EFFECT OF MEGIMIDE ON THE RECOVERY TIME AFTER THIOPENTONE ANAESTHESIA

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Initially synthesized in 1911 (Cass, 1956), ethyl methyl glutarimide (Megimide, Bemegride N.P. 13) aroused great interest when Shaw *et al.* (1954) demonstrated its pharmacological antagonism to the effects of barbiturates, stating this effect to be specific. This was followed by the successful clinical use of Megimide in the treatment of barbiturate poisoning by the same group of workers (Shulman *et al.*, 1955; Shaw, 1955). The efficacy of Megimide in the treatment of barbiturate poisoning was further confirmed by reports from other workers in this field (bingle and Whitwam, 1955; Holten, 1955; Perinpanayagam, 1955; Clemmesen, 1956; Pedersen, 1956; Louw and Sonne, 1956; Worlock, 1956). Doubt was expressed, however, that Megimide was indeed a pharmacological antagonist in the strict sense of the word and the definite analeptic properties of the drug were pointed out (Wright, 1955; Louw and Sonne, 1956; Pedersen, 1956). Albeit the precise nature of this antagonism of Megimide to the actions of the barbiturates is uncertain, the work of Cass (1956) indicates a high degree of specificity. This property of Megimide suggested its possible usefulness in the field of clinical anaesthesia for terminating or shortening barbiturate anaesthesia used for short surgical operations. Two reports have been published describing the use of Megimide in routine clinical anaesthesia (Harris, 1955; Bentel *et al.*, 1956). In order to provide something more than a clinical impression—to attempt to provide in particular an end point of observation, a comparable series of controls, and standardization of anaesthetic procedure and surgical intervention—we designed the following simple clinical trial.

METHOD

Operation

The operation chosen to provide a standard procedure was dilatation of the cervix uteri and uterine curettage for diagnostic purposes. A few cases of radium insertion into the uterus and vagina and a few cases of emergency evacuation of the uterus were included. Except for demanding general fitness of the patients, other than for their gynaecological complaints—all patients were adults—the cases were unselected.

Premedication

Atropine gr. 1/100 by intramuscular injection was the only premedicant drug administered in all cases.

Anaesthesia

A 5% solution of thiopentone sodium administered in divided doses was the sole anaesthetic agent used. A clinical level of anaesthesia was maintained at which the patient breathed satisfactorily yet did not respond with exaggerated movements to the surgical stimuli of the operation. In no case was there apnoea following administration of thiopentone nor was there clinical evidence of respiratory depression of a grade which required manual assistance of respiration or administration of oxygen.

Observations

Observations were made on a total of 160 patients of whom 75 constituted a control group. These had no further medication following thiopentone. Megimide was administered to the other 85 patients immediately on conclusion of the operation.

Factors noted

The factors noted in all cases in this trial were: Patient's weight, dose of thiopentone, dose of Megimide, duration of operation and recovery time.

Recovery time end point

The recovery time end point was measured as the time taken from the end of the operation until the patient could intelligibly and correctly answer the question 'what is your name'? Apart from this question, repeated at intervals during recovery time, no other stimulus was applied. This time was recorded to the nearest minute. It should be noted that workers using Megimide in the field of barbiturate poisoning have chosen to note the time taken to bring the patient to a 'safe state' (Shulman *et al.*, 1955) and it must be assumed that these patients commence recovery from a deeper state of anaesthesia than those in this series. From the time the 'end point' was reached no patient in this series showed signs of relapse into unconsciousness.

Megimide is supplied in vials containing 10 ml. of a 0·5% solution for intravenous administration. Dosage of Megimide administered is reflected in Table I.

Our first cases were given 50 mg. of Megimide intravenously as a single dose. In subsequent patients, if no response such as movement or biting on the airway was obtained after an initial dose of 50 mg., this was repeated after one minute, and repeated again after a further one minute if there was still no response. Initially a total dose

TABLE I

Total Dose of Megimide in mg.	*No. of Cases*
50	17
100	37
150	20
200	11
Total	85

of 150 mg. was not exceeded. Later in the series the maximum dose was raised to 200 mg.

RESULTS

The results of this trial are presented in Table II.

As barbiturate blood levels were not estimated, difficulty

TABLE II

	No. of Cases	*Mean Recovery Time (Minutes)*	*S.D. of Recovery Time*	*S.E. of Recovery Time*	*Mean Operation Time (Minutes)*	*S.D. of Operation Time*
Control Group ..	75	16	±13	±1·53	12	±6
Megimide Group ..	85	10	± 9	±0·99	13	±4

Difference in Mean Recovery Times: 6 minutes. This is statistically significant.

was experienced in relating the dose of thiopentone and the duration of anaesthesia (operation time) to recovery time. The weight, the duration of operation and the dose of

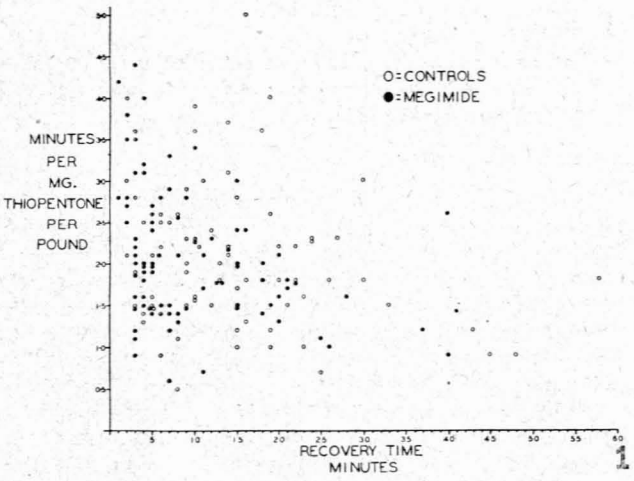

Fig 1.

thiopentone were combined into a single index by estimating the minute/mg. of thiopentone/lb. in each case. This index was then plotted against the recovery time. The result is presented as a scattergram (Fig. 1).

No correlation could be established between the size of the dose of Megimide (either on a total or on a mg./lb. basis) and the recovery time. The respective correlation coefficients are:

Megimide, total dose r = −0·06.
Megimide, mg./lb. dose r = 0·05.

UNTOWARD REACTIONS

Two patients developed clonic convulsions following the administration of a total of 200 mg. Megimide. Details are as follows:

Case 1. Weight 126 lbs. thiopentone 700 mg., time of operation 11 minutes. Megimide 200 mg., recovery time 4 minutes. Very shortly after administration of the Megimide twitchings of the face commenced, followed rapidly by a generalized clonic convulsion. Thiopentone 100 mg. intravenously controlled the convulsion immediately. Subsequent recovery was uneventful, except that the patient complained of a headache.

Case 2. Weight 120 lbs. Thiopentone 550 mg. Time of operation 7 minutes. Megimide 200 mg. Recovery time 9 minutes. This patient had an apparently normal recovery of consciousness nine minutes after conclusion of the operation. Sixty minutes after her return to the ward she had a short clonic convulsion, witnessed by the ward nursing staff. This subsided without treatment. On subsequent questioning, no history of epilepsy or previous convulsive episode could be obtained from the patient.

There were no other complications in either the control or the Megimide groups.

COMMENT AND CONCLUSIONS

In the use of barbiturate anaesthesia for short surgical procedures on outpatients, it has been frequently pointed out that a danger period exists during the recovery stage when constant supervision of the unconscious patient is essential. It was thought that Megimide might prove a useful drug to cut this period short and so to lighten the burden on the medical and nursing staff. To be efficient in this respect we considered that a *safe* and *consistent* shortening of recovery time should be demanded. The end point chosen in this study was taken as being consistent with a degree of recovery which would allow the patient to remain unattended with safety. It must be realized that it does not necessarily imply complete recovery of the patient to the point where discharge from the hospital could be allowed. The results show that Megimide produces a statistically significant shortening in the mean time for recovery of consciousness from thiopentone anaesthesia administered for short operations. The recorded recovery times, however, show a wide scatter and overlap with those of the control group, as is evidenced by the large standard deviations of the means. This is graphically demonstrated in the scattergram (Fig. 1). This means that in many cases the use of Megimide provided no gain at all in recovery time compared with a large number of cases in the control group.

This wide overlap with control cases in return to a 'waking state' is in conformity with the findings of Louw and Sonne (1956) that in spite of the fact that Megimide helped to bring about a 'safe state' in cases of barbiturate coma it 'did not apparently shorten the period of coma, hasten the elimination of barbituric acid or cause patients to recover consciousness before the blood level of barbituric acid had fallen to that at which return of consciousness would have been expected without Megimide'. Similar opinions are expressed by Pedersen (1956) and Clemmesen (1956). On the debit side too, it is noted that two cases in our series developed convulsions following administration of 200 mg. Megimide, a dose which does not exceed that mentioned in the manufacturers' pamphlet.

We are of the opinion that although this study demonstrates that Megimide displays antagonism to the action of thiopentone, the precise nature of this is uncertain and it is inconsistent. Because a mean saving of six minutes in the return to consciousness does not provide any very great benefit and must be balanced against the risk of convulsion, it appears to us to be of no real value in shortening the recovery time after routine barbiturate anaesthesia. Its use is not justified as a means of 'applying the brakes' to terminate such anaesthesia. It may, however, be of some use in cases of inadvertent overdosage with thiopentone.

SUMMARY

A clinical trial is described assessing the value of Megimide in reducing the period of unconsciousness following barbiturate anaesthesia. The mean recovery time of the control group was sixteen minutes. The use of Megimide resulted in a mean shortening of six minutes in the recovery time.

Two cases developed convulsions after the administration of 200 mg. of Megimide. We are of the opinion that though it may be of use in the treatment of inadvertent overdosage with barbiturates the drug is of no real value in routine barbiturate anaesthesia.

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