RITALIN® (METHYLPHENIDATE): CLINICAL EXPERIENCES[1, 2]

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METHYLPHENIDATE is a white, water-soluble crystalline compound. It is a piperidine derivative which can be administered orally, subcutaneously, intramuscularly or intravenously and is marketed under the name of "Ritalin" by Ciba Pharmaceuticals.

It is a behaviour-altering drug which is often included in the classification of tranquillizer or ataractic compounds (9). In contradistinction to the tranquillizers, however, its main pharmacologic action is stimulation of the mesencephalic reticular formations and accentuation of the arousal or alerting mechanism (8) This psychic stimulation of Ritalin has interested many investigators and it has been utilized to counteract barbiturate depression (1), (5), (6), (7), barbiturate (7) and non-barbiturate (3) poisoning and chlorpromazine (1), (4) and rauwolfia (2), (4) lethargy in psychiatric patients.

Gale (6) measured the effect of Ritalin on the recovery time of 272 patients who had a uterine dilatation and curettage performed under light pentothal and nitrous oxide anaesthesia. He reported that the optimum dose appeared to be between 0.1 and 0 2 mg /lb. This dosage was effective in shortening the recovery time to about one-half as compared to the controls. In a subsequent publication (5), he reaffirmed the above findings and suggested that dosages above 0.1 to 0.2 mg./lb. are less effective. He noted a mild transient rise in blood pressure, and occasional nausea and retching and emesis as the only side-effects of Ritalin therapy. He was favourably impressed with the effects of Ritalin on barbiturate-induced depression in the newborn infant.

Carter and Malley (1) studied the effects of Ritalin in 129 mentally retarded or brain-damaged patients who were classified into the following categories: (1) shock from chlorpromazine overdosage, (over 300 mg. T.I.D. for several days); (2) barbiturate poisoning and barbiturate anaesthesia, (3) moribund states such as severe pneumonia. They report beneficial results in all of these categories and mentioned that chlorpromazine overdosage responded more slowly and required higher doses of Ritalin. Their dosage ranged from 20 to 55 mg. intramuscularly and intravenously, repeated as often as every 20 min. to every 4 hrs.

Ferguson (2) administered 20 to 40 mg. of Ritalin orally to depressed psychiatric patients. He inferred that its main action was possibly in the thalamic area

[1]An abridgment of this paper was presented by the first author at the Canadian Anaesthetists' Society Annual Meeting, Montebello, Quebec, June, 1958.

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because the effect on his patients was much like that of a lobotomy. He stated, however, that in most of the patients the slow awakening to reality elicited by the drug produced an element of confusion.

Ferguson and Linn (4) administered 10 mg. doses intravenously to 164 hospitalized mental patients who were drowsy and lethargic owing to large doses of tranquillizing drugs. Of these patients 160 showed improvement However, eight out of the 164 became apprehensive and fearful after two to four injections of Ritalin and eight others became overactive They claimed that these side-reactions were alleviated when dosage was decreased.

Ivey (3) successfully resuscitated a 35-year-old woman who attempted suicide by ingesting approximately 10 gm of ethchlorvynol (Placidyl) and about 14 gm of methyprylon (Noludar) He administered about 100 mg of Ritalin intravenously in divided doses over a period of 3 to 4 hrs He noticed marked improvement in the patient who had been in a coma for about 45 hrs , and had become moribund despite intensive supportive treatment which included electrostimulation, caffeine sodium benzoate, and metrazol He noted that Ritalin potentiated the pressor effect of the levarterenol (Levophed) drip which was necessary throughout the supportive treatment of the patient.

Plummer and Yonkman (8) noted that Ritalin potentiated the pressor effect of norepinephrine but antagonized the hypertensive action of amphetamine and ephedrine.

Smith and Adriani (7) were impressed with the analeptic effects of Ritalin on barbiturate depression and barbiturate poisoning. They noted several side-effects in the 33 subjects treated with Ritalin for barbiturate depression These were listed as nausea in seven, disorientation after recovery in six, and garrulousness in eight The dose of the drug in these cases was based on 0 2 mg /lb body weight. The 26 cases of barbiturate poisoning required from 60 to 1,100 mg of Ritalin for resuscitation

Our interest in Ritalin was stimulated by the anticipation that its unique analeptic properties would be of great value to the anaesthesiologist in (i) reducing the time spent by the patient in the recovery room, (ii) expediting the recovery from dental office procedures done under general anaesthesia, and (iii) counteracting the barbiturate depression of the newborn when such sedation is administered to the mother during labour With regards to the last of these, we are convinced that even small doses of barbiturates have a prolonged depressing effect on the newborn Adelman (10) and Duchesne (11) have been similarly impressed with the depressant effect of barbiturates on the infant As a result, we have practically eliminated the use of barbiturates in our hospitals and have been administering such drugs as promethazine (Phenergan) (12), (13) and meprobromate (Equanil) for sedation during labour In our experience, these drugs have no apparent depressant action on the baby, and thus, the trial of Ritalin in our obstetrical patients has not been warranted.

However, we studied the analeptic effects of Ritalin on 60 patients Of these patients 52 had gynaecological surgery as follows (1) 40 patients had a dilatation and curettage performed under surital (500 mg) and nitrous oxide/oxygen

(6/2) ratio in a semi-closed circuit; (2) 6 patients had the same procedure performed under intravenous Nembutal (150 to 250 mg.) plus syncurine 2 mg. plus nitrous oxide/oxygen in a 6/2 ratio, (3) 6 patients had longer gynaecological procedures performed under spinal (Pontocaine) and sleep dose of intravenous Nembutal (150 to 250 mg). All of these patients were premedicated with Pantopon 10 mg. and hyoscine 0.2 mg. In three patients, promethazine 25 mg. was added to the above premedication.

At the termination of the surgical procedure, Ritalin, in doses of from 10 to 60 mg., was injected intravenously. The times taken to respond to painful stimuli, eyelid stimulation, and verbal command, and time of wakefulness as judged by purposeful movement and speech were recorded and compared to a control group to whom Ritalin was not given.

As shown in Table I which gives awakening times in 12 unselected cases and 12 controls, our results compare favourably with those of Gale (5, 6). Judging from the response to painful stimuli, the Ritalin series shows a response time of 2.3 minutes (average) as compared to 8.2 minutes (average) for the controls.

TABLE I

Patient no	1	2	3	4	5	6	7	8	9	10	11	12
Ritalin (mg.)	60	40	20	20	20	10	10	10	20	20	20	20
Time of pain response (min.)	5	5	2	2	2	2	1	1	2	3	2	1
Control patient no	13	14	15	16	17	18	19	20	21	22	23	24
Time of pain response (min.)	15	11	3	6	11	7	8	7	12	3	9	6

Thus the advantages of Ritalin may be summarized as follows:

(i) Ritalin definitely accelerates wakefulness of patients anaesthetized or depressed with intravenous barbiturates.

(ii) This awakening state is not transitory but appears to persist for some hours.

(iii) The action of the drug suggests independent central nervous system stimulation rather than biological competition with depressant drugs.

(iv) A dose of 10 to 20 mg. produces a state of alertness which allows gentle sleep from which the patient is readily rousable by the spoken voice. Larger doses seem to preclude sleep for 4 to 6 hrs. afterwards.

(v) An average rise of about 10 mg. mercury of systolic pressure was noticed within 1 minute of the Ritalin administration, but pulse rate and respirations were unaffected.

(vi) The three patients who received promethazine 25 mg. as additional premedication showed delayed awakening times despite the larger doses (40 to 60 mg.) of Ritalin.

Side-effects

Gale (6) listed as side-effects a mild transient rise in blood pressure and occasional nausea, retching, and vomiting. Ferguson (2) mentioned a period of confusion following the administration of Ritalin to psychiatric patients. However,

Smith and Adriani (7) found that a high percentage of their patients showed disorientation, nausea, and garrulousness.

Our incidence of side-effects was considerable and some of them were quite disturbing to the patient, the anaesthesiologist, and the nurses on the surgical ward.

Most of the patients in this series of 52 were restless for 2 to 3 hrs. after return to full consciousness and the nurses quickly got to recognize those who had received Ritalin. Three young healthy females who were given Ritalin following dilatation and curettage performed under surital and nitrous oxide-oxygen anaesthesia were fully conscious within 3 minutes. Two of these received 10 mg of Ritalin and the other 20 mg. intravenously. Upon return of consciousness, they became euphoric, noisy, and restless for several hours. They were serious nursing problems in that they constantly tried to get out of bed though they lacked the muscle co-ordination to even stand up. Two complained of severe headache despite normal blood pressures, and the following day each described her recovery as a most unhappy experience. They stated that they were aware of their actions but were unable to control them.

Another such healthy female was given 60 mg. of Ritalin at the end of a dilatation and curettage performed under surital–nitrous oxide–oxygen. She awakened within 3 minutes, but became hysterical. Her blood pressure rose from 130/80 to 160/90, but pulse and respirations remained unaltered. She complained of severe headache, thrashed around in her attempts to get out of bed, and had to be restrained for 3 hrs. and watched carefully the rest of that day. The next day she had a clear recollection of her recovery period but insisted that she was unable to control herself.

About 10 per cent of these patients had restless postoperative nights which did not respond well to the usual sedation. Other side-effects such as diplopia, vomiting, and milder forms of restlessness and headache were observed in several patients, but these were of no consequence.

In addition to the above-mentioned 52 cases, we used Ritalin in four dental cases who had been anaesthetized with pentothal–curare–nitrous oxide–oxygen and trilene; three elective neurological cases who had craniotomies performed under the "lytic cocktail," and had received on the average chlorpromazine 200 mg., promethazine 200 mg., and Demerol 300 mg.

One of the four dental procedures was done on an apparently healthy young man. He received 20 mg of Ritalin intravenously following the procedure and awakened immediately in a very disturbed state. He was able to walk over to the recovery-room bed and responded briskly to verbal command but persisted in reliving some events pertaining to his war experience. This lasted for 5 hrs., and he had to be restrained for most of the time. We had never seen this type of emergence delirium last for such a long time with the type of anaesthesia administered, and thus Ritalin must be suspected.

Ritalin appeared to raise the level of alertness in the three neurological cases done under the "lytic cocktail" and nitrous oxide–oxygen. The response was much less dramatic and full consciousness did not return in these patients until several

hours later. In one such patient who was on a Levophed drip, the administration of 60 mg. of Ritalin intravenously appeared to drop the pressure from 80/50 to 60/40. However, increasing the drip rate of the Levophed did restore the blood pressure rapidly In view of the reports of Plummer and Yonkman (8) and Ivey (3), we are not prepared to comment upon or explain this phenomenon.

We used Ritalin in one case of barbiturate poisoning. A young woman was admitted to hospital in a comatose, cyanotic, and shocked condition after having ingested an unknown amount of Tuinal. Blood pressure was not recordable, pulse barely palpable, and her respiratory movements were reduced to diaphragmatic gasps. She was given 40 mg. of Ritalin intravenously and within a few minutes her colour became pink, her blood pressure recorded at 100/60, her pulse became strong and her respirations returned to normal. She required no further treatment and was discharged from the hospital 12 hrs. later apparently having suffered no ill effects.

Summary and Conclusions

In our experience, Ritalin is effective in antagonizing the actions of barbiturates. The action does not appear to be a specific antagonism but rather an independent central nervous system stimulation which raises the level of alertness or wakefulness. In moderate doses it has little effect on the blood pressure, pulse, and respirations. In larger doses, it would appear to increase the blood pressure without affecting the pulse and respirations. In our one case of severe depression from barbiturate poisoning, it rapidly returned all three to normal.

The high incidence of euphoria, restlessness, mental agitation, and headache following its administration in moderate doses would seem to preclude its routine use for hastening recovery from barbiturate anaesthesia. However, in instances of severe depression from such drugs, Ritalin therapy appears to be safe and effective and its side-reactions become minor considerations.

Résumé

La Ritaline est efficace pour lutter contre l'action des barbituriques. L'action ne semble pas consister en un antagonisme spécifique mais en une stimulation indépendante du système nerveux central qui élève le niveau de la vigilance et du réveil. A doses réduites, elle a peu d'effets sur la tension artérielle, le pouls et la respiration A doses plus considérables, il semblerait qu'elle augmente la tension artérielle sans changer le pouls ni la respiration. Dans un cas de dépression grave par empoisonnement barbiturique, elle a ramené rapidement les trois à la normale.

L'observation fréquente d'euphorie, d'agitation physique et mentale, de céphalée à la suite de son administration à doses réduites, plaiderait contre son usage routinier pour accélérer le réveil après l'anesthésie aux barbituriques. Toutefois, dans les cas de dépression grave par ces médicaments, le traitement à la Ritaline nous semble efficace, de toute sécurité, et ses effets secondaires deviennent négligeables.

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