COMPARATIVE HYPNOTIC EFFICACY OF "PHENAGLATE"

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INTRODUCTION

THE widespread use of barbiturates as hypnotics for insomnia has greatly increased the risk of accidental overdosage and the number of suicidal attempts. The size of the problem concerning barbiturates and suicidal attempts is difficult to estimate as only suicidal deaths are recorded by the Registrar General, and his statistics for 1956 (R.G., 1958) reveal that out of a total of 5,282 suicidal deaths, drugs (mainly barbiturates) were second only to domestic coal gas poisoning as the effective agent. Stengel (1958) calculated that six times the number of suicidal deaths gives an approximate estimate of the number of attempted suicides. Locket and Angus (1952) found that of the patients admitted to their Unit, barbiturates were the drug involved in 80 per cent. of the cases and that in 90 per cent. of the cases it had been prescribed for the treatment of insomnia. Locket (1958) also estimated that some 6,000 patients were admitted annually to hospitals in England and Wales for treatment of barbiturate poisoning.

Less toxic, but equally effective hypnotics, would be one method of decreasing the danger inherent in prescribing barbiturate hypnotics. An alternative approach is the simultaneous oral administration of a barbiturate combined with a barbiturate antagonistic.

The use of central analeptics in the treatment of barbiturate intoxication has been the subject of both clinical and experimental studies in man and animals. Nilsson (1951) and Locket (1952) prefer to rely on medical management, without using analeptics, in the treatment of severe barbiturate intoxication, whilst support for this approach is found in the demonstration of a depressant effect on the central nervous system of rabbits, following the initial stimulant effect of nikethamide, caffeine and leptazol (Maloney, 1935).

Contrary views are held by Koppanyi and Fazekas (1953) who found that the simultaneous oral administration of barbiturate and leptazol prevented death in dogs compared with controls receiving the same dose of barbiturates without leptazol. The same authors found in human subjects that with a ratio of leptazol to barbiturates 3:1 and 1·5:1 using a dosage of 200 mg. of barbiturates, sleep was not disturbed and that narcosis was delayed or prevented

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when the combination was compared with barbiturate given alone. Following the introduction of bemigride (β-β-ethyl-methyl-glutanimide), a much stronger analeptic, by Shaw *et al.* (1954) the drug was successfully used as a barbiturate antagonist in anaesthesia (Harris, 1955), in continuous narcosis in schizophrenia (Trautner *et al.*, 1957) and in barbiturate poisoning by Shulman *et al.* (1955). Following Shaw and Shulman's original work on bemigride, Trautner found that a combination of barbiturate and 12 per cent. bemigride lessened the depth and duration of sleep in human volunteers from 18 hours to 10 hours. Most of the work done on the combination of analeptics and barbiturates had, as its main clinical concern, the prevention of death in patients admitted with barbiturate overdosage.

As indicated above, the development of a hypnotic drug combination which allows effective application of the hypnotic element and at the same time supplies its own equally effective antidote should overdosage occur, seems a useful therapeutic advance in preventive medicine. The introduction of "Phenaglate" (quinalbarbitone sodium 50 mg., phenobarbitone 25 mg., bemigride 7·5 mg.) allowed the present authors the opportunity of determining the hypnotic efficacy of this drug compared with the same dose of barbiturate.

METHOD

Thirty-one psychiatric in-patients requiring a hypnotic from two associated, separately staffed hospitals, were the subjects of the trial. Administration of the drugs was by randomized order (Latin square) and a self-controlled double-blind technique was used. The drugs were each given 6 times during a 24-day period and the identical looking capsules were constituted as follows:

(A) "Phenaglate", 2 capsules.

(B) "Phenaglate", 1 capsule, placebo 1 capsule.

(C) Quinalbarbitone sod., 50 mg. phenobarbitone 25 mg. 2 capsules.

(D) Quinalbarbitone sod., 50 mg. with phenobarbitone 25 mg., 1 capsule, 1 placebo capsule.

Sleep recording was done by the night nurse who, on a prepared chart, assessed the patient at ½-hourly intervals as asleep or awake. A "broken" night was defined as a night on which a subject woke between periods of sleep and a "restless" night was that recorded as such by the nurse.

RESULTS

Drug	Mean Minutes to Fall Asleep/ Subject/ Night	Mean Minutes Awake/ Subject/ Night	No. of "Broken" Nights	No. of "Restless" Nights
Barbiturate 150 mg.	32	91	51	24
"Phenaglate" 150 mg. ..	40	99	62	30
Barbiturate 75 mg.	37	106	65	25
"Phenaglate" 75 mg.	34	104	72	41

As regards the mean time awake the difference between barbiturate 150 mg. and barbiturate 75 mg. is significant at the 5 per cent. level (using the correlated t test); that between "Phenaglate" 150 mg. and "Phenaglate" 75 mg. is not significant nor is the difference between barbiturate 150 mg. and "Phenaglate" 150 mg.

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Discussion

No data are given on the age or sex or in which hospitals the patients were treated, as a previous study on the comparative efficacy of hypnotic drugs failed to reveal any statistically significant differences between two groups compared for these factors (Lodge-Patch *et al.*, 1959). In the present study no period in which placebo alone was given appears. The reason for excluding such an apparent control is based on the findings of Hare (1955) who found that the comparative response to two hypnotics remains constant during a trial and that new hypnotics may therefore, be compared with a standard barbiturate preparation, obviating the necessity of a placebo. Hare also found that a high positive correlation was found between the night nurse's record of sleep and the patient's self-administered record in a double-blind trial, irrespective of whether a hypnotic or placebo was administered.

The results of the present trial show that "Phenaglate" at the higher level of dosage (2 capsules) is almost as efficacious as the equivalent dose of barbiturate, though there is a slight suggestion in the figures that the patients on "Phenaglate" slept less well.

The failure to find a significant difference between the two dosage levels of the "Phenaglate" prescribed is an anomalous feature which suggests that further confirmatory trials are worthwhile to clarify more precisely the comparative efficacy of "Phenaglate".

Having found that "Phenaglate", at a dosage of 2 capsules, is efficacious as a hypnotic, the question which remains and which this study has not attempted to answer is whether a patient taking an overdose of "Phenaglate" will escape a fatality which would result from an equivalent dose of barbiturate alone. The evidence from the literature presented above warrants the conclusion that the therapeutic principle represented by such a combination as "Phenaglate" has a future in its application to clinical practice.

In view of its epileptogenic effect on the EEG of patients and the reports of grand mal seizures in known epileptics (Gershon and Shaw, 1957) its use in this group of patients should be avoided.

Summary

By use of a double-blind technique and randomized order, the comparative efficacy of "Phenaglate" with barbiturate has been tested at two levels of dosage. The failure to show any significant difference between the two, at the double level of dosage, suggests that "Phenaglate" is an equally effective hypnotic and in view of its containing a barbiturate antagonist, its value as a hypnotic is suggested for patients with insomnia who might be considered a suicidal risk.

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