THE EFFECT OF METHYLPHENIDATE (RITALIN) ON THIOPENTAL RECOVERY

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METHYLPHENIDATE HYDROCHLORIDE (Ritalin) is a mild stimulant of the central nervous system which has been administered in oral form since its introduction in Europe by Drassdo and Schmidt (1) in 1954. It has been effective in the treatment of depression of the central nervous system resulting from the administration of reserpine and other tranquilizers (2). It has also been effective in the treatment of various depressive mental states (3), and was deemed superior to other stimulants because of its relative freedom from circulatory side effects (2, 3, 4).

Methylphenidate hydrochloride, a white, water soluble, crystalline material, is a piperidine derivative with the chemical name α phenyl-d-pyridyl-2-acetic acid methylester monohydrochloride (5).

Methylphenidate can be administered orally, subcutaneously, intramuscularly or intravenously.

The pharmacology of methylphenidate was described by Meier, Gross and Tripod (5) in 1954, who reported that it stimulated coordinated motor movements in normal mice, rats, rabbits, and dogs in doses ranging from 0.5 to 1.5 mg./kg. Larger doses were said to produce ataxia and chronic tonic convulsions. The intravenous median lethal doses (LD_{50}) were very high compared to the intravenous effective doses and were four to thirty times higher than the effective subcutaneous and oral doses. Five to ten milligrams of methylphenidate after the administration of 30 mg./kg. of thiopental produced "a distinct analeptic effect" in rats, and doses of 25 mg./kg. of methylphenidate subcutaneously were required to abolish the barbiturate effect completely. The analeptic effect was less after the administration of chloral hydrate, urethane, barbital and phenobarbital.

In dogs, respiratory acceleration was observed after doses of 1 mg./kg. and was more marked after 2 mg./kg. Greater stimulation of respiration was noted in anesthetized animals than in unanesthetized ones. Its stimulating action was "particularly distinct" following morphine-induced respiratory depression.

A definite prolonged rise in blood pressure and tachycardia was seen in allobarbital (Dial) anesthetized cats. In regard to these circulatory effects, a distinct tachyphylaxis was apparent after repeated injections.

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In contrast to amphetamine, there were no adrenergic effects in isolated mammalian hearts, intestine, uterus or seminal vesicles. It was concluded that methylphenidate has much less peripheral sympathomimetic effects than the known phenylisopropylamine analeptics such as amphetamine. Maxwell (6) observed that methylphenidate reduced the hypertension caused by amphetamine and ephedrine, but potentiated that produced by epinephrine, norepinephrine and naphazoline (Privine). Drassdo and Schmidt (1) noted a reduction in recovery time when methylphenidate was given simultaneously with hexobarbital. In 1955, Ferguson (2) found methylphenidate effective in counteracting reserpine-induced depression in mental patients. Ferguson, Linn, Sheets, and Nickels (4) reported on the use of methylphenidate in the treatment of central depression caused by tranquilizing drugs or accompanying various mental disorders.

Apparently beneficial results from methylphenidate were reported by Carter and Maley (7) and Carter (8) in patients with convulsive disorders, clinical shock due to either chlorpromazine or reserpine, barbiturate intoxication, moribund patients and patients recovering from barbiturate anesthesia.

Bellucci (9), Rizzi (10) and Morpurgo, (11) in Italy, reported on the use of methylphenidate following surgical anesthesia. These investigators noted a rapid return of reflexes and increased respiration. In their first series, vomiting was observed in some patients with liver disease.

Except for the work of Drassdo and Schmidt, no controlled studies have been done in humans and much of the data reporting the effectiveness of methylphenidate in counteracting depression in man, while suggestive, were not conclusive. This study was therefore undertaken to determine whether or not methylphenidate does affect barbiturate depression significantly and whether it could be a useful agent. Recovery time from thiopental nitrous oxide anesthesia was selected as an index since it is objective and easily measured. A single operation, uterine dilatation and curettage, kept several variables as constant as possible. The patients were the same sex and from a relatively narrow age band, the variations in duration of operation, in depth of anesthesia, in the preparation and positioning of the patients, and in the degree of operative trauma were minimal.

Method

Premedication was limited to 50–75 mg. of meperidine and 0.4 mg. of scopolamine. Each patient was first given a test dose of 60 mg. of thiopental in a 2 per cent solution. Subsequent doses were varied depending upon the patient's reaction to the test dose and her weight. An attempt was made to avoid giving multiple, very small doses, and giving large doses which would be excessive. As soon as the eyelid reflex was lost, a face mask was applied and a nitrous oxide-oxygen

mixture (3L:1L) was administered from a semiclosed circle carbon dioxide-absorption anesthesia machine, Heidbrink or Foregger. The patient was positioned and the preparation started as soon as tolerated without waiting for the nitrous oxide to exert its analgesia. By using movement or swallowing as indicators of too light a plane of anesthesia, the patients were maintained at the proper anesthetic level. Recovery time was measured from the removal of the face mask at the end of the procedure to the following four end points: (a) response to verbal command (the ability to respond to a command to open her eyes), (b) sluggish verbal response (the ability to verbalize her name when requested), (c) alert verbal response (the ability to give her address), and (d) the Bender face-hand test (the ability to identify correctly simultaneous tactostimuli on the cheek and controlateral arm three times in quick succession).

The methylphenidate was administered intravenously immediately after the face mask was removed at the end of the procedure. A total of 108 control patients and 262 patients given methylphenidate were observed.

Two control series of 54 patients each were studied, one [identical with the previously reported control series (12)] before the methylphenidate series was started, and one after it was completed.

Results

In the tables, the sign "±" denotes the standard error of the preceding mean value. *P*, the probability of the observed or larger difference having been due to chance alone, was estimated by the *t* method of Student except where the use of the chi square method was indicated (13, 14).

As seen in table 1, the mean weights, ages, anesthesia times and dosages of thiopental did not differ significantly among the various series.

The recovery times for the control series are tabulated in table 2. Since the recovery times to the four end points did not differ significantly between the first and second control series, the two series were combined. The combined mean recovery times were 6.8 minutes for response to verbal command, 8.7 minutes for sluggish verbal response, 10.5 minutes for alert verbal response and 18.7 minutes for the face-hand test.

The methylphenidate treated patients were grouped according to the dose received as follows: 0.05 mg./pound, 25 patients; 0.10–0.19 mg./pound, 126 patients; 0.20–0.29 mg./pound, 32 patients; 0.30–0.39 mg./pound, 9 patients; and 0.40 mg./pound and over, 70 patients.

As shown in table 2, the 126 patients receiving 0.10–0.19 mg./pound had shorter recovery times than any of the other groups. The mean recovery times for this group of 126 patients was found to be 3.3 minutes to the response to verbal commands, 5.7 minutes to the sluggish

TABLE 1

CHARACTERISTICS OF THE PATIENTS IN CONTROL AND METHYLPHENIDATE SERIES

Series	Number Patients	Mean Weight	Mean Age	Mean Duration of Anesthesia Administration	Mean Thiopental Dosage	
					Total (mg.)	Total (mg./pound)
First control	54	132.9 ±3.5	33.1 ±1.2	19.4 ±1.1	368 ±15.8	2.77 ±0.12
Second control	54	143.6 ±5.2	35.0 ±1.5	19.4 ±0.86	383 ±17.2	2.76 ±0.10
Combined control	108	138.3 ±3.1	34.1 ±1.0	19.4 ±0.68	376 ±11.7	2.77 ±0.08
Methylphenidate-entire series	262	137.1 ±1.69	34.8 ±0.64	20.0 ±0.47	377.8 ±7.41	2.78 ±0.053

± S.E. of the mean.

verbal response, 7.1 minutes to alert verbal response and 13.5 minutes to the face-hand test. Each of these values is significantly different from the corresponding ones associated with the combined control groups which were respectively 6.8, 8.7, 10.5 and 18.7 minutes. Thus, as measured by the response to verbal command, the recovery time for the patients receiving the optimal dosage of methylphenidate was 49 per cent of those who did not receive this medication. The other three recovery times varied from 66 per cent to 72 per cent of those for the controls.

The recovery times for the patients who received 0.40 mg./pound or over were 4.5, 8.2, 9.8 and 18.1 minutes for the four measures. In each

TABLE 2

RECOVERY TIMES FOR PATIENTS RECEIVING METHYLPHENIDATE

Methylphenidate (mg./pound)	Number of Patients	Recovery Time in Minutes			
		R.V.C.	S.V.R.	A.V.R.	B.F.H.T.
0 (First control series)	54	7.0±1.1*	9.0±1.4*	11.0±1.5*	18.0±3.0
0 (Second control series)	54	6.5±0.74*	8.3±0.85*	10.0±0.87*	19.1±1.4*
0 (Combined control series)	108	6.8±0.66*	8.7±0.82*	10.5±0.88*	18.7±1.5*
0.05	25	6.0±1.2*	8.4±1.3*	9.2±1.6	17.6±2.4
0.10–0.19	126	3.3±0.31	5.7±0.56	7.1±0.66	13.5±1.0
0.20–0.29	32	4.3±0.93	6.6±1.47	8.0±1.68	16.3±2.85
0.30–0.39	9	4.4±1.41	7.3±2.37	8.4±2.67	17.0±7.18
Over 0.39	70	4.5±0.40*	8.2±0.87*	9.8±0.93*	18.1±1.7*
Entire methylphenidate series	262	4.1±0.25†	6.7±0.42†	8.2±0.49†	15.6±0.79†

* Recovery times significantly longer than 0.10–0.19 mg./pound group (at 5 per cent level or less).

† Recovery times significantly shorter than combined control series (at 5 per cent level or less).

R.V.C.—response to verbal command.

S.V.R.—sluggish verbal response.

A.V.R.—alert verbal response.

B.F.H.T.—Bender face-hand test.

case these are longer than the corresponding measurements for the 0.10–0.19 mg./pound group. Since there was considerable individual variation in the dose of thiopental administered, the methylphenidate dosage groups were subdivided according to the thiopental doses. As shown on table 3, five thiopental dosage ranges were used: (1) very low, below 1.6 mg./pound; (2) low, 1.6–2.5 mg./pound; (3) median, 2.6–3.0 mg./pound; (4) high, 3.1–4.0 mg./pound and (5) very high, over 4.0 mg./pound.

TABLE 3

RECOVERY TIMES FOR DETAILED THIOPENTAL-METHYLPHENIDATE GROUPS

Thiopental		Methyl-phenidate (mg./pound)	Number of Patients	Response to Verbal Command (minutes)	Sluggish Verbal Response (minutes)	Alert Verbal Response (minutes)	Bender Face-Hand Test (minutes)
Dose Range	mg./pound						
Very low	1.3–1.5	none	0				
		0.05	0				
		0.10–0.19	6	1.7±0.21	2.0±0.00	2.8±0.31	7.3±1.35
		over 0.39	4	2.8±0.75	5.3±1.03*	6.3±1.03*	14.3±3.89
Low	1.6–2.5	none	48	4.3±0.50*	5.2±0.56	6.8±0.68	17.3±1.89*
		0.05	9	3.0±0.67	4.7±0.71	5.1±0.63	12.9±1.82
		0.10–0.19	50	2.4±0.19†	4.1±0.58	5.2±0.62	11.0±0.88†
		0.39	20	3.2±0.36*	6.7±1.69	8.0±1.75	14.8±2.44
Median	2.6–3.0	none	26	6.5±0.80	9.0±1.15	11.3±1.45	15.9±1.76
		0.05	7	3.7±0.28	5.0±0.76	5.4±0.78†	13.4±3.27
		0.10–0.19	35	2.9±0.33	4.9±0.77†	6.1±0.85†	12.1±1.25
		over 0.39	25	3.4±0.38†	5.8±0.53†	7.7±0.69	14.6±1.52
High	3.1–4.0	none	27	8.3±1.08*	10.7±1.41	12.5±1.66	23.8±4.30
		0.05	7	8.0±2.36	11.0±2.52	12.6±2.44	20.3±4.00
		0.10–0.19	28	4.6±0.58†	8.6±1.30	10.7±1.39	19.1±3.32
		over 0.39	15	6.3±0.67	11.0±2.25	12.5±2.30	23.5±4.72
Very high	4.0	none	7	20.2±7.20	23.0±7.76	24.7±7.45	19.8±3.84
		0.05	2	20.0±1.00	28.0±4.00	29.0±5.00	44.0±9.00
		0.10–0.19	7	8.4±4.45	11.7±4.74	15.9±7.41	21.0±8.34
		over 0.39	7	9.6±1.74	16.4±3.63	19.1±4.15	32.3±7.36

* Significantly longer than 0.10–0.19 mg./pound group for the same thiopental dose range. $P < 0.05$.

† Significantly shorter than control times for the same thiopental dose range. $P < 0.05$.

Again, the recovery times of the 0.10–0.19 mg./pound methylphenidate group were the shortest at every thiopental level with three minor exceptions. The alert verbal response recovery times were shorter in the low and median thiopental ranges for the 0.05 mg./pound group, by 0.1 and 0.7 minutes, respectively, and the face-hand recovery times in the very high thiopental range was 1.2 minutes shorter for the 0.05 mg./pound methylphenidate group.

The effect of the 0.10–0.19 mg./pound dose of methylphenidate on recovery times at various levels of thiopental dosage is illustrated in

TABLE 4

RECOVERY TIMES FOR CONSOLIDATED THIOPENTAL-METHYLPHENIDATE GROUPS

Thiopental (mg./pound)	Methylphenidate (mg./pound)	Response to Verbal Command (minutes)	Sluggish Verbal Response (minutes)	Alert Verbal Response (minutes)	Bender Face-Hand Test (minutes)
Greater than 1.5	none	6.8 ± 0.66	8.7 ± 0.82	10.5 ± 0.88	18.7 ± 1.49
	0.05	6.0 ± 1.16	8.4 ± 1.26	9.2 ± 1.6	17.6 ± 2.34
	0.10–0.19†	3.4 ± 0.33	5.8 ± 0.56	7.3 ± 0.69	13.8 ± 1.09
	>0.39	4.7 ± 0.42‡	8.4 ± 0.92	10.0 ± 0.97	18.4 ± 1.73
Entire range	0.10–0.19	3.3 ± 0.31	5.7 ± 0.53	7.1 ± 0.66	13.5 ± 1.05
Corrected*	>0.39§	4.3 ± 0.39	7.8 ± 0.82	9.4 ± 0.90	17.5 ± 1.59

* Corrected for overpreponderance of very high thiopental doses in over 0.39 mg./pound group.

† All recovery times significantly shorter than controls—$P < 0.01$

‡ Recovery time significantly shorter than control—$(0.05 > P > 0.02)$. Odds of a difference as large or larger than observed by chance alone are between 2 in 100 and 5 in 100. Thus shorter recovery time was not likely to be accidental.

§ All recovery times significantly longer than optimum group $0.05 > P > 0.02$.

table 3. This shows a consistent shortening of recovery times by the methylphenidate.

Inasmuch as 6 of the 0.10–0.19 mg./pound patients received less than 1.6 mg./pound of thiopental in contrast to patients in the control group all of whom received more than 1.6 mg./lb. of thiopental, a stricter test of the effect of this dosage of methylphenidate on recovery times was obtained by considering only those patients who received more than 1.5 mg./pound of thiopental. As noted in table 4, even under these circumstances in all of the groups receiving the 0.10–0.19 mg./pound of methylphenidate recovery times were significantly lower than those of the controls. In table 4, the over 0.39 mg./pound methylphenidate group recovery times have been corrected to eliminate the

TABLE 5

CUMULATIVE PERCENTAGE OF PATIENTS RESPONDING

Period End of Minute	Response to Verbal Command		Sluggish Verbal Response		Alert Verbal Response		Bender Face-Hand Test	
	Control	Methylphenidate 0.10–0.19 mg./pound*	Control	Methylphenidate 0.10–0.19 mg./pound*	Control	Methylphenidate 0.10–0.19 mg./pound*	Control	Methylphenidate 0.10–0.19 mg./pound*
2	15.9	46.7	10.2	26.7	3.7	12.5	0	0
4	43.9	79.2	32.4	58.3	21.3	46.7	2.2	5.9
9	84.1	96.7	74.1	86.7	70.4	80.0	18.3	40.3
14	90.7	98.2	86.1	92.5	80.6	90.0	47.3	68.9
19	97.2	99.2	91.7	94.2	88.9	93.3	69.9	84.9
29	99.1	99.2	98.1	98.3	96.3	98.3	87.1	94.1
39	99.1	100.0	99.1	100.0	98.1	99.1	90.4	95.8

* In order to eliminate possible bias in favor of the methylphenidate group, only those patients who had received more than 1.5 mg./pound of thiopental are included.

effect of the disproportionately high number of patients in the very high thiopental dose range. The corrected times remain significantly longer than those of the optimum dose group. A further comparison of the control and 0.10–0.19 mg./pound methylphenidate groups who received more than 1.5 mg./ pound of thiopental is shown on table 5 which indicates the proportion of patients who recovered at specified times after the removal of the face mask. These data demonstrate that at any given time, a greater percentage of the methylphenidate patients will have responded than in the control series. The difference in the distribution of recovery times was significant by the chi square test with P less than 0.01.

TABLE 6

POSTANESTHESIA CHANGES IN BLOOD PRESSURE

Methylphenidate (mg./pound)	Number of Patients Observed	More than 10 mm. Hg Change in Blood Pressure					
		Systolic		Diastolic		Either or Both*	
		Number	Mean Change (mm. Hg)	Number	Mean Change (mm. Hg)	Number	Per Cent
0	43	4	+25.0	3	+18.3	6	14†
		10	−25.9	6	−18.3	12	28†
0.05	22	7	+22.4	6	+19.2	10	45
0.10–0.19	86	42	+20.5	31	+20.3	51	59‡
>0.39	63	45	+24.2	30	+21.2	48	76

* This column represents the number of patients who had a change in blood pressure, either systolic, diastolic, or both. Since some patients had a rise in both, it is not equal to the sum of the two previous columns.

† Significantly different from each of the methylphenidate groups $0.05 > P > 0.02$ or less.

‡ Significantly lower than 0.39 mg./pound group $0.05 > P > 0.02$.

SIDE EFFECTS

The most frequently noted side effect was a mild transient rise in blood pressure. Inasmuch as changes in blood pressure of up to 10 mm. of mercury were frequent in both the control and methylphenidate groups, even in a comparatively steady state, such changes were not considered significant. Only changes greater than 10 mm. were considered. Limiting our consideration to patients having a rise greater than 10 mm. of mercury in either diastolic or systolic pressure or both, we find that this criterion is met by 14 per cent of the controls, 45 per cent of the 0.05 mg./pound groups, 59 per cent of the 0.10–0.19 mg./ pound group and 76 per cent of the over 0.39 mg/pound group. As seen in table 6, 28 per cent of the control patients had a transient fall greater than 10 mm. of mercury in either the systolic or diastolic pressure immediately postoperatively. This drop was not noted in the methylphenidate patients. The probability of chance yielding this or a larger discrepancy was found to be less than 5 per cent by the chi square test.

Occasionally nausea, retching or emesis was noted postoperatively. The retching was considered slight if it lasted less than one-half a minute. In no case did these side effects last more than a minute or two. The differences between the control group and either the 0.05 mg./pound or the 0.10–0.19 mg./pound methylphenidate groups in the percentage of patients having nausea, retching or emesis, or all of these complications taken together, could not be shown to be statistically significant. However, the incidence of moderate retching and the three complications taken together, as shown in table 7, were significantly higher in the high dosage group than in the controls.

One patient receiving methylphenidate had a convulsive seizure about one hour postoperatively. However, this patient had a history of convulsive episodes occurring about once a month, and was not on regular anticonvulsant therapy. This episode did not differ from the others as far as could be determined.

TABLE 7

POSTANESTHESIA, NAUSEA, RETCHING AND EMESIS

Methylphenidate	Patients	Nausea	Slight Retching	Moderate Retching	Emesis	Total
0	108	0	3 (2.8%)	0	1 (0.9%)	4 (3.7%)
0.05	25	0	0	0	0	0
0.10–0.19	126	2 (1.6%)	3 (2.4%)	2 (1.6%)	1 (0.8%)	8 (6.4%)
0.20–0.39	61	0	0	4 (9.8%)*	0	4 (9.8%)
>0.39	70	0	4 (5.7%)	3 (4.3%)†	3 (4.3%)	10 (14.3%)‡

* Difference from control of questionable significance $0.1 > P > 0.05$.

† Difference from control statistically significant—$P < 0.01$.

‡ Difference from control statistically significant $0.05 > P > 0.02$. Difference from 0.10–0.19 mg./pound group of questionable significance $0.1 > P > 0.05$.

The incidence of postoperative coughing, crying and excitement was slightly less in the methylphenidate groups than the controls, but the difference was not significant.

CONCLUSIONS AND DISCUSSION

It is unfortunate that the introduction of a new drug, or a new use for an older one, is commonly associated with a certain amount of natural enthusiasm which tends to overrate the drug. In an effort to avoid this element of bias, considerable use of controls and statistical analysis has been made in this study.

The data developed in the course of this investigation show that methylphenidate is a reliable agent for the reduction of recovery time following thiopental anesthesia, with an average optimum dose between 0.10 and 0.19 mg./pound. While the evidence leaves no doubt that much higher doses are less effective than the optimum dose, an insufficient number of observations have been made in the 0.20–0.39

mg./pound dose range for its reliable evaluation. In view of these results, the administration of high doses would not seem advisable. While the mean recovery time after similar procedures and anesthetics can be expected to be shortened, it is recognized that an individual patient may have an optimum dose higher or lower than that shown to be the case in this study.

It has been demonstrated within the limits of variation in thiopental dosage of this study that higher doses of methylphenidate are not required for higher doses of thiopental. One can infer, therefore, that methylphenidate does not act as a biological competitor or blocking agent, but has an independent action on the central nervous system which tends to counteract the specific depressant action of thiopental. This would lead one to postulate that it would also be effective in counteracting similar depression of the central nervous system from other sources. Indeed its current clinical use to counteract Rauwolfia depression and in psychiatric disorders would tend to substantiate this hypothesis. It is the author's impression that methylphenidate is effective as an "alerting" agent against a wide variety of depressants.

It is evident that methylphenidate is a mild agent, in regard to both its potency and its side effects. The patients do respond more quickly after anesthesia, but not all patients respond immediately. It is therefore the author's opinion, based on the observation of a rather large number of patients that methylphenidate raises the level of "alertness" a definite, if limited, amount which in some patients may be sufficient to awaken the patients to a state of consciousness, and in others may not. The rise in level would seem to persist for at least a few hours, so that as the patient lightens from the depressant, he stays lighter than he would otherwise be, and thus awakens earlier. The duration of action of the methylphenidate cannot be determined from this study, except to say that in no case did the patient regress. Its duration must therefore be at least as long as it takes for the effect of the thiopental doses here administered to "wear off." Animal experiments would tend to indicate a duration of three to four hours. One should certainly observe any patients who are deeply depressed by agents which have a prolonged action for signs of regression. There would appear to be little likelihood of such regression in patients who had received a light anesthetic similar to the one in this study. At any rate, one could merely repeat the methylphenidate if regression should occur.

Just how useful the "alerting" effect of methylphenidate will prove to be can only be evaluated in time. However, it should very likely prove useful to shorten recovery time in those ambulatory surgical and dental clinics where such shortening is of great importance. It should also be useful in treating overdepressed postanesthetic patients, and oversedated patients in general, although it probably will not prove immediately effective in all cases.

Respiratory depression in heavily sedated obstetrical patients and

in the newborn can be a serious problem. A controlled investigation of the effect of methylphenidate in obstetrical patients is currently underway. Preliminary indications are that it may prove to be a useful agent for this purpose also. The effect of the intramuscular administration of 0.2 mg./pound of methylphenidate on newborn infants depressed by barbiturates especially is also being investigated. A dramatic improvement, almost certainly due to the methylphenidate, was observed in one infant treated about six hours after birth. Several others were treated very shortly after delivery (after oxygenation with intermittent positive pressure) and showed marked improvement subsequent to the methylphenidate administration. However, the timing so soon after delivery makes it less certain that the effect was due to the methylphenidate alone.

Although the "alerting" effect of methylphenidate should prove quite useful, its effect on respiration is also potentially advantageous. As mentioned earlier, respiratory stimulation was seen in animals. No ventilation measurements were done in the current series of patients undergoing uterine dilatation and curettage. However, a number of other patients with respiration moderately depressed by barbiturates, meperidine, or a combination of both were given methylphenidate. A prompt rise in respiratory minute volume as measured by a Bennet ventilation meter was noted in practically every case. Methylphenidata was administered during thiopental, meperidine, nitrous oxide anesthesia without affecting the maintenance of anesthesia noticeably, but with a similar prompt rise in respiratory minute volume. Methylphenidate was also administered to 11 patients during general anesthesia with prolonged apnea considered due to central respiratory depression and not muscular relaxation. Unsuccessful attempts to initiate respiration had been made in each case. Spontaneous respiration started in one to two minutes in 7 of the patients, and within six minutes in 2 others. Although these observations of respiration are not conclusive, they are highly suggestive and warrant further investigation.

Summary

The pharmacology of a central nervous system stimulant, methylphenidate (Ritalin) has been reviewed. Methylphenidate has been used clinically to counteract central nervous system depression caused by reserpine tranquilizers, anticonvulsants and anesthetics, as well as in various depressive mental states.

The effect of methylphenidate on recovery from thiopental nitrous oxide anesthesia for uterine dilatation and curettage and was measured in 262 patients, and compared to 108 control patients. Methylphenidate shortened recovery time to an appreciable and statistically significant degree. The maximum effect was obtained with doses between 0.10 and 0.19 mg./pound. Doses of 0.40 mg./pound and higher, though

effective, were not as effective as the lower dose. There was no relationship between thiopental dosage and the maximally effective methylphenidate dosage. It was concluded that methylphenidate was not a biological competitor of thiopental, but a central nervous system stimulant which tended to counteract the drug-induced depression of the central nervous system.

Methylphenidate was noted to be a respiratory stimulant in early laboratory animal experimentation. Ventilatory measurements indicated that it acted similarly in patients depressed by barbiturates, meperidine, or a combination of both. It also seemed to be effective in initiating respiration in patients after prolonged apnea due to central respiratory depression during anesthesia and in counteracting respiratory depression in the newborn.

Ritalin Hydrochloride (methylphenidate hydrochloride CIBA) was supplied by Ciba Pharmaceutical Products Inc., Summit, N. J.

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