THE COMPARATIVE AND ADDITIVE EFFECTS OF METHYLPHENIDATE AND BEMEGRIDE

ARNOLD S. GALE, M.D.

METHYLPHENIDATE (Ritalin) and bemegride (ethylmethylglutarimide, Megimide) are both central nervous system stimulants which have been administered intravenously to counteract drug-induced depression. Although both were originally considered to be specific barbiturate antagonists, more recent investigation has indicated that they are nonspecific stimulants.[1-7]

Although bemegride seems to be more effective in the treatment of drug-induced central nervous system depression, its administration may have to be curtailed because of the development of tremors or convulsions. Methylphenidate is also similarly effective, but reaches its maximum effectiveness at a comparatively low dosage. However, it does not cause convulsions, even after doses several times as great as the maximally effective one. It might be advantageous to administer methylphenidate and bemegride together if their analeptic effects were additive and if the incidence and severity of the bemegride induced tremors and convulsions were not increased. Accordingly, both drugs were administered to patients with drug-induced central nervous system depression, and an attempt was made to assess their potency, alone and in combination, by measuring their effects on recovery time after light thiopental-nitrous oxide anesthesia.

METHOD

The recovery-time study was an extension of a similar study utilizing methylphenidate alone.[3] Thiopental and a three-liter to one-liter mixture of nitrous oxide and oxygen were administered to patients undergoing uterine dilatation and curettage. All patients were uniformly premedicated with meperidine 50 mg. and scopolamine 0.4 mg. The level of anesthesia was maintained as light as possible, with only movement or swallowing being utilized as signs of too light a level. The face mask was removed abruptly at the end of operation without a "tapering off" period on 100 per cent oxygen. The analeptic drugs were administered intravenously immediately thereafter. Recovery times were measured to four end points: (1) the ability to open eyes on command (response to verbal command), (2) the ability to repeat her name (sluggish verbal response), (3) the ability to give her address (alert verbal response), and (4) the ability to identify correctly simultaneous tactile stimuli on the cheek and contralateral hand three times in rapid succession (the Bender face-hand test).

Bemegride was administered alone in doses of 0.05, 0.1, 0.2, and 0.4 mg. per pound of body weight to 100 patients. Combinations of methylphenidate and bemegride were administered to the number of patients indicated in table 1 and in the designated sequence.

RESULTS

Recovery Time Study. Small doses of bemegride (up to 0.2 mg./pound body weight) were found to be about as effective in shortening recovery times as similar doses of methylphenidate (table 1). Although large doses of methylphenidate (above 0.4 mg./pound) had been found to be less effective than the optimum dose range, (0.1–0.2 mg./pound), the largest dose of bemegride administered (0.4 mg./pound) was more effective than the smaller doses.

The administration of a small dose of methylphenidate (0.05 mg./pound) after the bemegride shortened recovery times markedly, especially to the lightest level tested (the face-hand test), from 11.5 minutes to 7.4 minutes in the case of the 0.4 mg./pound bemegride dose.

The 0.1 and 0.2 mg./pound doses of methylphenidate also shortened the bemegride

Accepted for publication November 21, 1960.
Dr. Gale is in the Department of Anesthesiology, Mount Sinai Hospital of Cleveland, Cleveland, Ohio.

TABLE 1

EFFECT OF METHYLPHENIDATE AND BEMEGRIDE ON RECOVERY TIME

Cases	Methylphenidate mg./lb.	Bemegride mg./lb.	Thiopental mg./lb.	Recovery Times			
				Open Eyes (minutes)	Name (minutes)	Address (minutes)	Face-Hand (minutes)
Control							
108	None	None	2.77±0.07	6.8±0.66	8.7±0.82	10.5±0.87	18.7 ±1.49
Bemegride Alone							
30	None	0.05	2.71±0.14	5.1±0.90	7.1±1.35	8.6±1.62	16.5 ±3.53
30	None	0.10	2.86±0.15	5.1±0.80	6.9±1.29	8.1±1.34	15.0 ±2.86
20	None	0.20	2.87±0.19	4.2±0.68	6.0±1.12	7.2±1.23	12.1 ±2.39
20	None	0.4	2.92±0.16	3.1±0.34	4.4±0.94	5.6±1.03	11.45±2.70
Methylphenidate Alone							
25	0.05	None	2.94±0.10	6.0±1.16	8.4±1.26	9.2±1.56	17.6 ±2.34
126	0.1–0.2 optimum	None	2.69±0.07	3.3±0.31	5.7±0.56	7.1±0.66	13.5 ±1.00
70	over 0.4	None	2.95±0.13	4.5±0.40	8.2±0.87	9.8±0.93	18.1 ±1.65
Bemegride Administered First							
21	0.05	0.05	2.97±0.16	4.7±0.78	5.9±1.16	7.0±1.23	11.9 ±1.88
22	0.05	0.20	2.76±0.14	3.3±0.48	5.1±1.43	6.1±1.50	8.05±1.54
21	0.05	0.4	2.79±0.15	3.0±0.34	3.4±0.43	4.0±0.48	7.4 ±1.06
20	0.1	0.05	2.94±0.21	3.7±0.58	5.1±0.85	6.3±0.90	9.6 ±1.63
20	0.2	0.05	2.79±0.15	2.5±0.22	4.3±0.20	5.1±0.69	8.2 ±1.23
20	0.1	0.4	2.88±0.21	3.5±0.70	4.8±0.79	6.1±0.93	12.0 ±3.15
21	0.2	0.4	2.98±0.15	3.1±0.63	4.5±0.84	5.7±1.00	9.1 ±1.76
20	0.4	0.05	2.78±0.16	4.3±0.61	10.3±2.54	11.4±2.60	15.5 ±3.28
20	0.4	0.4	2.76±0.16	3.4±0.67	6.1±1.45	8.1±1.85	13.1 ±2.67
Methylphenidate Administered First							
20	0.20	0.40	2.94±0.16	2.5±0.29	3.5±0.50	4.4±0.82	7.1 ±1.21
21	0.20	0.80	2.72±0.18	2.3±0.32	3.0±0.41	4.1±0.62	7.1 ±1.15

recovery times with the exception of the 0.1 mg./pound methylphenidate and 0.4 mg./pound bemegride combination which was virtually unchanged. The 0.4 mg./pound methylphenidate dose not only did not shorten the bemegride recovery times, but prolonged them. This was the same effect noted after a similar dose of methylphenidate administered alone.

Because of the protective effect of the methylphenidate which became evident during the study, and which will be described below, methylphenidate 0.2 mg./pound was administered first to two groups of patients. One group received 0.4 mg./pound of bemegride and the other, 0.8 mg./pound. The recovery times of these two groups were practically the same, and were the shortest of all the groups studied.

The recovery times to the first and last end points for the entire series of 226 patients who received both drugs were statistically significantly ($P < 0.05$) shorter than those of the entire series of 100 patients who received

TABLE 2

EFFECT OF METHLYPHENIDATE AND BEMEGRIDE ON RECOVERY TIME

Number of Patients	Methylphenidate *mg./lb.*	Bemegride *mg./lb.*	Thiopental *mg./lb.*	Open Eyes (minutes)	Name (minutes)	Address (minutes)	Face-Hand (minutes)
262	Entire series	None	2.78±0.05	4.1±0.25	6.7±0.42	8.2±0.49	15.6±0.79
100	None	Entire series	2.82	4.5±0.40	6.3±0.63	7.6±0.71	14.2±1.54
226	Both—Entire Series		2.84	3.3±0.17*	5.1±0.36	6.2±0.40	9.9±0.61*
108	None	None	2.77±0.07	6.8±0.66	8.7±0.82	10.5±0.87	18.7±1.49

* Significantly shorter than each of the other series ($P < 0.05$).

bemegride alone, and of the entire series of 262 patients who received methylphenidate alone (table 2).

Thirteen of the 100 patients who received bemegride alone exhibited visible tremors of the jaw or of the extremities (table 3). In one patient the tremors were marked enough to simulate a convulsion. In addition, a large, but unfortunately uncounted number of patients had slight jaw tremors detectable only by palpation. Both the visible and palpable tremors lasted several minutes. Only one of the 226 patients who received methylphenidate in addition to bemegride had a visible jaw tremor and this lasted less than a minute. Another patient jerked her legs spasmodically while in lithotomy position. A third patient had a palpable jaw tremor which persisted for about thirty seconds. The difference in the incidence of visible tremors was highly significant ($P < 0.01$) by the chi square test.

CLINICAL OBSERVATIONS

Seven patients with barbiturate intoxication sufficient to produce coma deep enough to eliminate tendon reflexes and reaction to a painful stimulus were treated with a combination of methylphenidate and bemegride. The first four, treated before the tremor inhibiting effect of methylphenidate was noted, received bemegride in increments of 50 mg. every three minutes until tremors were noted, at which time 25 mg. of methylphenidate were administered once or twice. The tremors stopped in two of the patients. Three of the four patients awakened promptly to the point of being able to speak. The fourth reacted to pain vigorously. The next day, while still at the same level of coma, he was given a second course of treatment immediately following which he was able to speak. The last three patients were treated after the tremor inhibiting effect of methylphenidate had been appreciated. Twenty-five milligrams of methylphenidate were administered first, and were followed by bemegride in increments of 50–150 mg.

One patient, a known epileptic, was lying on the operating table preparatory to a craniotomy for a suspected subdural hematoma. The operation was cancelled when she responded to the combined methylphenidate and bemegride treatment. She awakened immediately to the point of responsiveness to verbal command, and after a second treatment the next day, she was able to speak. Another patient was the most deeply comatose patient encountered. She was areflexic, hypotensive, hypothermic and apneic. She responded to the initial course of treatment by initiating spontaneous respiration and reacting to painful skin stimulation. Her blood pressure was maintained with an intravenous infusion of Levophed; this infusion could be slowed considerably after the methylphenidate administration. This patient received four courses of combined

TABLE 3

VISIBLE TREMORS IN PATIENTS RECEIVING BEMEGRIDE AND METHYLPHENIDATE

Number of Patients	Analeptic	Tremors	Incidence (Per Cent)
100	Bemegride	13*	13.0
226	Methylphenidate and Bemegride	2*	0.9

* Significant difference by the chi square test ($P < 0.01$)

methylphenidate and bemegride during a 36 hour period. After the last course she changed from unresponsiveness to verbal commands to being able to sit up unaided. She did not talk until a few hours later.

The seventh patient responded promptly to the treatment to the point of being able to talk rationally.

Other patients with lesser degrees of barbiturate intoxication, postoperative barbiturate depression, and deep sedation for labor have been treated with uniformly good responses.

Tremors were not noted in the patients treated with methylphenidate first, even though up to one gram of bemegride was administered during therapy. The deeply comatose woman with hypothermia on admission had generalized muscular hypertonicity after 900 mg. of bemegride had been administered during the third course of treatment. She had previously received two 25 mg. doses of methylphenidate, but the hypertonicity disappeared abruptly immediately after a third 25 mg. dose was administered.

One patient in coma after ingesting 20 Gm. of meprobamate (Equanil) responded well to combined methylphenidate and bemegride therapy. This 54 year old white woman was not comatose when first admitted. Although aspiration of stomach contents removed a quantity of chalky material, the patient nevertheless became unconscious. Twenty-three hours after admission she was breathing well with a nasotracheal tube in place, reacted weakly to skin pinching, but was otherwise unreactive. An infusion of mephenteramine (Aramine) was required to sustain her blood pressure. The infusion was stopped when methylphenidate-bemegride was started. She received two 25 mg. doses of methylphenidate (one at the beginning, and one at the end of the treatment) and six 50 mg.-doses of bemegride at 2–3 minute intervals. She improved markedly during the treatment and further vasopressor support was not needed. She was able to sit up, respond to simple commands, stand with assistance, and talk sluggishly, but was not rational. She improved steadily thereafter. By the next morning (six hours later) she was rational and alert.

Discussion

The results of the thiopental recovery time study indicate that at least one analeptic effect of methylphenidate is additive to that of bemegride. It is also evident that methylphenidate does not increase the toxicity of bemegride as regards to tremors and convulsions, and probably decreases it considerably. This observation is similar to that made by Brooks who found methylphenidate effective in counteracting parkinsonian type extrapyramidal signs which developed in patients reciving large doses of chlorpromazine and/or reserpine.[8]

The combination of methylphenidate and bemegride seemed to be effective in counteracting even deep barbiturate or meprobamate coma. Although it is impossible to say how it affected the clinical course as a whole, at least one patient recovered who seemed in danger of imminent death.

The marked response of the patient with meprobamate intoxication, together with the steady improvement and rapid recovery after treatment suggests that this patient's course was considerably altered by the methylphenidate and bemegride.

Although drug therapy has been emphasized in this article, in no case can the usual supportive therapy be delayed or omitted. Adequate ventilation and oxygenation is vital and cannot await other treatment.

It should be noted that methylphenidate acts synergistically with Levophed in producing hypertension.[9] This can be useful as the requirements for that vasopressor can be reduced considerably. It can also produce dangerously high blood pressure levels. To prevent this, Levophed should be stopped before administration of methylphenidate and then restarted at a slower rate when indicated.

Since the effects of methylphenidate and bemegride seem to be additive, and since methylphenidate counteracts the tremors and convulsions often noted after bemegride administration, it appears logical to administer methylphenidate whenever bemegride is to be given. In adults, 25 mg. of methylphenidate administered initially and followed by 50 mg.-increments of bemegride at 2–3 minute inter-

vals until the desired results are obtained, or until tremors or a plateau of improvement is noted, seems to be a safe and effective schedule. A final dose of 25 mg. of methylphenidate should also be given as it sometimes lightens the coma a bit more and counteracts tremors that may have developed. The corresponding children's increments are 20 mg. per 100 pounds body weight for methylphenidate, and 40 mg. per 100 pounds for bemegride. Twenty-five milligrams of methylphenidate followed by one or two 50-mg. doses of bemegride seems adequate for adult patients depressed from sedatives yet not in coma.

This combination seems to be effective for barbiturate depression, as well as other drug induced depression. Although we have treated only one patient with meprobamate intoxication, the response was so marked that further clinical trial is recommended.

Summary

The comparative and additive effects of methylphenidate (Ritalin) and bemegride (Megimide) on recovery time was studied in 696 patients who had undergone a uterine dilatation and curettage under thiopental nitrous oxide anesthesia. The combination was also administered to eight patients with drug-induced central nervous system depression. The recovery times were significantly shorter after the combination of drugs than after either drug alone. There was a statistically significant reduction in the incidence and severity of bemegride-induced tremors when methylphenidate was also administered. The seven patients depressed from barbiturate overdosage also improved after the administration of these agents. A patient with meprobamate intoxication responded especially well. It was concluded that the methylphenidate not only added to the analeptic effect of bemegride, but also reduced the incidence of tremors.

The dosage schedule adopted for adults was 25 mg. of methylphenidate followed by 50 mg. increments of bemegride until a plateau of improvement or toxic symptoms developed. The methylphenidate dose was then repeated.

Methylphenidate (Ritalin) was supplied by Ciba Pharmaceutical Company, Summit, N. J., and bemegride (Megimide) by Abbott Laboratories, Chicago.

REFERENCES

1. Drassdo, A., and Schmidt, M.: Ritalin, ein zentrales stimulans mit neuartinger chemischer konstitution. (Teil 1. Kreislaufuntersuchungen.) Med. Mschr. **8**: 306, 1954.
2. Shaw, E. H., Simon, S. E., Cass, N., Shulman, A., Anstee, J. R., and Nelson, E. R.: Barbiturate antagonism, Nature **174**: 402, 1954.
3. Gale, A. S.: Effect of methylphenidate (Ritalin) on thiopental recovery, ANESTHESIOLOGY **19**: 521, 1958.
4. Shulman, A., and Laycock, C. M.: Bemegride analepsis, Brit. Med. J. **1**: 871, 1958.
5. Kimura, E. T., and Richards, R. K.: Comparative study of bemegride (β, β-methylethylglutarimide; N P 13, Megimide) as analeptic in mice, Arch. Int. Pharmacol. Ther. **110**: 29, 1957; as reported by: Koppanyi, T., and Richards, R. K.: Treatment for barbiturate poisoning with or without analeptics, Anesth. Analg. **37**: 182, 1958.
6. Gale, A. S.: Clinical use of methylphenidate for central stimulation in oversedated patients, Anesth. Analg. **38**: 406, 1959.
7. Gale, A. S.: Clinical evaluation of methylphenidate (Ritalin) hydrochloride in newborn infant, J. A. M. A. **170**: 1408, 1959.
8. Brooks, G. W.: Experience with use of chlorpromazine and reserpine in psychiatry, N. Engl. J. Med. **254**: 1119, 1956.
9. Povalski, H. J., and Goldsmith, E. D.: Effect of methylphenidate on cardiovascular actions of pressor amines, Proc. Soc. Exp. Biol. Med. **101**: 717, 1959.