SAFE SEDATION?

A CONTROLLED TRIAL OF "MEGIMATED" AMYLOBARBITONE*

By

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DEATH due to barbiturate overdosage has been an increasing problem, rising steadily in England and Wales from a death rate of 2 per million population in 1949 to 5 per million in 1958 (1). Of 2,044 consecutive fatal poisonings studied in Denmark between 1953 and 1959, over a quarter were due to barbiturates (2). 300 tons of barbiturate are consumed in the U.S.A. every year and acute poisoning with it in that country accounts for 1,500 deaths per year (3).

Among a number of attempts to reduce this danger, one has been to combine the antagonist bemegride ("Megimide") (4) with the barbiturate in a compound tablet. The effectiveness and safety of this mixture was noted first in narcosis treatment by Neville (5), by Trautner *et al.* (6) and by Gershon and Shaw (7) who, in a series of 58 cases, gave doses of over 2½ g. of phenobarbitone together with 10 to 25 per cent. of bemegride and sometimes amiphenazole as well. Their case 14, for example, became narcosed with 500 mg. of phenobarbitone alone, but with twice this dose plus the two antagonists he became merely drowsy. The authors also noticed, with this mixture, an unusual absence of barbiturate-withdrawal symptoms after sleep therapy given thrice weekly for up to 6 weeks. Frankau and Stanwell (8) commented on this lack of after-effects and used the megimated preparation in the treatment of barbiturate-dependent drug addicts. Trautner *et al.* (6) believed that up to 23 per cent. of bemegride mixed with a number of standard barbiturates did not detract from the quality of sleep. Their 12 healthy volunteers reported, however, that other barbiturate antidotes—caffeine, amphetamine, methyl phenidate—impaired sleep considerably. In the 58 cases mentioned above, side-effects due to bemegride were few, but one chronic schizophrenic became abusive and hyperactive with doses of bemegride approaching 0·5 gm., 2 showed mild epileptiform twitches and 2 others vomited once on similar high doses; doses which are some twenty times those used in the compound tablet for average sedation by day or night. One death in sleep therapy was probably due to asphyxia after a major fit in a woman discovered subsequently to have been epileptic (5).

A sedative tablet was marketed which combined quinalbarbitone sodium 50 mg., phenobarbitone 25 mg., and bemegride 7·5 mg. ("Phenaglate"). This was carefully compared for night sedative effect with the same barbiturates but without bemegride in 31 psychiatric patients by Eilenberg, Lodge Patch and Hare (9). No significant difference emerged, but the figures showed a trend against the "megimated" preparation. Suicidal overdosage was reported by Heffernan (10) whose patient took 24 of the compound preparation without apparently going off to sleep at all, and by Skinner (11) whose patient took 50 of them, plus some 400 mg. of quinalbarbitone and developed a confusional state without drowsiness or respiratory depression. However, McGuinness and Roberts (12) recorded a successful suicide with 120 tablets and the preparation was subsequently withdrawn in favour of one combining 100 mg. amylobarbitone with

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10 mg. bemegride ("Mylomide")—which is the subject of this paper. During the 18 months in which this preparation has been available, no fatality has yet been reported, but a number of instances are known where recovery followed suicidal overdosage.

Case 1.

A woman of 25, reported by Hellon (13), took 94 tablets (9,400 mg. amylobarbitone). On admission 10 hours later she was narcosed, responding to painful stimuli and with reflexes intact. Following intravenous methylamphetamine hydrochloride she appeared to have a modified epileptiform seizure but improved thereafter, remaining drowsy for 24 hours and recovering completely within 48 hours.

Case 2.

A woman of 33 took 50 tablets and was not seen by a doctor for 21 hours, when it was recorded that she was sleepy but rousable, B.P. and pulse normal and respiration slightly depressed. Gastric lavage produced no tablets. Two hours later, with no further treatment, she was talking and crying.

Case 3.

A woman of 26 took 25 tablets and was found, 4–5 hours later, to be semi-conscious, confused and lethargic and responding sluggishly to command. Respiration was slightly depressed and the reflexes were intact. Stomach washout gave a negligible product and she recovered overnight without further treatment.

Case 4.

A woman of 31 took 24 tablets and on admission to hospital about 18 hours later, no treatment having been given, she was fully conscious and physically normal though hysterical and unco-operative.

With unprotected doses of amylobarbitone of this size one would have expected cases 1 and 2 to have been severely poisoned and cases 3 and 4 to have been moderately severely poisoned (3).

Having reason therefore to suppose that this preparation of megimated amylobarbitone was safe in large doses, an experiment was set up to assess its value as a sedative. Mainly, of course, one feared that the bemegride would detract from the sedative effect of usual therapeutic doses as it does from that of very large ones.

Method

The trial was conducted with 60 adult psychiatric patients, co-operative and coherent enough to complete a short questionary each morning, and requiring a moderate dose of sedative at night (almost all were having sodium amylobarbitone, 200 mg.). Depressives formed the largest group, with neurotics and schizophrenics following, but in the final analysis neither diagnosis, sex nor age appeared to affect a patient's consistency in his reporting of sleep.

Three apparently identical tablets were prepared of amylobarbitone 100 mg. alone, of amylobarbitone 100 mg. plus bemegride 10 mg. and of an inert material. The dose was 2 tablets o.n., repeat one if required, each kind being given to each patient for 3 consecutive nights, the order of administration being randomized by latin square. The trial lasted therefore 9 days with each patient. Only the pharmacist knew the identity of the tablets. Sleep was recorded on a 3-point scale: a "good" night was what the patient would so describe normally at home, and a "poor" one would be characterized by prolonged wakefulness or repeated arousal. A "moderate" one lay between—usually taken as one or two arousals or some difficulty in getting off. Difficulty in waking, drowsiness the following morning and side-effects were also enquired into. Similar forms

were completed independently by patient and night nurse on the following morning. Almost all of the subjects were in single rooms, which made noise disturbance less likely but detracted from the nurses' observations.

Results

Fifty-two patients completed the trial, 4 having withdrawn early on owing to general distress (all these went on to placebo first), 2 owing to other medical considerations and 2 were omitted because of sequence errors in administration. Comparing patients' and night nurses' records showed that while the trend was the same, the patients were more consistent in their reports of each tablet and much more sensitive to poorer nights with the dummy tablet. The nurses' records were therefore discarded for statistical purposes.

1. *Sedative Effect:* A good night's sleep was rated 1, a moderate night 2 and a poor night 3. Calculation of order effect revealed only the smallest differences in mean values whether the tablet was given first, second or third in sequence.

Table I

Order Effect. A = Amylobarb. plus bemegride. B = Amylobarb. alone. C = dummy tablet

	1st three days	2nd three days	3rd three days
17 patients	B 88	C 122	A 80
20 patients	A 101	B 90	C 133
15 patients	C 113	A 81	B 75
Per patient average ..	B 5·18	C 7·18	A 4·71
	A 5·01	B 4·50	C 6·65
	C 7·53	A 5·40	B 5·00
Group Means	5·90	5·69	5·45

Therefore the order effect may be ignored

From an analysis of variance on the sleep results as a whole it was computed that the standard error was 0·15 and the mean for amylobarbitone alone was 4·89, for amylobarbitone plus bemegride 5·04 and the dummy 7·12. The difference between the means for the two active tablets was the same as the standard error but the difference between each and the dummy was very highly significant ($p < \cdot 001$).

2. *Hangover Effect:* Questions were asked (*i*) if the patient had difficulty in waking and (*ii*) if he had been drowsy during the morning. Thirty-seven of the 52 cases answered "yes" to one or more of these queries and a trend was observed with each question for the compound tablet to produce less hangover than the barbiturate alone, but the mean values did not differ significantly:

Table II

	Difficulty in Waking	Drowsiness
Mean Values	A = 0·40	A = 1·06
	B = 0·61	B = 1·34
	C = 0·32	C = 1·11

It might be worth constructing a further trial to study this factor exclusively.

3. *Side-Effects:* were reported on only 16 of the total of the 468 patient-nights. Complaints were randomly distributed between the 3 preparations and seemed quite unrelated to any pharmacological activity.

Conclusions

The trial shows that with 52 patients studied in an ordinary clinical situation 20 mg. bemegride did not detract from the hypnotic action of 200 mg. amylobarbitone, nor did it occasion any toxic effects. Bemegride made little difference, however, to the "hangover" experienced the next morning, although the trend was towards lessening it. Four cases surviving large overdosage (10 to 40 times the normal hypnotic dose) suggest that the mixture may be safer to use than amylobarbitone alone.

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