THE EFFECTS OF METHYLPHENIDATE ON POSTOPERATIVE PAIN AND VASOCONSTRICTION

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SUMMARY
The peripheral vascular reaction to postoperative pain has been studied from plethysmograms in 60 patients. The pain caused constriction of the alpha adrenoceptor vessels and dilatation of the beta adrenoceptor vessels. Methylphenidate relieved the pain and blocked the alpha vasoconstrictor reaction. It had no effect on the beta vasodilatation. Papaveretum relieved the pain and had no effect on the peripheral vascular reaction to pain. The clinical evidence for the alpha adrenoceptor blocking action of methylphenidate is presented and the pharmacological evidence is discussed in relation to the clinical findings. It was concluded that methylphenidate, with its analeptic and other actions, is preferable to opiates for pain relief in the immediate postoperative period.

During a previous study of the inhibitory effect of methylphenidate (Ritalin) on post-halothane muscular spasticity it was noticed that the patients who were given the drug before recovering consciousness after anaesthesia were indifferent to or unaware of pain after the recovery of consciousness (Brichard and Johnstone, 1970). In many of them the need for postoperative opiates was delayed for several hours although they were otherwise fully conscious and co-operative. The effect was very obvious in the elderly patients. The precise influence of the methylphenidate on the relief of pain was not clearly defined because many of the patients had received other drugs which inhibit pain perception.

It is generally agreed that the objective assessment of postoperative pain is impossible. There is no alternative to the patient's word. The physiological reaction to postoperative pain is measurable and may be an important approach to the study of pain because it is the physiological reaction which determines whatever pathological consequences the pain may have. Surgical pain reflexly constricts the blood vessels of the alpha adrenoeceptive vascular beds (Green and Kepchar, 1959). Facial pallor, widespread constriction of the superficial veins and cyanotic tinging of the extremities are seen in patients suffering from postoperative pain, despite a normal arterial pressure and blood volume. Similarly constrictive ischaemia of the alpha adrenoceptor blood vessels of the renal and splanchnic areas may be related to the development of postoperative visceral dysfunctions. It would seem that the measurement of the peripheral vascular reaction to pain is a logical approach to the problem of assessing the overall effects of drugs which are alleged to relieve pain.

As the study of methylphenidate progressed it was noticed that the vasoconstrictor reaction to postoperative pain appeared to be less in the patients treated with the drug. It was decided to investigate, by means of volume-pulse plethysmography, the reactions of the blood vessels of the finger and of the skeletal muscle of the forearm to the pain of the immediate postoperative period and to measure the effects of methylphenidate and of papaveretum on them.

PATIENTS AND METHOD
Relatively fit adult female patients requiring abdominal hysterectomy for non-malignant metropathia were selected for the study. There were two reasons for the selection: first, the sympathetic nervous system is most reactive in young adults, its reactivity diminishing with age (Frolkis, 1968; Nelson and Gellhorn, 1957); second, the operation requires the use of the more severe surgical stimuli, both somatic and visceral, and is associated with severe postoperative pain in most patients. Another advantage is that the patients who require abdominal hysterectomy are often in good general health, unlike those who require other forms of
abdominal surgery. Thus their physiological reactions to pain and trauma will be unaffected by disease.

Sixty patients between the ages of 30 and 49 years were selected. Each had clinically normal cardiovascular, respiratory and other systems. Each was normotensive, normovolaemic, afebrile and free from pain. A standard anaesthetic procedure was used. Each patient received pethidine 50 mg with droperidol 10 mg intramuscularly 2 hours before operation. Anaesthesia was induced with propanidid 250 mg mixed with atropine 0.5 mg followed by pancuronium 5 mg intravenously and endotracheal intubation. Anaesthesia was maintained with a mixture of nitrous oxide 6 l./min, oxygen 2 l./min and halothane 0.5–1%, vaporized from a Fluotec vaporizer, delivered from a Blease Pulmoflator set to give a respiratory minute volume of 8 litres. Each patient was given 250 ml of 5% dextrose in water and 250 ml of dextran 40 by intravenous infusion during the operation. The durations of the operations were between 55 and 100 min. No unexpected surgical or anaesthetic incidents occurred during the operations. The arterial systolic pressure was virtually unchanged during and after the operations. Blood loss was minimal and blood transfusion was not required in any patient. Each patient was given neostigmine 2.5 mg with atropine 1 mg intravenously at the end of the operation.

The patients were divided into two groups according to the method of pain relief. Group 1 consisted of 40 patients who recovered consciousness and complained of pain before the pain-relieving drug was given. Twenty of them were each given methylphenidate 40 mg intravenously and each of the other twenty patients was given papaveretum 20 mg intramuscularly. Four patients in the methylphenidate group each received an additional dose of methylphenidate 40 mg intravenously 15 min after the first dose, for reasons which will be described later in this report. Group 2 consisted of 20 patients each of whom was given methylphenidate 40 mg intravenously shortly before the end of the operation whilst still anaesthetized. All the patients of both groups were under close supervision in a recovery unit for at least 2 hours after operation. The assessments of the postoperative pain and the effects of the drugs thereon were made in consultation with the medical and nursing staffs of the recovery unit. The “blind” administration of the drugs was not attempted as it was agreed that the intravenous administration of papaveretum 20 mg to patients was potentially dangerous in these circumstances.

Volume-pulse plethysmograms of a finger and the forearm muscle were displayed continuously throughout the anaesthesia and the period of postoperative observation of all patients. A crystal transducer (Johnstone, 1974a) was used for the muscle plethysmography and a photoelectric system (Johnstone, 1974b) for the finger plethysmography. The transducer outputs were processed by fixed-gain amplifiers and fed into a Mingograf 12B writer with its sensitivity fixed at 5 mm per 1 mV throughout the study. Plethysmograms were recorded at intervals during anaesthesia, during and after the recovery of consciousness and pain perception, at intervals after the recovery of consciousness and pain perception, and at appropriate intervals after the administration of the pain-relieving drug. Arterial systolic pressure was measured by brachial cuff occlusion.

**RESULTS**

**During anaesthesia (Groups 1 and 2).**

All patients showed vasodilatation of the finger vessels and constriction of the muscle vessels constantly during anaesthesia. The range of amplitude of the finger pulse waves in the 60 patients was 19–27 mm (mean 24) and that of the muscle pulse waves was 5–12 mm (mean 9). The arterial systolic pressures ranged between 95 and 145 mm Hg (mean 113).

**After anaesthesia (Group 1).**

Each of the 40 patients of this group developed persistent constriction of the finger vessels within a few minutes after the end of the anaesthetic and before the recovery of consciousness, the amplitude of the pulse waves being less than 5 mm in each patient. The superficial veins of the forearms and hands also became constricted. The muscle pulse waves remained relatively unchanged until consciousness returned and they then became larger, reaching a range of 16–30 mm (mean 21) when voluntary movement and pain were present. All patients were conscious and in pain within 30 min after the withdrawal of anaesthesia. Several were shivering and feeling cold. Arterial systolic pressures were either unchanged or moderately increased. The typical plethysmogram changes...
associated with the recovery of consciousness after anaesthesia are shown in figure 1.

Each of the 20 patients who received methylphenidate after the recovery of consciousness became virtually pain-free, alert, warm and ceased to shiver within 45 sec after the injection of the drug. Several became talkative and smiling and were happy to discuss topics unrelated to their surgical predicament. Over periods of up to 5 min the finger blood vessels gradually became fully dilated in 12 patients and partially dilated in the others, the range of amplitudes after the methylphenidate being 12–25 mm (mean 19). The vasodilatation was persistent in 16 patients and transient in 4, lasting about 2 min in the latter. The administration of a second dose of methylphenidate 40 mg intravenously to each of these 4 patients produced persistent vasodilatation in 2 of them and little change in the other 2. The superficial veins of the forearms and hands became dilated in most patients after the administration of methylphenidate. The muscle plethysmograms were unchanged in all patients. Moderate increases of the pulse rate and the arterial systolic pressure occurred in 16 patients, 3 were unchanged and in 1 the systolic pressure was diminished slightly. The vasodilator effect of the methylphenidate lasted for about 90 min and was followed by the gradual reappearance of vasoconstriction. The duration of pain relief was between 45 min and at least 2 hours for the group. The typical plethysmogram changes after methylphenidate are illustrated in figure 1.

The intramuscular injection of papaveretum caused sleep in 17 patients after about 20 min. Three became sleepy and restful and their pain seemed to be less. The constriction of the finger vessels and superficial veins persisted in all patients after the administration of the papaveretum. The vasodilatation of the muscle vessels was unchanged. The typical plethysmograms before and after papaveretum are shown in figure 2.

After anaesthesia (Group 2).

The administration of methylphenidate to each of the 20 anaesthetized patients of this group had no effect on either the finger or muscle plethysmograms. The finger vessels remained vasodilated and the muscle vessels remained vasoconstricted. Before the injection of the methylphenidate the range of amplitude of the finger pulse waves was 19–23 mm (mean 21) and that of the muscle pulse waves was 5–11 mm (mean 7). The pulse rate and the systolic blood pressure were moderately increased in each patient.

In the 20 patients the vasodilatation of the finger vessels persisted after the withdrawal of the anaesthesia and the recovery of consciousness. The amplitude of the pulse waves recorded after the recovery of consciousness were similar to those obtained during anaesthesia in 14 patients and smaller in the others. The range of amplitude of the finger pulse waves after the recovery of consciousness was 12–24 mm (mean 17). During and after the recovery of consciousness the muscle pulse waves showed a progressive increase in amplitude similar to that observed in the patients of Group 1. The typical plethysmogram changes are illustrated in figure 3.
The patients of this group were conscious and alert, and 19 were pain-free within 15 min after anaesthesia. One complained of severe backache and seemed to get some relief from the injection of papaveretum 20 mg intramuscularly. Seventeen patients remained free from pain for at least 2 hours postoperatively. Eight were conscious of soreness at about 45 min after operation but did not request treatment with an opiate for a further 1–2 hours.

**DISCUSSION**

The results of this study show that methylphenidate not only relieves pain but also blocks the vasoconstrictor reaction to pain. The drug has no effect on the skeletal muscle vessels when they are constricted in anaesthetized patients or when they are dilated by the adrenergic stress of postoperative pain in conscious patients.

It is unlikely that the vasodilator effect of methylphenidate is associated with increases in the arterial systolic pressure and the pulse rate. The pressor effect is of cardiac origin as it is not associated with peripheral vasoconstriction. The cardiac stimulation is of sympathetic origin as it is reversed or prevented by beta adrenoceptor blockade (Brichard and Johnstone, 1970). The alpha vasodilator effect of methylphenidate was uninfluenced by phentolamine. The pressor effect was less in the spinal cat preparation in contrast to the effects of adrenaline or noradrenaline, which suggests a central sympathomimetic action by methylphenidate. The drug had a negative inotropic effect on the isolated mammalian heart and showed no evidence of a sympathomimetic action in isolated perfused blood vessels.

The influence of methylphenidate on the responses of rabbit vascular tissue to noradrenaline was studied by Maxwell (1965) using aortic strips and a perfused isolated ear preparation. He observed that concentrations of $10^{-6}$ M augmented sensory nerves from the painful site by drugs, such as procaine, and second, by the blockade of the efferent sympathetic nerves to the vessels at pre-ganglionic, ganglionic or receptor levels.

It is unlikely that methylphenidate depresses the function of sensory receptors in the painful tissues or the afferent nerves therefrom. Blockade of the sympathetic efferent pathways to the blood vessels is a more likely explanation of the vasodilator effect of methylphenidate. Sympathetic blockade at ganglionic or preganglionic levels dilates the finger vessels and constricts the vessels of the skeletal muscles (Green and Kepchar, 1959). As methylphenidate has no appreciable effect on the muscle blood vessels it may be concluded that it does not impair the sympathetic conductivity at either ganglionic or preganglionic levels. Similarly, the lack of effect on the muscle vessels excludes a direct depression of the vascular smooth muscle (Johnstone, 1972). The selective effect of methylphenidate on the alpha adrenoceptive blood vessels suggests that the drug inhibits their adrenergic receptor mechanism.

The cardiovascular effects of methylphenidate have been studied in cats (Meier, Gross and Tripod, 1954). It increased the arterial pressure and the pulse rate and did not have a stimulant action on the smooth muscle of the peripheral blood vessels like that of adrenaline and noradrenaline. The pressor effect of methylphenidate was uninfluenced by phentolamine. The pressor effect was less in the spinal cat preparation in contrast to the effects of adrenaline or noradrenaline, which suggests a central sympathomimetic action by methylphenidate. The drug had a negative inotropic effect on the isolated mammalian heart and showed no evidence of a sympathomimetic action in isolated perfused blood vessels.
noradrenaline-induced contractions of the aortic strips, whereas concentrations of 10^{-5} M or greater antagonized the noradrenaline-induced contractions in a dose-related manner. Similar effects were observed in the isolated perfused ear preparation. These concentrations of methylphenidate antagonized the contractions caused by 5-hydroxytryptamine and histamine. Maxwell concluded that methylphenidate in the higher concentrations is an alpha adrenoceptor blocker with a limited specificity against agonists.

There is a similarity between the cardiovascular effects of methylphenidate and phentolamine. Both are alpha adrenoceptor blockers and both indirectly stimulate the heart. Das and Parratt (1971) reported that phentolamine, in small doses, is a cardiac stimulant in the intact cat. It increases heart rate, cardiac output and arterial systolic pressure. The cardiac effects of phentolamine are antagonized by beta adrenoceptor blockade, which indicates their sympathetic origin. The mode of action of phentolamine in stimulating the cardiac sympathetic system of the cat is not clear.

There is substantial pharmacologic and clinical evidence to show that methylphenidate is an alpha adrenoceptor blocker. This effect explains its ability to prevent the vasoconstrictor reaction to postoperative pain. It also explains the increase in skin temperature which follows its use in the treatment of shivering in patients suffering from accidental hypothermia (Bortoluzzi et al., 1963). It is interesting to note that the shivering of accidental hypothermia, like that of the recovery from halothane anaesthesia, is abolished by methylphenidate. It is unlikely that the suppression of the shivering is related to the increase in skin temperature which follows the administration of methylphenidate to vasoconstricted patients. The suppression of the shivering in the hypothermic patients occurred many minutes before the increase in skin temperature. The simultaneous recording of electromyograms and digital plethysmograms showed the disappearance of the post-halothane spasticity whilst the finger vessels remained constricted (Brichard and Johnstone, 1970). It may be concluded that the inhibitory effect of methylphenidate on muscular spasms of various kinds, including hiccup (Macris et al., 1963) is part of its action on the central neuroregulatory mechanisms.

Methylphenidate has a wide range of effects which are beneficial to patients recovering from anaesthesia after major surgery. The alleviation of pain, the blocking of the vasoconstrictor reaction to pain, the elevation of consciousness, the suppression of tremor and hiccup, the antagonism of the respiratory and other depressant effects of narcotic drugs (Hoagland, 1965) and the brisk circulatory activity with widespread vasodilatation would seem to be desirable in patients recovering from major surgical operations. The effects are particularly valuable after general surgical procedures in elderly patients with advanced cardio-pulmonary diseases which preclude the safe use of opiates. They are also of help in the management of postoperative pain in children.

It should be noted that the effects of methylphenidate as described in this report are not necessarily those which occur when the drug is given to patients who are not under the influence of other drugs. The drugs used for preoperative sedation and anaesthesia modify the psychic effects of methylphenidate. Mental excitation, confusion and restlessness have not been encountered in the postoperative period despite the use of large doses of methylphenidate. The increased vagal activity caused by neostigmine conceals the cardiac stimulation which often occurs in patients who do not receive neostigmine before the administration of methylphenidate. Whilst it is obvious that methylphenidate provides freedom from pain in the immediate postoperative period it is not known what its effect on pain will be when it is given to patients after the effects of the other drugs have disappeared.

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BOOK REVIEW


This book is based on practice at the Karolinska Hospital in Stockholm. It is written for medical students, nurses and paramedical workers, rather than for the medical specialist.

Unfortunately the book has two major disadvantages. Despite a very comprehensive table of contents it has no index, and the turgid style and often quaint translation make it difficult to read.

The book covers such topics as the design and administration of intensive care units, the use of various clinical monitoring techniques, and the management of respiratory, cardiovascular, neurological, nutritional and paediatric problems. It also deals with some special problems such as poisoning, tetanus, trauma and burns. The balance, however, is uneven. Some topics, for example acid-base state, reach a standard to be expected only from the candidate for the F.F.A.R.C.S., while others, of more importance to the nurse, such as cardiac arrest, shock, coma, mechanical ventilation and parenteral nutrition, are only superficially examined.

There are thirteen appendices. One is a list of recommended literature, about half of which is in Swedish.

There are a very few books on intensive care for nurses or doctors, which cover the whole field in practical detail, and which can be recommended. This book is not one of them. However, the keen nurse or junior doctor might care to borrow it for a couple of evenings from the library.

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