AN ELECTRO-ENCEPHALOGRAPHIC STUDY OF THE ANALEPTIC ACTION OF $\beta\beta$ ETHYL METHYL GLUTARIMIDE (MEGIMIDE)

I. Against several Barbiturates and other Hypnotics
II. Compared with other Analeptics and Convulsants

BY

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$\beta\beta$ ETHYL methyl glutarimide (Megimide) was first synthesized in 1911. Its anti-barbiturate activity was first observed by Shaw and others in 1951. It was subsequently investigated by him, in animals (Shaw et al., 1954) and in man (Shulman et al., 1955).

Megimide is of particular clinical interest because attempted suicide and accidental overdose with barbiturates are common, and an effective antidote would help to reduce the morbidity and mortality which results. Such an antidote must be free from dangerous side actions, e.g. convulsions, and effective because careful conservative care without the use of drugs has already brought the mortality down to 1.6 per cent (Clemmensen, 1954) in Scandinavian centres devoted to this problem.

A further clinical application of an antidote is the reversal of barbiturate anaesthesia in outpatients who have had minor surgical procedures. Finally, following neurosurgery performed during anaesthesia maintained by thiopentone, it is desirable to have a quick return to consciousness as variations in the level of consciousness assist in assessing the post-operative course.

Some preliminary electro-encephalographical work was done by the author previously (Shaw et al., 1954) and this work is an extension of it.

EXPERIMENTAL PROCEDURE

Rabbits were used exclusively. No particular type was chosen but most animals weighed about 2 kg. They were kept in equable surroundings, $70 \pm 2^\circ F$, and fed on a standard diet (Bruce and Parkes No. 18).

Skin electrodes were used, the hair being shaved and the skin cleaned with acetone. Cambridge electrode jelly was rubbed into the skin and a little placed between the disc electrode and the skin. The electrode was fixed to the skin by celloidin. The use of these electrodes is recommended by the makers of the Grass electro-encephalograph which was used. The resistance between electrodes was repeatedly measured and values below 10,000 ohms were always obtained.

The Grass electro-encephalograph used is a four-channel instrument and proved
absolutely reliable throughout the experiments.

Recordings were made from frontal and occipital electrodes throughout, an indifferent electrode being attached to the right back leg. Fronto-occipital electrodes provide an adequate record of cortical activity in the rabbit and overcome the problem of the limited space which is provided by the small head and large ears.

The animals were allowed to feed and drink normally up to the commencement of the experiment in order to avoid hypoglycaemia or dehydration, and oxygenation was carefully maintained during the respiratory depression caused by the barbiturates. In this way it was hoped to reduce frequency changes, e.g. loss of fast rhythm, which may follow these changes.

The animals were placed in a box to prevent their moving about with subsequent displacement of electrodes. A waking E.E.G. was taken and then the hypnotic drug given by intravenous injection through the marginal ear vein. When hypnosis was sufficiently deep and stable, a further tracing was recorded, and then the analeptic drug was given by intravenous injection. Subsequent to this, tracings were made from control animals who had been given hypnotics but no analeptics.

In this manner it was possible to determine the analeptic effects of Megimide on several barbiturates and other hypnotics, and then to compare the analeptic effect of Megimide with that of other analeptics and convulsants on a rabbit anaesthetized with pentobarbitone. Repeated experiments were performed and the results recorded in this paper are representative of those obtained.

**EXPERIMENTS**

1. **Pentobarbitone and Megimide.**
   
   40 mg/kg of pentobarbitone were given after a waking record (fig. 1A). Deep anaesthesia resulted (fig. 1B). This tracing has some alternating current interference, but shows a marked loss of fast frequencies and high voltage seen in the waking record. 20 mg/kg of Megimide were then given, and produced a considerable increase both in fast activity and voltage (fig. 1C).

   For comparison with figure 1C, figure 1D is a control taken at a similar time interval in an animal who has had 40 mg/kg of pentobarbitone but no Megimide. This trace shows the very slight electrical activity interrupted by periodic "bursts" characteristic of deep barbiturate hypnosis.

2. **Thiopentone and Megimide.**
   
   40 mg/kg of thiopentone was given after a waking trace was taken (fig. 2A). This produced a very deep anaesthetic pattern (fig. 2B) with little activity and small bursts of slow waves.

   20 mg/kg of Megimide restored the pattern to that of a considerably lighter depth of anaesthesia (fig. 2C) with steady slow waves and some faster waves.

   For comparison, figure 2D is taken at a similar time interval after 40 mg/kg of thiopentone without Megimide. It shows less activity both in slow and fast waves.

3. **Amylobarbitone and Megimide.**
   
   60 mg/kg of amylobarbitone was given after a waking trace was taken (fig. 3A). A subsequent tracing (fig. 3B) shows profound depression of electrical activity with occasional spindles of slow waves.
FIG. 1

(A) Awake.
(B) Pentobarbitone (Nembutal) 40 mg/kg.
(C) 5 minutes after (b). Megimide 20 mg/kg.
(D) Control. 5 minutes after (b). No Megimide given.

FIG. 2

(A) Awake.
(B) Thiopentone 40 mg/kg.
(C) 8 minutes after (b). Megimide 20 mg/kg.
(D) Control. 8 minutes after (b). No Megimide given.
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10 mg/kg of Megimide restored the tracing to an appearance (fig. 3c) approaching the waking pattern, the main difference being in the increased number of slow waves and the lower voltage. These are typical of the lightest stages of hypnosis with barbiturates.

Figure 3D is a tracing taken at a much later time from an animal who had 60 mg/kg of amylobarbitone without Megimide. It shows only moderately slow waves at a low voltage and indicates a considerably greater depth of depression than figure 3c.

(4) **Thialbarbitone (Kemithal) and Megimide.**

A waking tracing was made (fig. 4A) and thialbarbitone 200 mg/kg given. This produced a tracing (fig. 4B) with very little activity apart from spindles of slow waves. (This tracing has regular electrocardiographic artifacts.)

20 mg/kg of Megimide restored much fast activity (fig. 4C) and increased the voltage of the slow waves, thus restoring the typical wave pattern of light barbiturate hypnosis.

(5) **Chloralose and Megimide.**

After a preliminary tracing (fig. 5A) 70 mg/kg of chloralose was given. A tracing (fig. 5B) was obtained with high voltage slow delta waves (about 2 per second) predominating.
A. Awake.
B. Thialbarbitone (Kemithal) 200 mg/kg (E.G.G. complexes produce regular artifacts on this record).
C. 6 minutes after (B). Megimide 20 mg/kg.

Fig. 4

A. Awake.
B. Chloralose 70 mg/kg.
C. 5 minutes after (B). Megimide 5 mg/kg.

Fig. 5
Megimide 5 mg/kg was given when some faster $\beta$ activity was restored (fig. 5c). The delta frequency persisted, however, and the rabbit showed no signs of awakening.

It was noticed that the rabbit was twitching (see electromyogram in fig. 5c) and very restless after the Megimide, suggesting that chloralose did not antagonize the convulsant property of the drug. The restlessness was controlled by pentobarbitone 5 mg/kg.

(6) Diethyl Ether and Megimide.

After a preliminary tracing (fig. 6A) a rabbit was given an ether/air anaesthetic. When a deep plane was reached and the intercostals were paralysed, figure 6B was obtained, showing the characteristic low-frequency activity.

10 mg/kg of Megimide were given when an increase in electrical activity resulted (fig. 6c) both in voltage and frequency. This increased activity is small compared with the response to Megimide during barbiturate anaesthesia (cf. figs. 1B and 1C).

(7) Methylpentynol and Megimide.

A 5 per cent solution of methylpentynol (Oblivon) was given, 250 mg/kg producing a deep stage of sleep (fig. 7B) with a very sluggish corneal reflex. Repeated small doses of the drug were necessary to maintain this stage, suggesting that redistribution from the blood was occurring. The record shows very slow frequencies (1–2 per second) and very little fast activity. There is a regular electrocardiographic artifact.

![](https://academic.oup.com/bja/article-abstract/28/7/324/263833/fig-6)

**Fig. 6**

(A) Awake.
(B) Ether anaesthesia (3rd plane).
(C) 3 minutes after (B), Megimide 10 mg/kg.
Megimide 5 mg/kg was then given. This produced a minimal change (fig. 7c), the slow frequencies being increased to 2–3 per second.

(8) Pentobarbitone and Nikethamide.

Pentobarbitone was given until the characteristic electro-encephalographic features of deep barbiturate anaesthesia were obtained; 55 mg/kg were required to obtain this.

Nikethamide 75 mg/kg was then injected and a further tracing (fig. 7c) shows no alteration in the electrical activity of the brain. No change in the depth of anaesthesia was observed directly.

(9) Pentobarbitone and Methylamphetamine.

Deep anaesthesia (fig. 8b) was obtained by pentobarbitone, 40 mg/kg being required.

Subsequent administration of methylamphetamine (Methedrine) 2 mg/kg produced a minimal electrical change (fig. 8c) consisting of bursts of about 18 cycles per second, and no visible change in the depth of anaesthesia.

(10) Pentobarbitone and Picrotoxin.

Deep anaesthesia (fig. 9b) was obtained by 40 mg/kg of pentobarbitone.

Picrotoxin in a dose of 0.5 mg/kg produced an increase in both frequency and amplitude of the electrical waves (fig. 9c). This indicates a small reduction in depth of anaesthesia, but there is no fast β activity such as is obtained by Megimide (compare fig. 1c).
(A) Awake.
(b) Pentobarbitone (Nembutal) 40 mg/kg.
(c) 6 minutes after (B). Nikethamide (Coramine) 75 mg/kg.

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(A) Awake.
(b) Pentobarbitone (Nembutal) 40 mg/kg.
(c) 5 minutes after (B). Methylamphetamine (Methedrine) 2 mg/kg.
(11) **Pentobarbitone and Leptazol.**

40 mg/kg of pentobarbitone produced a deep stage of anaesthesia (fig. 10B) which was unchanged after 7.5 mg/kg of leptazol were given (fig. 10C). This tracing in figure 10C has a regular electrocardiographic artifact.

**DISCUSSION**

The biophysical processes resulting in the electrical changes shown in the electroencephalograph are not fully known at present. In this work the assumption is made that a drug which restores an electrical pattern similar to that of light anaesthesia is antagonizing the anaesthetic used.

There are several types of antagonism possible but the evidence obtained in these experiments does not suggest any particular type although Megimide shows specificity in antagonizing only barbiturates. There is a similarity in part of their molecules, the grouping $R\backslash C-\text{CO-NR-CO}$ being common to both (Marshall et al., 1954).

![Meggimide](image)

![Barbituric Acid](image)
It is interesting to note that the \( \alpha \) phenyl glutarimides resemble the barbiturates in their anticonvulsive action, whereas \( \beta \) ethyl methyl glutarimide is a convulsant. Its convulsant actions are readily opposed by small doses of barbiturates, and it can in turn shorten the duration of sleep produced by the barbiturates.

A further observation of interest has been made during preliminary experiments with \( \alpha \) ethyl \( \alpha \) phenyl glutarimide (Doriden, Ciba). It was found that sleep induced by this agent in mice was antagonized rapidly by Megimide. The similarity of structure of the two molecules suggest that competitive inhibition may account for this.

The existence of convulsive and anticonvulsive compounds with the same nucleus is seen also in the derivatives of barbituric acid. Powell et al. (1943) discuss this and describe a compound which is convulsant in warm-blooded animals and depressant in cold-blooded.

The effects of depressant and excitant drugs and anaesthetics on the electroencephalogram have been described by Gibbs and Maltby (1943) and Gastaut et al. (1951). Their results were reproduced in these experiments and were used in the interpretation of the changes observed. In general, anaesthetics and depressants reduce the frequency and amplitude of the wave traces. Other effects, such as the high amplitude and very low frequency theta waves seen in figure 5B, are mentioned as they occur in the experimental data.

**CONCLUSIONS**

In figure 1 it can be seen that Megimide (20 mg/kg) given after pentobarbitone (40 mg/kg) restores the trace to a nearly normal pattern (1c), while the animal to whom no Megimide has been given retains the pattern of deep depression (1D). Figure 2 compares the activities of two animals who were given thiopentone (40 mg/kg). The pattern of light depression of (2c) after Megimide (20 mg/kg) contrasts the very slow high-voltage theta waves of (2D) in which no antagonist was used and deep depression persists.

A similar reversal of pattern is shown in figure 3c by Megimide (10 mg/kg) after amylobarbitone (60 mg/kg). Figure 3d is a control tracing with persistent slow waves at a lower voltage.

The response to Megimide (20 mg/kg) following thialbarbitone (Kemithal), 200 mg/kg, shown in figures 4b and 4c, again suggests a lightening of the depression due to this thiobarbiturate.

From these results, therefore, it can be seen that Megimide reverses the e.e.g. changes induced by commonly used barbiturates and thiobarbiturates. Attention is therefore directed to some nonbarbiturate hypnotics.

A typical pattern of deep chloralose depression (70 mg/kg) is shown in figure 5b, with very slow high-voltage waves predominating. Megimide (5 mg/kg) increases the activity (fig. 5c), some faster low-voltage waves appearing, but the dominant pattern is still slow high-voltage waves. There was no sign of waking in the rabbit and it is concluded that Megimide does not antagonize chloralose to any extent. The appearance of muscle twitching is interesting as it suggests that chloralose does not antagonize Megimide as do the barbiturates.
Ether anaesthesia was induced and a deep plane obtained (fig. 6B). Activity in this tracing is minimal. Megimide (5 mg/kg) increased both fast and slow waves (fig. 6C) but this improvement is small compared with that typically seen with the barbiturates (figs. 1B and 1C).

Methylpentynol (250 mg/kg) produced a tracing (fig. 7B) in which very little fast activity is seen and the slow high-voltage waves seen with deep chloralose depression are dominant. Megimide (10 mg/kg) had scarcely any effect on the pattern of activity (fig. 7C).

It was concluded from the observations that Megimide produced minimal change in animals depressed by nonbarbiturate hypnotics. These changes are probably caused by a nonspecific physiological antagonism due to the convulsant action of the drug and can be produced by other drugs stimulating the central nervous system (e.g. leptazol).

The more pronounced reversal of activity which Megimide produces after barbiturates may indicate a more specific pharmacological antagonism to them. To investigate this it is proposed to synthesize a nonconvulsant form of Megimide by substituting an o-phenyl group on it. This alteration has been shown to produce anticonvulsant activity in other glutarimides (Marshall et al., 1954).

Megimide was next compared with other commonly used analeptics and convulsants. In each case pentobarbitone was given until a pattern of deep depression was obtained (figs. 8B, 9B, 10B, 11B). Nikethamide (75 mg/kg) produced virtually no change (fig. 8C). Methylamphenol...
tamine (2 mg/kg) was followed by regular, even bursts of low-voltage waves (18 cycles/second) but no further evidence (fig. 9c) of lessened depression.

Picrotoxin (0.5 mg/kg) resulted in a greater return of activity (fig. 10c) than the former analeptics. The pattern is predominantly slow, however, and does not compare with that following Megimide (fig. 1c).

The convulsant drug leptazol was given in a dose of 7.5 mg/kg. Virtually no change in the tracing resulted (fig. 11c). Allowance must be made in this record for the regular electrocardiographic complexes.

It is concluded from these observations that Megimide is a more effective barbiturate antagonist than the commonly used analeptics. Its chief disadvantage is its convulsant action when given to patients who have not had barbiturates previously. The same difficulty accompanies the use of picrotoxin.

This activity is very readily suppressed by very small doses of barbiturate given intravenously. As mentioned previously, an attempt is being made to reduce the convulsant activity by slight alteration to the drug.

SUMMARY

An electro-encephalographic study of Megimide has demonstrated the following:

1. It markedly reverses the pattern of deep depression due to all barbiturates and thiobarbiturates tested.
2. It does not reverse the pattern of deep depression due to some nonbarbiturate hypnotics and anaesthetics.
3. It is capable of reversing the deep barbiturate pattern more than the commonly used analeptics and convulsants.

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REFERENCES


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