EFFECTS OF BEMEGRIDE ON BARBITURATE OVERDOSAGE IN HUMANS

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Shaw *et al.* (1954) and Shulman *et al.* (1955) have shown that bemegride (β -ethyl- β -methylglutarimide) is a valuable and effective barbiturate antagonist. Since then many reports have been published on the treatment of barbiturate poisoning by the use of bemegride, sometimes in combination with amiphenazole (2:4-diamino-5-phenylthiazole hydrochloride). Altogether the reports of the treatment of more than 200 cases of barbiturate poisoning (Canbäch, 1955; Holten, 1955; von Planta and Klingler, 1956) have been communicated to us or published.

Perinpanayagam *et al.* (1955) reported the case of a child aged 15 months who was successfully treated with bemegride after taking 21 gr. (1.5 g.) of barbiturate, consisting of seven 3-gr. (0.2-g.) capsules of "tuinal" (quinalbarbitone sodium and amylobarbitone sodium). Clemmesen (1956) published his results on the treatment of over 70 cases of barbiturate poisoning, and this is the most extensive series treated with bemegride so far reported. Two cases of barbiturate poisoning were recently reported (private communication) in which bemegride treatment led to a successful outcome after the ingestion of doses of barbiturate within the fatal range. One had taken 16 g. of phenobarbitone and the other 23 g. of barbitone.

As a result of further work and the study of the results in the literature, bemegride alone is now used in the treatment of barbiturate poisoning. The use of amiphenazole is unnecessary, unless there is severe respiratory depression which is not amenable to bemegride. The results recorded below give further evidence that amiphenazole (orally) has little antidotal effect on barbiturate overdosage.

Animal experiments would suggest that parenterally administered bemegride was a convulsant drug; this, however, is not the case in humans, as has been shown by Harris (1955), using doses of up to 50 mg. intravenously. Coirault *et al.* (1956) and Delay *et al.* (1956) have shown that bemegride could be administered safely without the prior administration of barbiturate. These workers were primarily interested in the use of bemegride as a provocative test for epilepsy (Drossopoulou *et al.*, 1956). In summary, it has been shown that bemegride evokes changes in the E.E.G. in all subjects, normal or abnormal, as follows: (1) progressive modification in the form of slow bilateral synchronous activity; and (2) paroxysmal modifications in the form of bisynchronous multiple spikes and waves, either spontaneously or provoked by flicker and apt to end in the development of a generalized epileptic discharge.

However, in subjects with cerebral disorder it causes the appearance of changes which are never seen in normal subjects: (1) bisynchronous discharges of rhythmic 3 c./sec. spikes and waves, and (2) focal discharges of spikes, slow waves, or spikes and waves.

Sporadic discharges unaccompanied by clinical symptoms (interseizure discharges) or rhythmic discharges accompanied by partial epileptic seizures (seizure discharges) have been observed. Further details of the pharmacology of bemegride are given by Delay *et al.* (1956). Koppányi and Fazekas (1953) and Fazekas *et al.* (1956) have endeavoured to prepare a mixture of the various barbiturates and leptazol, whereby the effect of the accidental or intentional administration of large doses of barbiturate would be nullified and consequently poisoning would be prevented. They carried out trials on human volunteers, giving the barbiturate orally together with three times the amount of leptazol. Pentobarbitone sodium was given orally to 10 volunteers in doses ranging from 1.3 to 2 g. together with three times this amount of leptazol. All the subjects exhibited some signs of mild acute barbiturate intoxication, strongly resembling those of acute alcoholism. They either remained awake till their usual bedtime or were easily aroused if they fell asleep. They all showed ataxic gait and station; nystagmus, both horizontal and vertical; and difficulty in accommodation. Evidence of central nervous stimulation was observed in most of the subjects. Frank convulsions were not seen, but in four subjects involuntary clonic jerks and infrequent torsion spasms were observed. Also 7 out of 10 showed nausea, retching, and vomiting within one to four hours after ingestion.

This procedure was repeated on six volunteers using both secobarbitone and phenobarbitone. The results with both these barbiturates were much the same as recorded above with pentobarbitone except that one of the subjects receiving secobarbitone exhibited olfactory hallucinations. It was suggestive also from these results that, in humans, leptazol is more completely antagonistic to the central depressant effects of phenobarbitone.

Finally, it was found that leptazol stimulates the vomiting centre when administered in the doses used, even in the presence of large doses of barbiturate.

Present Investigation

In view of the above work we decided to determine the effects of oral bemegride on barbiturate overdosage in man. The possibility of a safe trial and a successful outcome was enhanced by the knowledge that Trautner *et al.* had successfully combined large doses of barbiturate and bemegride for the purpose of producing a continuous narcosis in psychiatric patients (see paper by Trautner *et al.* (1957) at page 1514). They report on the use of amylobarbitone together with a fixed proportion of 12% bemegride. The dose of barbiturate was given in the morning and progressively increased from 250 mg. up to a dose of 1,750 mg. Normal sleep resulted from the ingestion of the lower dose levels, but the resultant duration and depth of sleep progressively decreased or was completely absent on reaching the higher dosages. In each case the patients slept well during the night and with the higher dosages were mildly sedated during the following day. No untoward after-effects were observed in any of these cases.

The barbiturates studied in the present work were phenobarbitone and pentobarbitone, as representatives of the short- and long-acting groups respectively. The possible dangers inherent in this type of experiment were obviated by gradually increasing the dose of barbiturate in each patient. Furthermore, it was known from the work of Fazekas *et al.* (1956) that 2 g. of pentobarbitone could be successfully antagonized by leptazol, a much weaker antagonist than bemegride. Also from the literature it was known that about 1 g. of pentobarbitone would render a subject comatose with severe central nervous depression, whilst a

similar state would be produced by doses of phenobarbitone ranging from 1.5 to 4.8 g., with death resulting from doses ranging from 4.8 to 5.2 g.

Method

The subjects used in this investigation were all psychiatric patients. The procedure adopted was to place the patient on a couch at 9 a.m., about one hour after breakfast, when a physical examination was carried out and the blood pressure, pulse rate, temperature, and respirations were recorded. The patients were then given the appropriate mixture of barbiturate and bemegride in the form of a tablet. At half-hourly intervals the level of consciousness of the patients was noted, together with a record of the blood pressure, pulse rate, temperature, and respirations. The degree of depression of the central nervous system was assessed as:

Awake: when the patient was fully conscious and alert with clear orientation.

Drowsy: indicates that the patient was lightly and fitfully asleep but could at all times respond to the spoken voice. The patient may exhibit ataxic gait or station, slightly dysarthric speech.

Sleep: indicates that the patient was asleep but could at times respond to the spoken voice, and at all times to tactile and painful stimuli. All reflexes were normally present.

Narcotized: indicates a state in which the tendon and/or cutaneous reflexes were present but there was no response to the spoken voice, and no oral response to painful stimuli, the subject, however, still responding to this latter stimulus by withdrawal response.

Coma: indicates loss of response on strong supraorbital pressure with loss of reflexes, and unresponsiveness to any stimuli.

The commencing dose of barbiturate was a therapeutic one—namely, 250 mg. of phenobarbitone and 100 mg. of pentobarbitone—and the dose of barbiturate was then gradually increased by steps of about 25% with bemegride in the proportion of 10 to 25.6%. The interval between the administration of doses was three days in the lower dose range and one week at the higher levels. It is unlikely that with this procedure any degree of tolerance to the barbiturates would develop within the duration of the experiment. The lack of the development of tolerance was further shown by first increasing the dose gradually to the maximum figure recorded and then reducing it again over the same dose range. Identical effects were obtained at the same dose level on both occasions (see Tables I and II).

TABLE I.—*Effect of Oral Administration of Pentobarbitone Sodium and Bemegride With or Without Amiphenazole in Psychiatric Patients*

Case No.	Total Dose Pentobarbitone	Bemegride	Amiphenazole	Before Ingestion	Hours After Ingestion				Comments
					1	2	3	4	
1 3	500 mg.	17%	7%		Awake	Sleep	Sleep. Awakened and ate full dinner, and returned to sleep	Drowsy	Awake and out of bed in 7 hours
	750 "	17%	7%		Drowsy	"	Narcotized. Too sleepy to eat dinner		Awake and out of bed in 9 hours. Had full evening meal and slept well throughout night
	1,000 "	17%	7%		"	Narcotized	Narcotized	Deep sleep	As above
	1,250 "	17%	7%		Awake	Awake. Given 100 mg. tabs. amiphenazole. Total 15%	Drowsy. Had dinner and very drowsy	Drowsy, then sleeping soundly	As above. Drowsy on following day, but able to get up to go to work
	1,250 "	17%	7%		"	Drowsy. Given 100 mg. tabs. bemegride. Total 25%	Sleep. Awakened and ate dinner	Sleeping	Awake and out of bed in 7½ hours, when vomited
	1,250 "	10%	0		Drowsy	Sleep	Narcotized. Unable to waken for dinner	"	Awake and out of bed in 9 hours
	1,250 "	0	18%		"	"	Narcotized. Did not eat full lunch	Sleepy	Awake and able to answer to vocal stimuli in 13 hours
	1,500 "	24%	7%	B.P. 115/75. P.R. 64. R.R. 17	"	"	" "	Sleeping. B.P. 110/70. P.R. 68. R.R. 18	Awake and out of bed in 7 hours. Ate full meal
4	500 "	0	0		"	"	Narcotized. Unable to eat meal	Sleep	Awake and out of bed in 7 hours. Shows absence of tolerance
	750 "	0	0		Deep sleep	Narcotized	Narcotized	"	Awake in 8 hours, and slept well throughout night
	1,250 "	10%	0		Awake	Drowsy. Given 100 mg. bemegride. Total 18%	Sleep	"	Awake in 6 hours
5	1,500 "	17%	7%		Sleep	"	"	"	" " 5 "
	500 "	17%	7%		Awake	Drowsy	Deeply asleep	"	Awake in 6½ hours, and able to get up and get dressed
10	500 "	0	0		Sleep	Narcotized	" "	Asleep	Awake in 8 hours. Had a light tea and then fell asleep again. Drowsy next morning
	666 "	14%	6%		Drowsy	"	Sleep	Drowsy	Awake in 5 hours. Able to get dressed and out of bed
11 12	2,000 "	14%	6%	B.P. 125/85. P.R. 84. R.R. 20	"	Narcotized. B.P. 115/82. P.R. 86. R.R. 20	Deep sleep	Drowsy. Had light lunch and drowsed	Awake in 8 hours. Had full evening meal
	666 "	0	0		"	Narcotized	Sleep	Drowsy. Ate light lunch	Drowsy, and remained in bed all day. Shows absence of tolerance
11 12	2,000 "	14%	6%		Awake	Sleep	Sleep	Narcotized	Awake in 8 hours, ate light meal, then very drowsy and had to remain in bed. Drowsy next morning and dozed on and off till lunch time
	2,333 "	14%	15%	B.P. 130/85. P.R. 86. R.R. 20	Drowsy	"	Narcotized	Drowsy	Awake in 5½ hours, and ate light meal. Able to get up out of bed and steady on feet. Slightly drowsy next morning

TABLE II.—*Effect of Oral Administration of Phenobarbitone Sodium and Bemegride With or Without Amiphenazone in Psychiatric Patients*

Case No.	Total Dose Phenobarbitone	Bemegride	Amiphenazone	Before Ingestion	Hours After Ingestion				Comments
					1	2	3	4	
1	1,000 mg.	17%	7%		Drowsy	Sleep	Sleep	Sleep	Awake in 8 hours. Ate full meal. Then able to get out of bed
3 4 5	1,000 "	25.6%	10%		Awake	Awake	Drowsy. Unsteady gait	Drowsy	After 4 hours went to sleep for 2 hours. Then woke and had meal
6 8	1,500 "	25.6%	10%		"	Sleep	Awake	"	Drowsy for rest of day, but after 5 hours got out of bed
10	1,250 "	17%	7%		"	"	Narcotized	Sleep	Awake in 5 hours, but still a little drowsy. Able to get out of bed
	750 "	0	0		Drowsy	Narcotized	"	Narcotized	Awake in 9 hours, but unable to get out of bed
11	1,500 "	17%	7%		Awake	Awake	Drowsy	Sleep	Awake 7 hours after ingestion of tablets; able to get out of bed
	1,500 "	0	17%		"	Deep sleep	Deep sleep	Drowsy	Awake in 9 hours and slept well throughout night
	1,500 "	10%	0		Talkative. 100 mg. bemegride given. Total 17%	Sleep	Sleep	Awake. Talkative	Awake in 4 hours, talkative during afternoon, slept well during night
	1,750 "	17%	7%		Talkative	Drowsy	Sleeping	Asleep	Awake in 5 hours, then light meal, drowsy for about 1 hour then fully awake
12	750 "	0	20%		Drowsy	Drowsy	Drowsy. Had light lunch	Sleep	After 4 hours, fell deeply asleep, with deep respiration. Awake in 8 hours, had full meal
	1,000 "	10%	0		Awake. Given 100 mg. bemegride. Total 20%	"	Drowsy	"	Awake in 6 hours. Only light sleep of short duration
	1,500 "	24%	7%		Awake	"	"	Drowsy	Drowsy, no sleep recorded
13	1,750 "	24%	7%		Sleep	Sleep	Drowsy	Awake	Awake in 4 hours, drowsy during afternoon, slept well throughout night, drowsy next day
	1,750 "	10%	0%		Drowsy	Drowsy	Sleep	Sleep	Awake in 6 hours but drowsy next day and all following day
14	500 "	0	0		"	Deep sleep	Narcotized	Deep sleep	Awake in 9 hours, but still very drowsy
	1,000 "	17%	7%		"	Drowsy	Drowsy	Drowsy	Slept lightly for 2 hours during afternoon. Awake in 8 hours
16 17	1,250 "	17%	7%	B.P. 130/95. P.R. 74. R.R. 18	Awake	Awake	Drowsy. B.P. 125/90. P.R. 74. R.R. 20	Sleep	Awake in 7 hours
	2,000 "	17%	7%		Drowsy	Drowsy	Drowsy	"	Awake in 8 hours, but only drowsy without falling properly asleep all day. Drowsy all next day
	2,000 "	23%	7%		"	Awake	Awake	Drowsy	Did not sleep at all, but remained drowsy all day and following day
18	1,000 "	17%	7%		Drowsy	Drowsy	Drowsy	Sleep	Awake in 8 hours, but still drowsy. Drowsy all next day
	1,750 "	17%	7%		Drowsy. Given 100 mg. bemegride. Total 23%	Awake	Awake. Had dinner	"	Awake in 8 hours, drowsy all afternoon. Drowsy next day
	2,000 "	17%	7%		Drowsy	Very drowsy	Narcotized	Drowsy	Awake in 7 hours, drowsy rest of day. Slept well throughout night and still somewhat drowsy for following two days
	2,250 "	21.5%	11.5%		"	" "	Very drowsy	"	Did not sleep at all, but otherwise condition as above
	2,666 "	25.6%	10%		"	" "	Sleep	Very drowsy	Drowsy all rest of day and following morning
	1,250 "	25.6%	10%		"	Drowsy	Drowsy	Sleep	Awake in 5½ hours. Otherwise as above. No tolerance observed
19 20	1,250 "	17%	7%	Restless. Talkative	Drowsy	Drowsy	Drowsy. Ate full meal	"	Awake in 5½ hours. Slept well throughout night
21	1,250 "	25.6%	10%		Awake	Awake	Awake. Ate full meal	Drowsy	Awake in 7½ hours, able to get up and dress himself. Ate full meal and slept well throughout night. Drowsy following day
	2,000 "	25.6%	10%		"	"	Drowsy	Talkative. Ate full meal	Did not sleep during day. Slept well throughout night
23	1,000 "	25.6%	10%		Drowsy	Drowsy	"	Sleep	Awake in 9 hours. Slept well throughout night
	2,000 "	25.6%	10%		Showed twitching of limbs, lasted for about 1 minute, then vomited	"	Sleep	Drowsy	" "

During the trials all the routine resuscitative measures were on hand, but recourse to them was not required on any occasion.

However, with the moderate doses of barbiturate used and the availability of bemegride as an antidote the risk was assessed as nil. This conclusion was justified by the successful outcome of the work.

Results

This study was carried out on a total of 58 subjects. This number included those treated by Trautner *et al.* (1957) together with those observed by us. This group of 58 subjects received altogether 361 treatment doses of the various barbiturate-bemegride mixtures.

The groups studied were as follows: (1) amylobarbitone sodium, (2) phenobarbitone sodium, and (3) pentobarbitone sodium.

Group 1. Amylobarbitone Sodium and Bemegride

The eight subjects in this group received 58 treatments. The observations made with the mixture of amylobarbitone and a fixed dose of 12% bemegride are fully reported in the paper by Trautner *et al.* (1957). Their purpose was to produce by this form of medication a prolonged state of sleep and sedation in an attempt to promote a sleep pattern as similar as possible to normal sleep. The state obtained in these patients was such that they could be treated and dealt with easily and swiftly by the nursing staff.

These subjects were given various doses of amylobarbitone up to a maximum dose of 1,750 mg. at approximately 9 o'clock each morning, and all were awake by 6 p.m. and able to eat a meal. Vomiting occurred in one subject on three separate occasions, one to three hours after the ingestion of the tablets. Grand-mal seizures occurred on two occasions in one subject who was a known epileptic and who had had no seizures and no anticonvulsant medication for the previous two years. One seizure occurred one day after the ingestion of 500 mg. of amylobarbitone with 12% bemegride, and the other two days after taking 750 mg. of amylobarbitone and 90 mg. of bemegride. No further medication was given to this subject.

Group 2. Phenobarbitone Sodium and Bemegride

The 37 subjects in this group received 255 treatments with varying doses of phenobarbitone given with amounts of bemegride varying from 10 to 25.6% of the barbiturate dose. Amiphenazole was sometimes included in the mixture. A representative selection of the findings is presented in Table II, and a graphic representation of the effects obtained can be seen in Fig. 1.

Vomiting occurred in four of the subjects on a total of seven occasions out of 255 administrations. It occurred with different doses of barbiturate and bemegride and at time intervals between half to six hours after ingestion.

FIG. 1.—Diagrammatic representation of the effect of bemegride on the hypnotic action of phenobarbitone. Solid line, 17% bemegride. Dotted line, 25.6% bemegride.

Minor convulsions were observed in one subject on two occasions. Twitching of the limbs in this subject was observed on the first occasion after the ingestion of 1,750 mg. of phenobarbitone containing 25.6% bemegride and a minor convulsion after the ingestion of 2,000 mg. of phenobarbitone and 25.6% bemegride. These convulsive responses took place approximately two to three hours after ingestion of the tablets. On both occasions the convulsant responses were minimal, requiring no specific therapeutic measures. The patient's colour remained good, there was no injury to the tongue or incontinence of bowel or bladder, and the subject was not in any way distressed by the occurrence and had no memory of it. This patient did not show this response on lower doses of the tablets. So far as could be ascertained, this subject had no history of epilepsy, but it may be that the bemegride provoked a latent cerebral dysrhythmia (Drossopoulos *et al.*, 1956).

A group of six subjects were given a dose of 1,250 mg. of phenobarbitone sodium one day a week for 10 weeks. The amount of bemegride given together with this varied, being on some occasions 17% and on others 25.6%.

Some of these results are presented in Table II. They indicate that the same dose of barbiturate and bemegride given over a prolonged period results in the production of approximately the same depth and duration of sleep, and that with the higher dose of bemegride the duration and depth of sleep is diminished. This effect was most clearly seen when the different mixtures of barbiturate and bemegride were given to noisy, restless, and overactive subjects. A dose of the barbiturate-bemegride mixture that exerted a sedative effect on these subjects with psychomotor activity did not fully control them when the dose of bemegride was increased. An example of this effect is seen in Case 13 in Table II.

It was also observed, when large doses of the barbiturate-bemegride mixture of the order of 1,000 mg. or more of barbiturate were given, that in the majority of cases the subjects were still somewhat drowsy on the following day. If the dose of barbiturate was repeated with 15% or more bemegride when these subjects were still drowsy they showed a transient arousal about an hour after this ingestion before again becoming drowsy. A similar response was produced by the ingestion of 100 mg. of bemegride (bringing the total to 23%) when the subject became drowsy, with a resultant delay in the onset of sleep. An example of this delay in onset of sleep by an additional dose of bemegride was seen in Table II, Case 18, with the ingestion of 1,750 mg. of barbiturate.

Group 3. Pentobarbitone Sodium and Bemegride

This group comprised 13 patients who received treatment. The effects of bemegride on pentobarbitone sodium overdosage were essentially similar to its effects on the other barbiturates mentioned. However, the impression

FIG. 2.—Diagrammatic representation of the effect of bemegride on the hypnotic action of pentobarbitone.

was gained that the antidotal effect of bemegride with regard to pentobarbitone was somewhat less than that exerted against amylobarbitone and phenobarbitone. Furthermore, the resultant depth and duration of sleep produced by equivalent amounts of the pentobarbitone-bemegride mixture was deeper and longer than with equivalent amounts of the other two barbiturates (Fig. 2). But, apart from this, the general effects of bemegride on pentobarbitone overdoses are identical to those recorded above. The incidence of vomiting was also low in this series, occurring only once in two subjects. Convulsions or muscular twitching did not occur in this series.

Bemegride has been shown to have no haemotoxic effects in animal experiments (Dr. G. Bentley, 1956, personal communication). This was found to be the case in carrying out routine blood examinations in humans. Three subjects were given 200 mg. three times a day, after food, for six weeks; and haemoglobin and red- and white-cell examinations were carried out before, during, and after the completion of medication. None of these examinations revealed any abnormality. These examinations were repeated on four subjects receiving long courses of medication in each of Groups 2 and 3, with the same results as above. A general perusal of the results would suggest that the antagonistic effect of bemegride against the various barbiturates tested was not significantly influenced by the presence of amiphenazole.

Discussion

The present study was carried out to determine whether the well-known antagonism between bemegride and barbiturates also occurs following their simultaneous oral administration. In this work full control studies with the barbiturates were not carried out because data in the literature indicate that barbiturate doses of the magnitude used may produce anaesthesia and coma with serious complications (Hambourger, 1939, 1940). The maximum doses of the barbiturates used were of the magnitude usually considered to produce severe poisoning in humans (Fazekas *et al.*, 1956).

Coma following oral ingestion of pentobarbitone sodium has been reported to result from approximately 1 g. (Krantz and Carr, 1954; Sollmann, 1948). Fisher *et al.* (1948) reported that patients who had taken 0.8 to 2 g. of pentobarbitone passed into coma. Fazekas *et al.* (1956) reported that 1 g. of pentobarbitone was capable of producing severe central depression.

Table I shows that 2 g. and over of pentobarbitone when given in combination with bemegride is well tolerated and no serious depression of the central nervous system or other vital functions occurs. The acute toxic dose of phenobarbitone is larger than that of either pentobarbitone or amylobarbitone. Coma has been reported from doses varying from 1.5 to 4.8 g., with death occurring from doses varying from 4 to 5.2 g. (Koppanyi and Fazekas, 1950).

Worlock (1956) reported the successful treatment of 12 cases of barbiturate poisoning with bemegride (and amiphenazole). Seven of these cases are relative to this present study and that of Trautner *et al.* (1957). Four cases of amylobarbitone poisoning are reported in which the dose ranged from 1.5 to 2.8 g. of amylobarbitone, and three of phenobarbitone poisoning (0.75–2.8 g.). In all cases the patients were admitted "in an unconscious state and were unresponsive to any stimuli." In most cases deep reflexes were absent. The dosages of amylobarbitone and phenobarbitone which produced unconsciousness in these cases caused only a state varying from light sedation to sleep when combined with bemegride (see Tables I and II). Furthermore, as much as 2.6 g. of phenobarbitone when administered with 25.6% bemegride failed even to produce deep sleep in these subjects. In all the subjects investigated the vital functions of blood pressure and respiration were adequately maintained even on occasions when the subject was narcotized or in a deep sleep. It should be noted that in several cases the addition of amiphenazole had a

beneficial effect on respiration, and appeared to be effective in maintaining a good respiratory amplitude.

Bemegride itself has been found to have no chronic toxic effects in animals (Dr. G. A. Bentley, 1956, personal communication), and when administered orally to three subjects in doses of 300 mg. daily and to another three in a dose of 200 mg. three times a day for a period of eight weeks failed to produce any untoward or harmful effects. No abnormalities were seen in the red or white blood cells, and urinalysis did not show any changes. These doses did not produce any form of stimulation of the central nervous system either objectively or subjectively, and did not interfere in any way with the subjects' normal sleep pattern.

The results of this study would indicate that combinations of bemegride and barbiturates can be given in such amounts that they will not interfere with the sedative or hypnotic action of barbiturates, and the ingestion of similar combinations in larger amounts will protect against anaesthetic or toxic doses of barbiturates. Such a protection from the toxic effects of orally administered barbiturates by bemegride in man is not seen so readily in animals. Some degree of protection is evident in rats. In dogs there is only slight protection. It would appear that barbiturates cause a cardiovascular death in dogs which is not antagonized by bemegride (Dr. G. A. Bentley).

The present findings show that when bemegride was given with high doses of barbiturate for prolonged periods as sleep therapy to 58 subjects no barbiturate withdrawal symptoms of any kind occurred. The dosage used in these subjects can be seen from Tables I and II. One group of seven subjects was given a dose of 1.250 mg. of phenobarbitone with 17% bemegride, three times a week for six weeks, without any toxic effects either during or on discontinuance of administration. This observation is of particular interest in view of the statement by Kjaer-Larsen (1956) that bemegride produced an acute hallucinatory state in cases of acute barbiturate poisoning treated with this drug. Such states had not been reported by other workers in the same field. The hallucinatory phenomena as described by Kjaer-Larsen are a well-known complication of high barbiturate dosage, especially as the case material investigated by this author consisted of barbiturate addicts and psychotics. (For a previous communication on this problem see Gershon *et al.*, 1956.)

Barbiturate withdrawal symptoms of varying severity have been considered to be an almost constant accompaniment of the various forms of sleep treatment. Azima (1955) reported on 25 cases which received sleep treatment produced by giving approximately 550 mg. of barbiturates together with 50 mg. of chlorpromazine daily for approximately 20 to 25 days. In that series 13 developed complications of varying severity. Post-sleep convulsive seizures and a hallucinatory delirious syndrome are the most serious complications according to the literature on this subject (Kalinowsky and Hoch, 1952; Sargent and Slater, 1954; Floris and Della Rocca, 1955). When bemegride was given together with the barbiturates in this study there was a complete absence of such complications. This would agree with the results of Palmer (1956).

A combination of bemegride with a long- or medium-acting barbiturate seems to offer the following advantages: (1) Sleep therapy in psychiatric practice is made safer and more simple. A light sleep, not a coma, is produced, thus relieving the nursing staff of a great deal of responsibility. Withdrawal symptoms are not produced on cessation of administration. (2) Sedation of psychoneurotic cases in private practice is made safer. The possibility of suicide and addiction is greatly lessened. This combination allows of the production of a safe level of sleep for prolonged periods with complete safety, and as such may be of special use as a first-aid measure or treatment in dealing with disturbed psychiatric patients in private practice, in hospital, or for front-line military psychiatric casualties. However, further work would be required before this could be established as a routine therapeutic procedure.

Summary

The findings indicate that 10% or more bemegride in combination with barbiturates affords protection against the central depressant effects of the latter.

In humans bemegride is a more effective antidote to the central depressant effects of phenobarbitone than to those of amylobarbitone and pentobarbitone.

As a result of the ingestion of bemegride simultaneously with the barbiturate there is a delay in the onset of sleep, especially in those cases given a large dose of bemegride. This delay in onset of sleep was demonstrated more clearly when additional bemegride was given if the subject became drowsy.

Bemegride given in the amounts used in this investigation did not produce excessive stimulation of the central nervous system, as frank convulsions were never seen. The blood pressure was lowered but was maintained at a satisfactory level in all cases (see Tables I and II). The pulse rate and respiration were not greatly altered. It was found in some cases that the addition of amiphenazole had a beneficial effect on respiration, especially in maintaining a good amplitude. It is difficult to ascribe to amiphenazole any marked effects against barbiturate depression apart from that on respiration as noted above.

By using the appropriate concentrations of bemegride with barbiturate the depth and the duration of sleep could be modified. Those subjects given large doses of barbiturate (2 g. or more) with 25.6% bemegride showed signs of barbiturate overdosage for one or more days following ingestion, even though these signs were minimal on the day of treatment. Almost all cases, including those that remained awake on the treatment day, retired at their usual bedtime and slept well throughout the night. This was the case also in several disturbed subjects who usually required sedation at night.

Apart from the cases of vomiting mentioned, all the other subjects retained a good appetite and ate their meals with relish, even those who were roused from a drowsy state to eat their meals.

The treatment should not be given to persons with a known or suspected history of epilepsy.

The possibility of using a barbiturate-bemegride mixture to prevent accidental or intentional barbiturate overdosage is discussed.

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MODIFICATION OF BARBITURATE SLEEP TREATMENT BY THE USE OF BEMEGRIDE

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Sleep treatment of neurotic or psychotic patients is a therapeutic procedure which consists mainly in keeping the patient in a condition of relaxed sleep in excess of the normal sleeping-time. The total sleeping-time is increased to 18–20 hours a day and the treatment is carried on for about four weeks.

The clinical indications and procedure vary from author to author, but a standard procedure was laid down by Kläsi (1922). This method has been widely used for the treatment of psychiatric cases in Russian medicine (Kerbikov, 1955; Ivanov, 1955). An extensive review of the Russian literature on this subject is given by Wortis (1953).

Other fields in which prolonged or intermittent sleep treatment has been advocated are as follows: acute coronary insufficiency, hypertension, post-operative convalescence, asthma, stuttering, and peptic ulcer (Wortis, 1953).

Kalinowsky and Hoch (1952) describe the standard practices and indications as usually employed in Western medicine.

In general, the most reliable employment of sleep treatment by itself is in the acute anxiety neuroses, particularly in persons of usually stable personality who have broken down. Once over the acute phase of anxiety other treatment may be considered and is then more easily implemented. The acutely ill anxiety neurotic is a much commoner phenomenon of war than of peace. This is a consequence of precipitating environmental factors involved. In such cases continuous sleep treatment is a form of first aid.

The risks of sleep treatment as routinely applied are far from negligible, especially in disturbed psychotic patients in whom the depth of the narcosis may have to be pushed to maximal limits. With continuous sleep