Clinical and electroencephalographic effects of Megimide in patients without cerebral disease

Martin A. Green, M.D., and Max Fink, M.D.

Following the introduction of Megimide (beta, beta methylethylglutarimide) as an antagonist for barbiturate intoxication in 1955, considerable interest has been stimulated in its clinical applicability. Initial reports noted its efficacy in barbiturate poisoning,[1–4] but subsequent studies failed to substantiate this application.[5–8] In this laboratory, barbiturates are frequently administered under the standardized conditions of the "amobarbital test."[9] It was thus possible to assess the efficacy of Megimide in altering the behavioral response of human subjects to physiologic equivalent amounts of barbiturate.

In addition to its suggested antagonism to barbiturate, Megimide induces both paroxysmal discharges in the electroencephalogram and clinical grand mal seizures.[10–14] The present report concerns our experience with both the behavioral and electroencephalographic effects of Megimide.

MATERIAL AND METHODS

Thirty-four hospitalized voluntary psychiatric patients with psychoneurosis, depression, or schizophrenia, ranging in age from 27 to 64 years, were studied. Megimide in a concentration of 5 mg. per cc. was administered intravenously at the rate of 0.5 mg. per kg. per minute, until definite changes were observed in the electroencephalogram and often beyond this point. The amount of Megimide varied from 45 mg. to 250 mg.

In 15 subjects Megimide was administered without prior amobarbital. In 19 patients it was given following the administration of intravenous amobarbital which was injected at 0.5 mg. per kg. every 40 seconds, in amounts necessary to induce nystagmus, slurred speech, and marked drowsiness or sleep.

All experiments were undertaken in the electroencephalographic laboratory. An electroencephalogram was made prior to the injections and was run continuously during the administration of both drugs. The electrode placement consisted of frontal, motor-parietal, occipital, anterior temporal, posterior temporal, vertex, and earlobe. Both scalp-to-earlobe and scalp-to-scalp combinations were used.

RESULTS

The electroencephalogram in all subjects prior to the administration of the drugs was "normal," that is, symmetric and non-dysrhythmic.

Electroencephalographic Response

In the amount and rate of injection of Megimide employed, electroencephalographic changes occurred in every patient. The type of response and the amount of drug necessary to induce such a response were highly variable. The electroencephalographic changes included irregular low- and moderate-voltage slow activity, bursts of slow activity (usually of high voltage), single spike discharges, and spike-wave forms (figure 1 A, B, and C). These effects were diffuse and symmetric, with greatest prominence in the temporal leads.

The sequence of these responses was inconstant. Irregular, low-voltage slow activity was the most frequent initial change in the record. In other instances, bursts of high-voltage slow activity or spike activity appeared initially. As the injection continued, the amplitude and per cent time delta activity in-

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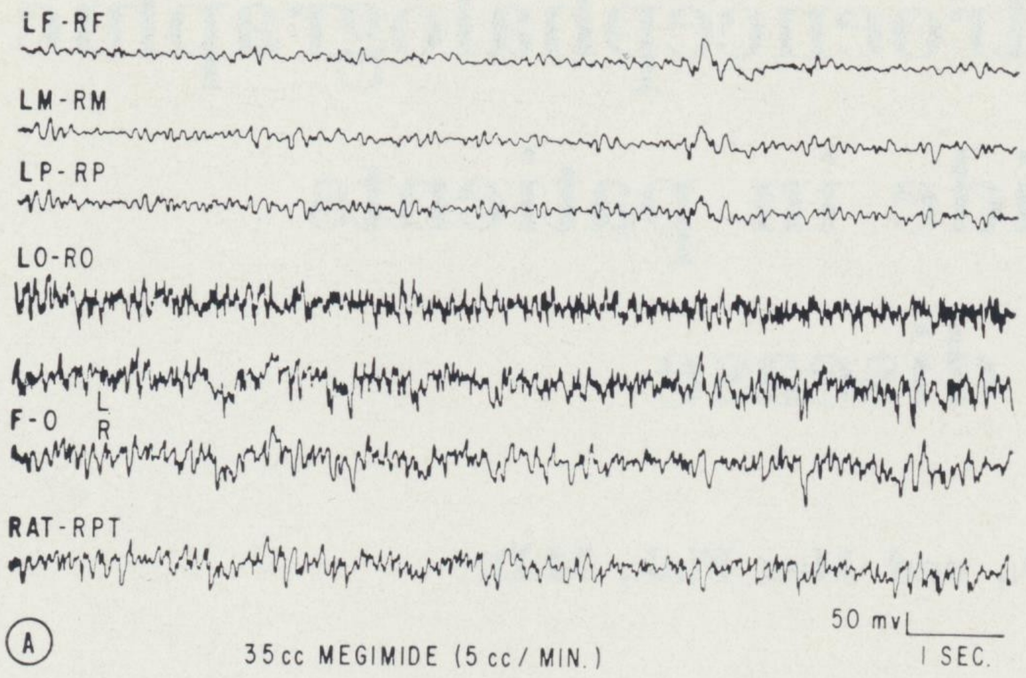


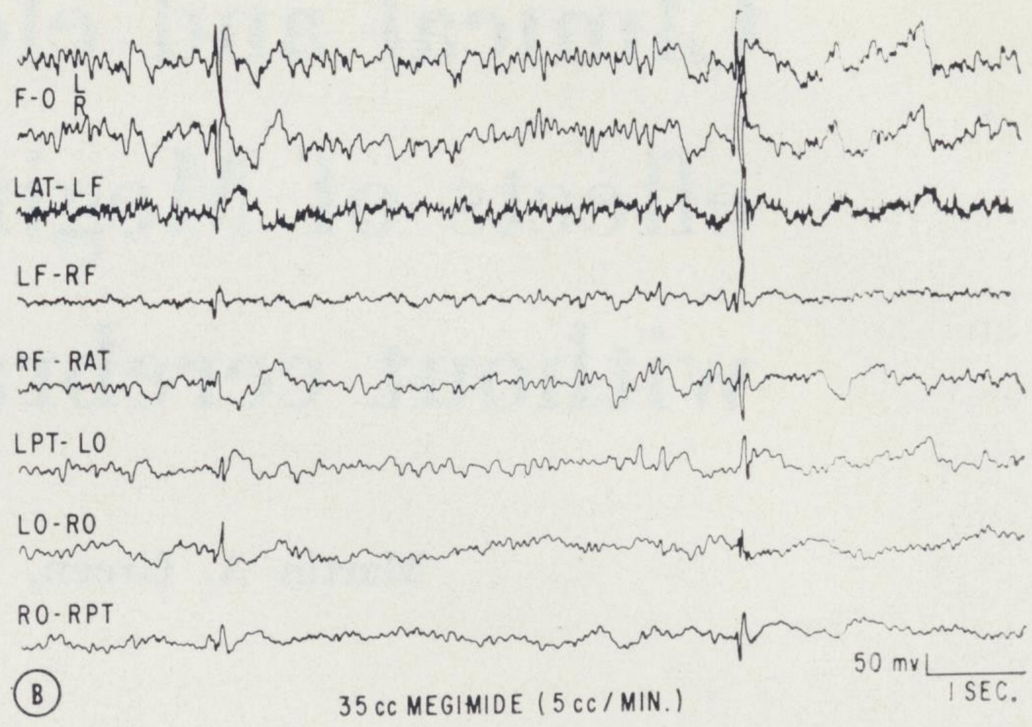
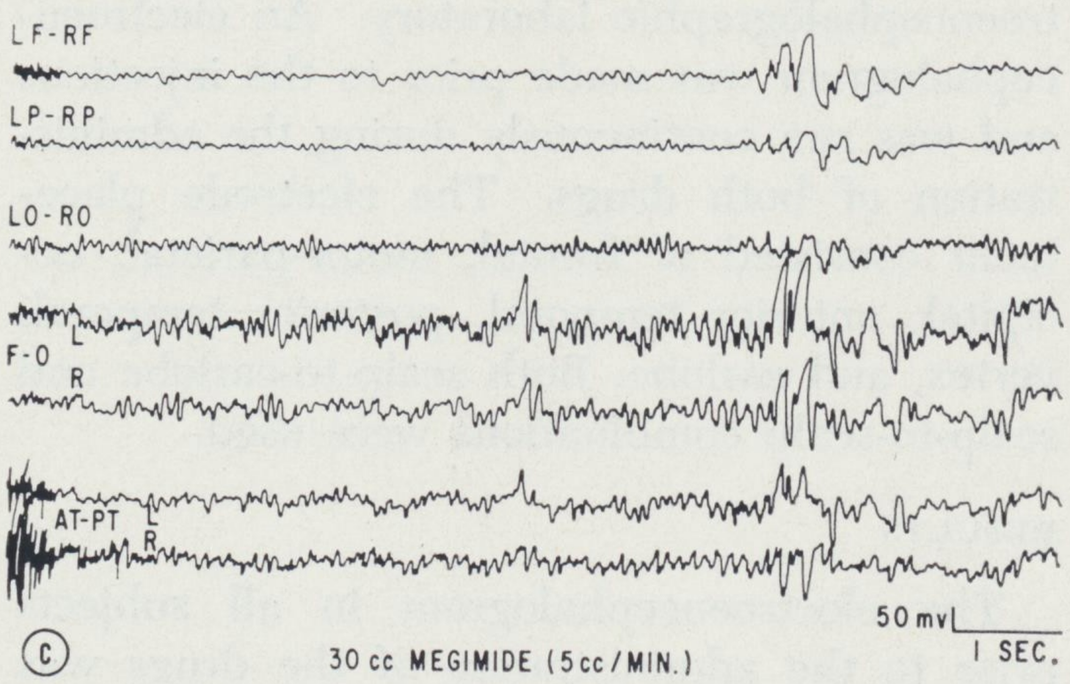


FIG. 1. Different types of electroencephalographic response to Megimide. *A*, delta activity, irregularly and in bursts, *B*, single spike activity, *C*, spike-wave activity



creased. Bursts of high-voltage slow activity were seen eventually in almost all patients. Spike discharges, however, were less frequent, even with relatively large doses of Megimide. For example, the tracings in one subject after receiving 220 mg. of Megimide and in another after receiving 250 mg. showed irregular diffuse slow activity without spike activity.

Seizures

Because of the nature of the population and the goals of our study, we specifically avoided administering Megimide in rates and amounts that would produce clinical grand mal seizures. Despite these precautions, a grand mal seizure was inadvertently induced in one patient. A 33 year old woman was given 200 mg. of Megimide at the rate of 50 mg. per minute. Up to 150 mg. there was only a decrease in the voltage of the alpha activity. After 200 mg. there was a sudden long run of diffuse, rhythmic 4 to 5½ cycles per second high voltage activity, with intermixed spike activity which was immediately followed by the seizure. The electroencephalogram during injection and prior to the seizure showed minimal changes, and the seizure was not anticipated

Subjective Response

The subjective reaction to Megimide was minimal, even when the induced changes in the electroencephalogram were severe. A few subjects complained of nausea, "dizziness," "shakiness," or a peculiar sensation in the abdomen. It was possible, however, to continue the injection without further increase in the symptoms. Two subjects became apprehensive, and in one of these the injection had to be discontinued.

Myoclonic jerks occurred frequently. They were usually mild and confined to one extremity. Less frequently they were bilateral and more severe. The relationship between these movements and spike activity was inconstant. The myoclonic jerks usually preceded the appearance of spike activity, although the reverse occurred occasionally. The simultaneous appearance of spike activity with myoclonic jerks was infrequent.

The effect of Megimide was short-lived. There were no instances of seizures or other abnormal responses later in the day following its administration. However, since intravenous amobarbital followed in all patients, this may have prevented such occurrences.

The clinical and electroencephalographic responses to intravenous amobarbital following Megimide appeared similar to those seen in subjects in whom amobarbital is administered without prior medication. The slow-wave or spike activity induced by Megimide disappeared and the usual patterns associated with barbiturates developed (figure 2). However,

the well-modulated high per cent time beta activity usually noted after barbiturate administered was less prominent.

Megimide Following Amobarbital

One group of subjects received intravenous amobarbital prior to Megimide until drowsiness, slurred speech, and nystagmus were induced. The electroencephalogram showed the patterns commonly associated with barbiturates, that is, an increase in voltage and per cent time fast activity and a decrease in amount and voltage of alpha activity. The most prominent clinical change was the awakening of the subject. Within the few minutes necessary for the injection, the patient became more responsive, slurred speech disappeared, and drowsiness, both on subjective and objective evaluation, was minimal or absent. Nystagmus became inconstant, unsustained, or disappeared completely. Gait, including heel-to-toe walking, was steady. However, the awakening effect was not uniform for all aspects of behavior altered by barbiturate. For example, if the subject became euphoric and more talkative with barbiturate, such behavior may have persisted in a milder form, even after the drowsiness of amobarbital was abolished by Megimide.

These clinical changes were accompanied by alterations in the electroencephalogram (figure 3). Patterns of drowsy activity disappeared. Alpha activity increased both in amount and voltage. Fast activity induced by amobarbital usually persisted unchanged or was reduced only sightly. In some instances it increased in amount and voltage. The prior administration of amobarbital did not prevent the appearance of paroxysmal discharges. Bursts of high-voltage slow activity, spike activity, or spike-wave activity often appeared, usually during or after awakening. Such activity was not a necessary accompaniment of the awakening response, however, since other subjects in whom clinical drowsiness disappeared did not show such discharges.

DISCUSSION

Megimide is similar to pentalenetetrazol (Metrazol) in that it induces delta activity, spike and spike-wave activity in the electroencephalogram, and clinical grand mal seizures. Such changes occur in nonepileptic subjects without brain disease, and considerable individual variability in the threshold for these changes exists. These discharges are nonspecific and cannot be used as evidence of the presence of a seizure disorder.

The possibility of using Megimide in activating the electroencephalogram has received study.[10–12] Several investigators have noted a more gradual onset of the electroencephalographic and clinical changes with Megimide than with Metrazol. For this reason, the opinion is expressed that Megimide may be more facile in reproducing both clinical and electroencephalographic seizures in patients with seizure disorders. It should be emphasized, however, that in the one patient in the present study in whom a grand mal seizure occurred, the seizure began suddenly and was not anticipated either from the electroencephalogram or previous clinical responses.

Megimide is effective in counteracting the clinical effects of small doses of intravenous amobarbital. This property has been previously demonstrated in animals[3] and is being utilized

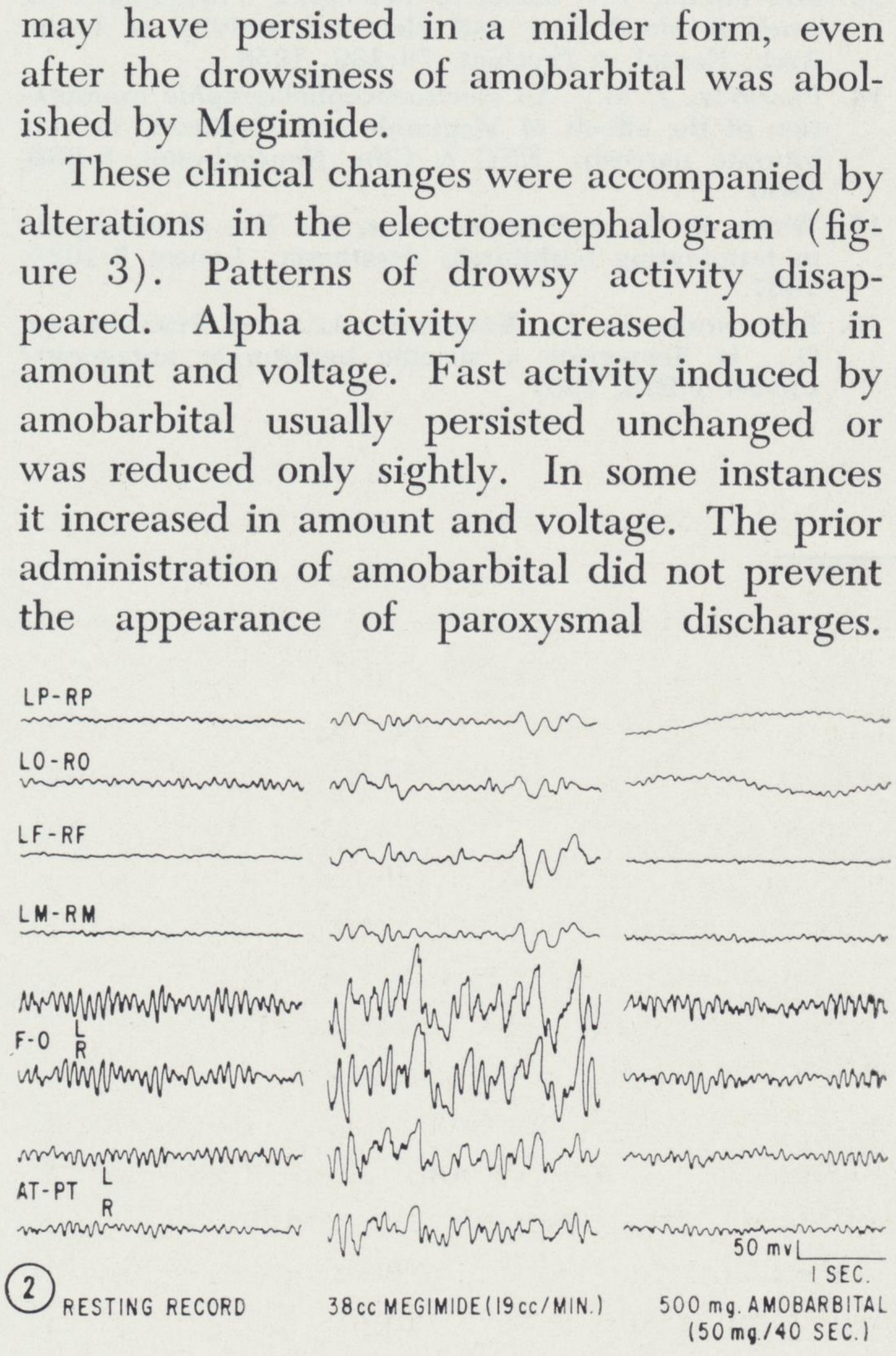


FIG. 2. Effect of amobarbital following administration of Megimide

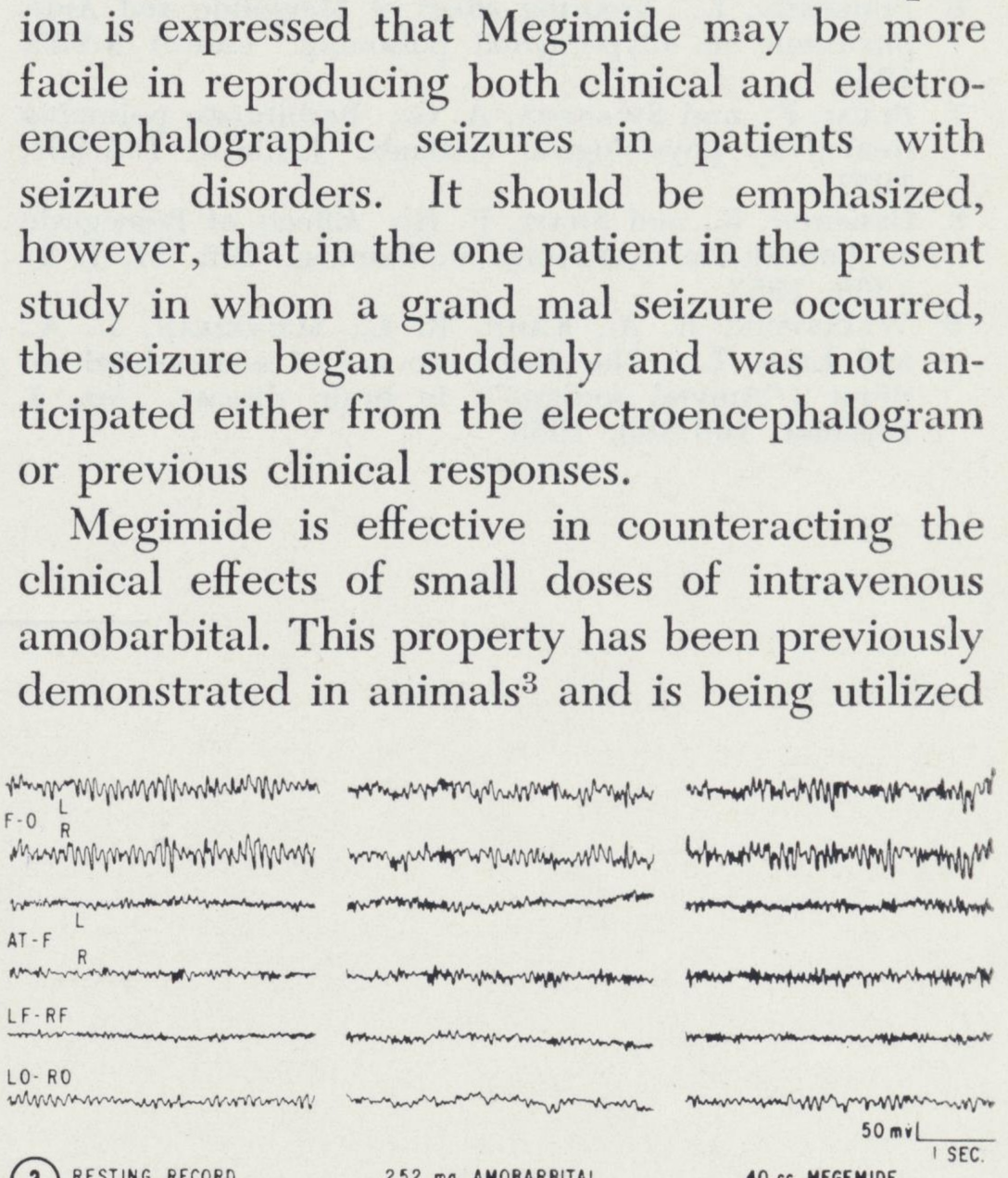


FIG. 3. Effect of Megimide following administration of amobarbital

in anesthesiology to shorten the recovery period from barbiturate anesthesia postoperatively.[15] It is questionable whether this action is specific for barbiturates or whether it also applies to states of altered consciousness due to other agents as well.[16]

CONCLUSIONS

1. Thirty-four psychiatric patients without cerebral disease were given Megimide (beta, beta-methylethylglutarimide) before and after the administration of intravenous amobarbital.

2. Megimide produces irregular delta activity, bursts of delta activity, and spike and spike-wave activity in the electroencephalogram. Such effects are similar to those produced by pentalenetetrazol (Metrazol).

3. Considerable individual variability exists in the amount of drug necessary to produce these changes.

4. A grand mal seizure was inadvertently induced in one patient. The electroencephalogram during the injection and prior to the seizure showed minimal changes and the seizure was not anticipated.

5. Megimide counteracts the clinical and some of the electroencephalographic effects of small doses of intravenous amobarbital.

Megimide supplied through the courtesy of A. & J. Nicholas Ltd., Slough, Bucks, England.

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RESULTS:

The electroencephalogram in all subjects prior to the administration of the drugs was "normal," i.e. symmetric and non-dysrhythmic.

EEG Response: In the amount and rate of injection of Megimide employed, EEG changes occurred in every patient. The type of EEG response and the amount of drug necessary to induce such a response were highly variable. The EEG changes included irregular low and moderate voltage slow activity, bursts of slow activity (usually of high voltage), single spike discharges and spike-wave forms (Figs. A, B, C). These effects were diffuse and symmetrical, with greatest prominence in the temporal leads.

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accompaniment for the awakening response, however, since other subjects, in whom clinical drowsiness disappeared, did not show such EEG discharges.

DISCUSSION:

Megimide is similar to pentalenetetrazol (Metrazol) in that it induces delta activity, spike and spike-wave activity in the EEG and clinical grand mal seizures. Such changes occur in non-epileptic subjects without brain disease and considerable individual variability in the threshold for these changes exists. These discharges are non-specific and cannot be used as evidence of the presence of a seizure disorder.

The possibility of using Megimide in activating the EEG has received study (10, 11, 12). Several investigators have noted a more gradual onset of the EEG and clinical changes with Megimide than with Metrazol. For this reason the opinion is expressed that Megimide may be more facile in reproducing both clinical and electroencephalographic seizures in patients with seizure disorders. It should be emphasized, however, that in the patient in the present study in whom a grand mal seizure occurred, the seizure began suddenly and was not anticipated either by the EEG or previous clinical responses.

Megimide is effective in counteracting the clinical effects of small doses of intravenous amobarbital. This property has been previously demonstrated in animals (3) and is being utilized in anesthesiology to shorten the recovery period from barbiturate anesthesia post-operatively (15). It is questionable whether this action is specific for barbiturates or whether it also applies to states of altered consciousness due to other agents as well (16).

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