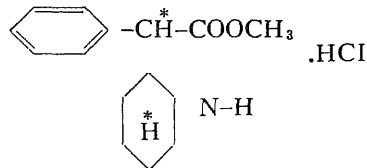


POSTOPERATIVE ADMINISTRATION  
OF  
METHYLPHENIDATE

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THE EXTENSIVE RANGE of drugs known as stimulants can give rise to some confusion of judgment as to their ultimate usefulness. However, classification according to their pharmacodynamic properties will serve as a guide to their appropriate application. Among the central stimulants there are several groups, and the drug under discussion in this paper is associated with the phenyl-piperidyl-acetic acid derivatives. Methylphenidate or Ritalin® is phenyl piperidyl<sup>2</sup> acetic acid methylester. This drug has been shown to have a particularly strong central stimulating action in both humans and animals.



According to the observations on animals by Gross<sup>1</sup> and co-workers, psychomotor stimulation is produced by methylphenidate in the unanaesthetized animal. The intensity of activity produced by a dose of 0.5 to 1.5 mg./kilo varies from mild restlessness to complete exhaustion. Larger doses of 2 mg./kilo and above can produce compulsive movements of such great intensity that the animals run around until they reach a severe state of exhaustion with subsequent death. Some typical individual movements observed in dogs were twitching and turning of the head associated with movements of the eyelids and ears. An acceleration of respiratory rate was noted by Gross<sup>1</sup> after an intravenous injection of 1 mg./kilo, and apparently with the higher range of doses this was increased. A distinct analeptic effect was found to be produced by methylphenidate after the administration of thiopentone. Doses of 25 mg./kilo of the former administered subcutaneously completely abolished the thiopentone effect. This arousal persisted up to the fourth hour after the injection of the methylphenidate, and was accompanied by a considerable increase in motility. However, the analeptic effect of this drug was only slight on the longer acting barbiturates. The respiratory stimulation in the anaesthetized animals was even more marked than in the unanaesthetised. The cardiovascular changes were a prolonged rise in blood pressure and an acceleration in heart rate.

A clinical survey was conducted on patients during the immediate postoperative period, that is, in the recovery room. A double blind method of administration was employed, the methylphenidate or placebo being supplied by the hospital

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pharmacy. Minor operation cases only were included in the trial, so that a fairly constant range might be observed. On arrival in the recovery room the blood pressure was checked, and immediately afterwards a spirometry recording was made. Following the recording, 1 c.c. of the solution supplied was injected intramuscularly, and a careful watch made for the first sign of arousal of the patient. Fifteen minutes after the injection, a second spirometer recording was made, regardless of whether the patient was awake or not. In all, 294 patients were observed, and records from the pharmacy eventually revealed that 174 patients had received Ritalin®, and 120 the placebo. If the solution administered was methylphenidate, 1 c.c. contained 20 mg. of the drug.

### RESULTS

Certain variables entered into the investigation and these will be considered before the analysis of the results is attempted.

(1) Although the preoperative medication was kept fairly constant by the administration of meperidine and atropine, a small number of patients received anti-emetics with the sedation. On examining the distribution of the additional drugs in the two groups, there appears to be no statistically significant difference in the numbers.

(2) Similarly, the anaesthesia was slightly variable, but out of the total of 294 patients, 265 received thiopentone combined with nitrous oxide and oxygen.

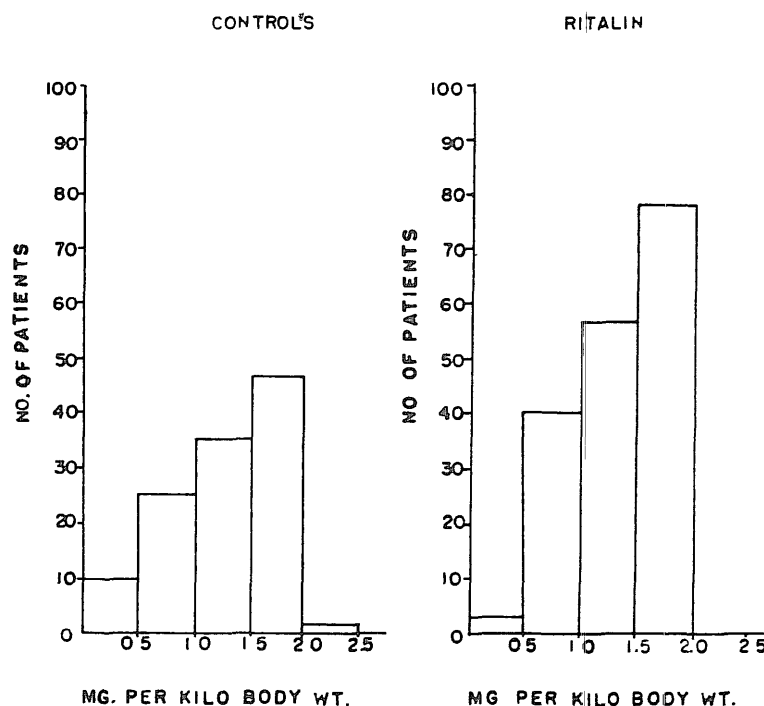


FIGURE 1. The amount of meperidine administered has been worked out in mg./kilo body wt. The distribution is moderately asymmetrical, and the values when tested by the statistic of  $\chi^2$  show that P is 0.20, indicating that there is no significant difference in distribution of dosage in the two groups of patients.

CONTROLS

RITALIN

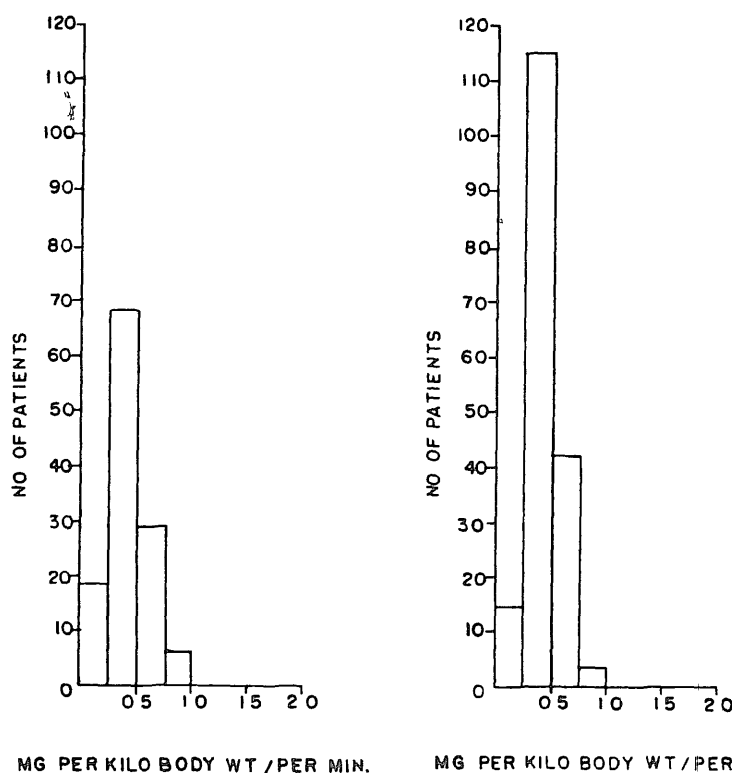


FIGURE 2. The amount of thiopentone given to each patient has been presented in mg./kilo/min. (per min. of actual anaesthesia). This histogram, too, shows moderate asymmetry and the value of P is 0.3, which is not significant.

The remaining 29 were given cyclopropane, trichlorethylene or halothane in addition. This distribution was examined as in the case of preoperative sedation, and here also there was no significant difference in the distribution.

There is some disagreement as to the specific antagonistic influence of methylphenidate on the narcotic action of meperidine, and so it was decided to consider the frequency distribution of this drug, as well as that of the thiopentone. These distributions are shown in the form of histograms (Figs. 1 and 2).

After having considered these additional factors and presuming that the drugs and the amount administered are fairly evenly distributed in the two groups of patients, the main results can be analysed. There were four major points of consideration: the time taken for the patient to recover from the anaesthetic; the alteration in minute volume of respiration after the injection given in the recovery room; the changes in blood pressure in response to the injection; the incidence and type of side-effects.

There was a strong tendency to believe that patients who received the methylphenidate were more alert on the return to consciousness, according to observations recorded at the time when the nature of the injection was not known. However, an analysis of the psychic function is too difficult for one not trained

in psychoanalysis, and consequently I am not prepared to say more than that this alertness was a visual appreciation on the part of the observers. More detailed attention has been given to the variation in the awakening time.

TABLE I  
A STATISTICAL ANALYSIS OF THE RECOVERY TIME IN  
THE TWO GROUPS OF CASES  
(P. being 0.5 is not significant)

	No. of cases	Mean awakening time
Ritalin	162	23 mins.
Controls	113	26 mins.
S.E.D. = 5.5217    t = 0.5415    P = 0.5		

Table I shows the mean awakening time after the injection in the two groups. All patients awakening within 10 minutes of receiving the injection have been eliminated from this analysis, since one cannot expect any real effect from an intramuscular injection within that time. It will be seen that the difference between the two arithmetic means is only three minutes. The standard error of the difference between the means is so near to the values of the means themselves that it is not surprising that P. is .50. Consequently, there is no significant difference between the recovery times in the treated and control groups.

TABLE II  
THE SIGNIFICANT DIFFERENCE BETWEEN THE VALUES  
OF THE MINUTE VOLUME IN THE METHYLPHENIDATE  
AND CONTROL GROUPS  
(P = .01)

	No. of cases	Mean gain
Ritalin	174	857 ml.
Controls	120	517 ml.
S.E.D. = 118.01    t = 2.881    P = .01		

Table II presents the results of analysis of the spirometry recordings made while the patient was in the recovery room. The difference between the mean increase in each group is shown, and it is interesting to note that there is a definite increase in the mean minute volume in the methylphenidate group, and the statistical analysis gives the value of P. as 0.01, that is, a significant value. This increase in minute volume was produced more by an improved tidal air measurement rather than by an increase in respiratory rate. That this was owing to general arousal was not the case, since patients who continued to sleep on for anything up to 30 minutes after the second spirometry recording sometimes showed this improved respiratory activity.

The blood pressure changes were slight and the difference between the two means of the systolic readings was 5 mm. Hg. This cannot be presented as a reliable figure, since a number of people were concerned in the recording of these pressures, and consequently a certain degree of personal error would enter into

the evaluation. One might presume from such a small difference that methylphenidate did not have any marked effect on the blood pressure.

The side-effects produced by any drug are of considerable importance, since one which can produce a state of wild excitement is hardly likely to recommend itself to clinical use. Previous investigators, Gale,<sup>2</sup> Percheson, and Carroll,<sup>3</sup> have recorded marked psychical disturbances following the administration of methylphenidate. In this series, there were nine patients who showed signs of overstimulation of psychomotor function, of which there were six in the methylphenidate group and three in the control series. The degree of disturbance can be classified as follows:

	<i>Methylphenidate Group</i>	<i>Control Group</i>
General restlessness	3	1
Crying and restlessness	2	2
Crying and thrashing around	1	0

Since some of control patients showed signs of reaction, it is felt that there must have been some underlying mental disturbance at the time. It is interesting to note that the constant head movement seen in animal experiments was noticed in some of these patients. Fortunately the period of restlessness did not interfere with the spirometry recordings since all but two had not shown signs of arousal at the time of their second recording. The two patients who were awake had settled down by the time the second recording was due to be made. Two very restless patients could not be recorded, but they have not been included in this series.

A very limited experience of the use of methylphenidate on the anoxic newborn infant indicated that the drug had definite stimulant effect, especially in the presence of sedation and general anaesthesia. Two infants born by caesarean section and one by a difficult forceps delivery were given methylphenidate, 2 mg. administered intramuscularly after the usual methods of resuscitation (including intubation) had been applied without success. In each case it was approximately five minutes after birth that the methylphenidate was injected. In all three cases there was a definite response within 10 minutes, although in the case of the forceps delivery, the infant showed marked cerebral irritation for at least 24 hours after. Since the infant weighed 9 lb. 6 oz., the dose of methylphenidate was not thought to be excessive, and it was presumed that the cause of crying and increased tone might have been due more to the difficult delivery than the stimulant. The infant improved with sedation.

#### DISCUSSION

It has been stated that an analeptic with a brief effect (even though the intensity of effect is great) will abolish the anaesthesia only temporarily when it is due to a drug with a prolonged action. According to Gros *et al.*<sup>1</sup> the analeptic effect of methylphenidate is only slight when tested against large doses of barbiturates, with the exception of thiopentone, and is not comparable with that of true analeptics, although its ability to produce psychic stimulation has caused

it to be utilised for barbiturate depression (Carter and Maley,<sup>4</sup> Gale,<sup>2</sup> and Smith and Adriani<sup>5</sup>). Plummer and Yonkman<sup>9</sup> point out that the effect of methylphenidate is in contradistinction to that of tranquilizers, since its main pharmacological action is the stimulation of the mesencephalic reticular formations and accentuation of the arousal mechanism. The effect of methylphenidate on the patients in this survey does not produce significant results in arousal time, with a dose varying between 0.2 to 0.5 mg. per kilo body weight (the majority of patients receiving 0.3 or 0.4 mg. per kilo). Gale<sup>2</sup> noted that doses above 0.1 to 0.2 mg./lb. were effective in shortening the recovery time, but that larger amounts were probably ineffective. Yet, Dokin<sup>6</sup> records a significant reduction in the recovery time when methyl-phenidyl-acetate (1 mg./kilo) was added to thiopentone (25 mg./kilo) in a controlled series of dogs. It may be that the patients in this series were not sufficiently depressed by the anaesthesia to show any significant improvement in awakening time over the control cases. This conclusion would concur with Gale's<sup>2</sup> statement that the effectiveness of methylphenidate seems to be related more to depth of depression than the actual depressant agent. Methylphenidate does not appear to be antagonistic to one group of drugs only, as in the case of levallorphan, since a number of investigators (Ferguson *et al.*<sup>7</sup> and Carter *et al.*<sup>4</sup>) have reported beneficial results of its use in central nervous system depression caused by chloroform, reserpine, barbiturates, and general anaesthesia.

The stimulant effect on respiration was significant in this experiment, but it is interesting to note that there did not appear to be any relationship between the dose of thiopentone and the degree of respiratory stimulation. Gale<sup>2</sup> pointed out the lack of correlation between the optimal dose and the amount of thiopentone administered, and concluded that methylphenidate acts not as a biologic competitor but rather as a central nervous system stimulant. The usefulness of methylphenidate lies in its ability to counteract the respiratory depression caused by a variety of anaesthetic and sedative agents, although other studies have shown it more effectively than this one.

Blood pressure changes were minimal in both groups of patients, and there was no opportunity to test the potentiating property in relation to epinephrine and norepinephrine as reported by Maxwell and associates.<sup>8</sup> Plummer and Yonkman<sup>9</sup> noted the same potentiation but in addition recorded that the hypertensive action of amphetamine and ephedrine was antagonized by methylphenidate.

The side-effects of emotional reactions were established in this series but were not so marked as in the reports of some other observers. Percheson<sup>5</sup> has described a case of almost maniacal reaction after the administration of 60 mg. intravenously. There may be some relation between dose, route of administration, and degree of psychomotor response, and since the methylphenidate was administered intramuscularly in the cases recorded in this paper, the sudden bombardment of intravenous therapy did not occur. Smith and Adrian<sup>5</sup> have listed nausea, disorientation, and garrulousness as some of the side-effects occurring after dosage of 0.2 mg./lb. body weight, but they were impressed by the analeptic effect of methylphenidate on barbiturate depression and/or poisoning.

Gale<sup>2</sup> considered one of the most gratifying effects of methylphenidate was its ability to stimulate depressed newborn infants. Out of eighteen infants, all but three responded within two minutes of administration of methylphenidate, 1 mg./5 lb. He also noticed that general body activity was increased, was at its maximum after 15 minutes, and maintained for about one hour. Therefore, the marked degree of irritation in the infant delivered by forceps mentioned in this study may have been owing partly to the difficult delivery and partly to the methylphenidate. However, in the three infants observed, the response to the methylphenidate was positive.

#### SUMMARY

Methylphenidate (Ritalin<sup>®</sup>) has been studied in relation to its stimulant effect after anaesthesia. A control series was established by a double blind method of administration. A total of 294 patients were observed in the recovery room; 174 received methylphenidate and 120 normal saline. These patients had had only minor operations. On arrival in the recovery room, the blood pressure was recorded, a spirometer recording made, and then the patient received 1 c.c. of the unknown solution. The time of injection was noted carefully, and also the awakening time. A second recording was made with the spirometer 15 min. after the first one, whether the patient was awake or not. Analysis of the results indicated that there was no significant decrease in the awakening time of the methylphenidate series, but that the degree of respiratory stimulation due to the drug was statistically significant. Blood pressure changes were minimal and of no importance. Psychomotor stimulation occurred in both groups, but slightly more in the treated group than in the controls. Three depressed newborn infants responded to intramuscular injections of methylphenidate after the routine methods of resuscitation had failed to produce satisfactory results.

#### RESUME

Nous avons étudié le méthylphenidate (Ritalin<sup>®</sup>) et particulièrement ses effets stimulants après l'anesthésie. Nous avons fait l'étude avec une série de témoins en employant la méthode du double inconnu. Nous avons étudié un total de 294 malades dans la salle de réveil: 174 d'entre eux ont reçu du méthylphenidate et 120 n'ont reçu que du sérum salé. Ces malades n'avaient subi que des opérations mineures. A l'arrivée à la salle de réveil, la pression artérielle était prise et notée, le volume des échanges était évalué au spiromètre et noté et, ensuite, nous donnions au malade 1 ml d'une solution inconnue. Nous notions le moment de l'injection soigneusement et ensuite le moment du réveil. Nous faisons également, 15 minutes après la première, que le malade fut réveillé ou non, une deuxième détermination du volume des échanges avec le spiromètre. L'analyse des résultats nous permet de conclure que, dans la série où le méthylphenidate a été employé, le réveil n'a pas été plus précoce de façon marquée, mais nous pouvons affirmer que le médicament a produit une stimulation respiratoire importante. Les modifications de la tension artérielle ont été minimes et sans importance. Nous avons

observé une stimulation psychomotrice dans les deux groupes mais légèrement plus marquée chez les sujets traités. Trois nouveau-nés déprimés ont bien répondu à l'injection intramusculaire de méthylphenidate alors que les méthodes ordinaires de resuscitation n'avaient pu donner de résultats satisfaisants.

#### ACKNOWLEDGMENTS

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