.

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REFERENCES


CORRESPONDENCE

PARADOX OF CARDIAC ARRHYTHMIA IN ANAESTHESIA

Sir,—With reference to the case described in Dr Borg's article (Brit. J. Anaesth. (1969), 41, 709), I wish to record a similar case. A patient with multiple extrasytostles was to be anaesthetized for a temporal lobe brain tumour. Preparations were made to counter any instance of ventricular fibrillation. To my surprise the electrocardiograph tracing reverted to sinus rhythm soon after induction and remained so during the operation. Multiple extrasytostles reappeared postoperatively. It seems as though general anaesthesia suppressed activity in some ectopic sites in the heart. As suggested by Dr Borg, the cause of the suppression may not be halothane since in this case anaesthesia was maintained using nitrous oxide, oxygen and tubocurarine.

V. M. DIVEKAR

Bombay

STICKING ROTAMETERS

Sir,—We have, over the last few years, renewed all our Boyle-type anaesthetic apparatus, and have had considerable trouble with the Rotameters in all the new pieces of equipment. The Rotameters have been sticking or working erratically, because of electrostatic charges, and we have been able to show that the charge is on the surface of the glass both inside and outside the tube and not primarily on the bobbin.

Charges on the outside of the Rotameter tube are easily removed by spraying with an antistatic spray, but charges on the inside surface of the tube are more difficult to remove. We have found that coating the inside surface of the tube with an antistatic fluid at the time of servicing will prevent trouble for approximately one month, but the apparatus is usually serviced once every three months.

I am very anxious to find out how much of a problem this is to anaesthetists in Great Britain. I understand from the makers, that it is a considerable problem in Sweden and Canada, and they are investigating a method of making the tubes so that they will not pick up a static charge. However, if this is a problem to anaesthetists in this country, it would be worth looking for some way of treating existing tubes so that electrostatic charges do not build up.

I wonder whether I could ask your readers to write to me, letting me know if they have trouble with their Rotameters, whether this occurs often or only occasionally, and whether this is confined to the 9-inch tubes or whether they have trouble with the older machines in which 6-inch tubes are used.

J. CLUTTON-BROCK

Bristol

THE INFLUENCE OF ANAESTHESIA AND SURGERY ON PLASMA CORTISOL, INSULIN AND FREE FATTY ACIDS

Sir,—I was most interested in the recent paper by Dr R. S. J. Clarke and his colleagues (Brit. J. Anaesth. (1970), 42, 295) which came to more or less the same conclusions as ourselves (Allison, Tomlin and Chamberlain, 1969). However, I would like to offer some comments.

Dr Clarke states "The negative findings in relation to plasma insulin levels show that there has been no inhibition of insulin production during surgery". He bases this statement on the finding that the fall in plasma insulin after 30 minutes of intra-abdominal surgery (5 ± 1.6 μU/ml) was not statistically significant. If one examines this finding in the light of a rise in blood sugar at this time of 21 ± 2.2 mg/100 ml, then his results strongly suggest a suppression of insulin release.

I agree with Dr Clarke that the conclusions based on statistical computation would only have been valid if there has been no change in blood sugar. Insulin levels must be interpreted in the light of such changes.

I look forward to reading Dr Clarke's findings on adrenaline secretion during major surgery. He states "the suggestion that adrenaline is liberated during major surgery has not been confirmed". In the absence of data on adrenal vein blood, it is difficult to comment on this statement, but I would find it difficult to explain the changes in blood sugar, free fatty acids and insulin on the basis of changes in plasma cortisol alone. I would also be surprised to learn that major surgery produced no increase in sympathetic activity.

S. P. ALLISON

Bristol

REFERENCES
