MEGIMIDE AND METRAZOL

A comparison of their convulsant properties in man and cat

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(Received for publication: February 13, 1958)

The report by Shaw *et al.* (1954) on the effectiveness of Megimide (beta-beta-methyl-ethyl-glutarimide — Bemegride — Mikedimide) as a barbiturate antagonist, led to the European use of this compound as an activating agent in clinical electroencephalography. In preliminary reports several authors, Delay *et al.* (1956), Coirault *et al.* (1956), and Courjon and Bonnet (1956), were favorably impressed with the use of Megimide as an EEG activating agent. Although Courjon and Bonnet stated that Megimide was not always as efficient as Metrazol, all investigators seemed to note a better tolerance and more gentle action. Drossopoulo *et al.* (1956), concluded that Megimide activation was superior to Metrazol because of less disagreeable side effects, EEG changes were less abrupt, partial seizures that may be set off were less liable to become generalized, and drug seizures more closely resembled spontaneous ones. A less favorable report by Flodmark *et al.* (1957) indicated pronounced similarity between Metrazol and Megimide activation especially in respect to subjective dizziness, anxiety, and nausea. In this country the use of Megimide as an activating agent was reported by Green and Fink (1957). They suggested that the drug appeared to be similar in action to Metrazol on psychiatric patients.

The present study was undertaken to evaluate the relative efficacy of the two drugs in man and in experimental animals and to test the above observations that Megimide is subjectively better tolerated by the patient than Metrazol.

Fifteen chronic schizophrenic patients, 5 chronic epileptic patients, and 5 normal volunteers were examined. The patients were taken off all medications for a period of at least 48 hours prior to the tests. There was a usual minimum of one week and a maximum of one year between Metrazol and Megimide tests on each subject. In some patients Metrazol was the first drug used, in others it was Megimide. Intravenous Metrazol was injected at the rate of 50 mg. per min. to 750 mg. or until EEG activation or a clinical seizure occurred. The Megimide procedure was to rapidly inject 20 mg. intravenously followed by 5 mg. every 15 sec. to a total of 250 mg. or until EEG activation or a clinical seizure developed.

It was apparent in all three groups of subjects that the results of the activating procedures were comparable under the two drugs. Two records are shown in figure 1. If an individual, irrespective of diagnosis, was activated by Metrazol, activation occurred in a similar fashion with Megimide. Likewise, if no change was seen with Megimide there was also none with Metrazol. One schizophrenic patient was exceptional inasmuch as no activation had occurred one year earlier with 500 mg. of Metrazol while 70 mg. of Megimide produced atypical spike-wave responses. It is possible that the long interval between tests might be responsible for this result, although in one other case of schizophrenia, with an equally long inter-drug interval, EEG changes under the drugs were comparable.

The type of discharges induced by either drug was quite variable. High voltage paroxysmal discharges, atypical spike-waves, and focal activation, especially of the temporal areas, were most common. Slowing of the back-ground rhythms to a 5-7 c/sec. was observed less frequently. Though there were large inter-individual variations both drugs induced EEG changes which seemed to be specific for the individual. For example, a patient would not respond with a focal temporal discharge to Metrazol and with an atypical spike-wave burst to Megimide or vice versa. Figures 1 and 2 represent typical examples. The exception to this result was that twice out of 25 comparisons Megimide activation manifested itself initially by high voltage paroxysmal discharges, while Metrazol led to atypical spike-wave bursts. This would suggest a milder action of Megimide. However, in 6 instances Megimide produced atypical spike-wave bursts as the first indication of activation, as did Metrazol.

No overt seizures were seen with either drug in two epileptics but EEG activation occurred with 500 mg. of Metrazol. Two hundred and fifty mg. of Megimide produced similar EEG activation and likewise no overt seizures. The 3 other epilepties responded with seizures to both drugs. These attacks were of the grand mal variety and the ward attendant stated they were typical for the particular patient. There were no clinical differences between Metrazol

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and Megimide seizures especially not in terms of duration or mildness.

Two of the 5 normal subjects had discharges with both drugs, 2 failed to activate with either, and one who had such a profound spinning sensation with 350 mg. of Metrazol that the procedure was stopped, showed a spike-wave paroxysm under 180 mg. of Megimide.

The 20 schizophrenic and epileptic patients were largely uncommunicative and no statements could be elicited concerning side effects of either drug. All normals reported similar subjective sensations from both drugs but under Megimide the sensations were less intense. With Megimide no subject reported a "funny" smell or taste which was often observed during Metrazol administration. Amytal (150 mg. i.v.) after Megimide, led to a rapid disappearance of the subjective discomfort as well as a return of the EEG to the pre-activation level in the normals and psychiatric patients. Activation of the EEG persisted longer in the epileptic group but at no time was barbiturate fast activity observed. It was generally found that one-half to one-fifth of the mg. dose needed for Metrazol activation sufficed in producing Megimide changes. This apparent advantage of Megimide is somewhat offset by the fact that it is commercially available only in a 0.5 per cent solution while Metrazol is prepared in a 5 or 10 per cent concentration. One may thus have to inject, *e.g.*, 40 cc. of fluid in order to reach effects comparable to 8 cc. of Metrazol.

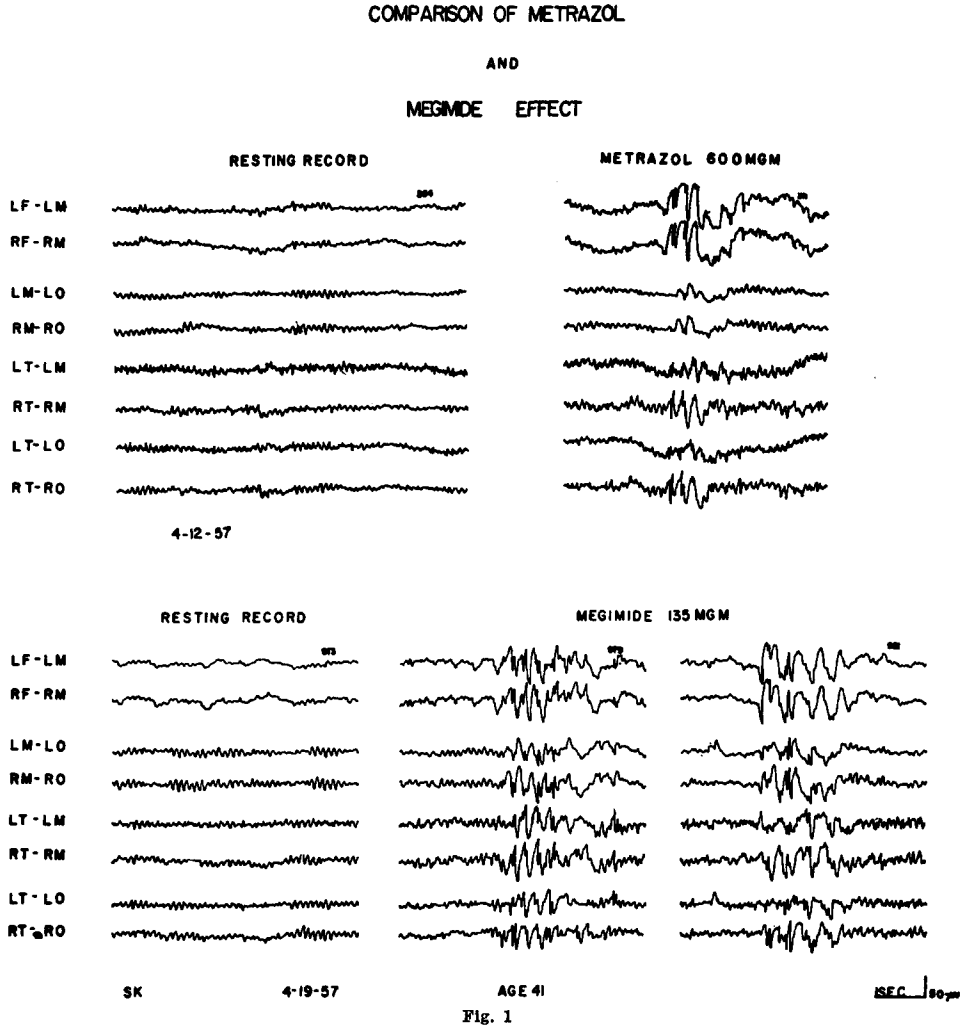

Fig. 1

Examples of individual responses to Metrazol and Megimide in schizophrenic patients.

Five acute cat preparations were employed for further tests of the relative effectiveness of EEG activation with the drugs. Under ether, bipolar electrodes were stereotactically inserted into the ventral lateral nucleus of the thalamus, caudate nucleus, hippo-

campus, and reticular formation of the midbrain and rostral medulla, although all of these were not studied in each animal. Surface electrodes on the cerebral and cerebellar cortex were screw-type. All electrodes were fixed and insulated with dental acrylic and incised tissues, ear regions, etc. were procainized. After anesthesia wore off the animals were immobilized with Flaxedil and maintained on artificial respiration. Electrical recordings were made with a Grass 8-channel EEG machine. Seizures were precipitated by slow intravenous injection of Metrazol (20 mg. every min.) in 2 cats and following a recovery period of one and a half hours they were observed under intravenous Megimide induced seizures. The other 3 received Megimide first and Metrazol later. Convulsant Megimide doses ranged from 5 to 10 mg/kg. depending on rate of injection, Metrazol 20 to 30 mg/kg. In all instances there were no appreciable qualitative differences between the types of seizure discharges observed with the two drugs (fig. 3) nor was there evidence that Megimide seizures were shorter in duration.

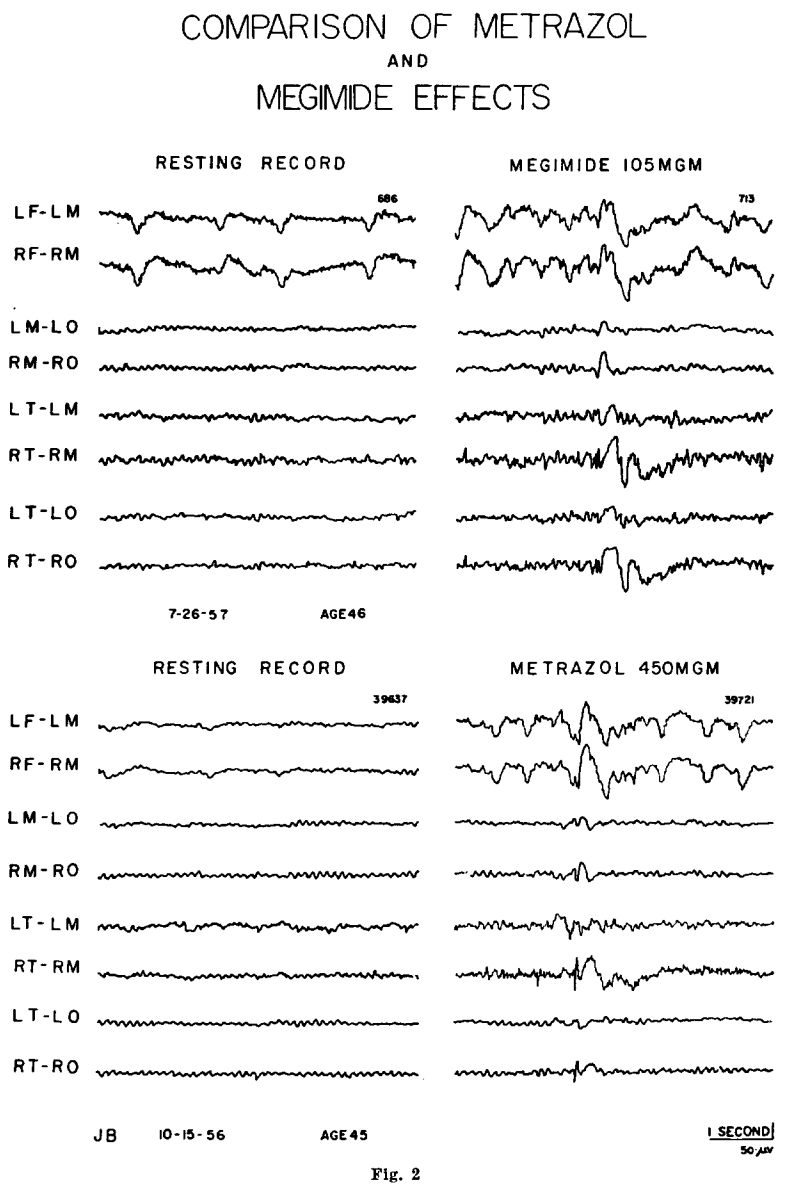

Fig. 2
Examples of individual responses to Metrazol and Megimide in schizophrenic patients.

Figure 4 shows that the first change in the electrical activity at a preconvulsive level occurred with

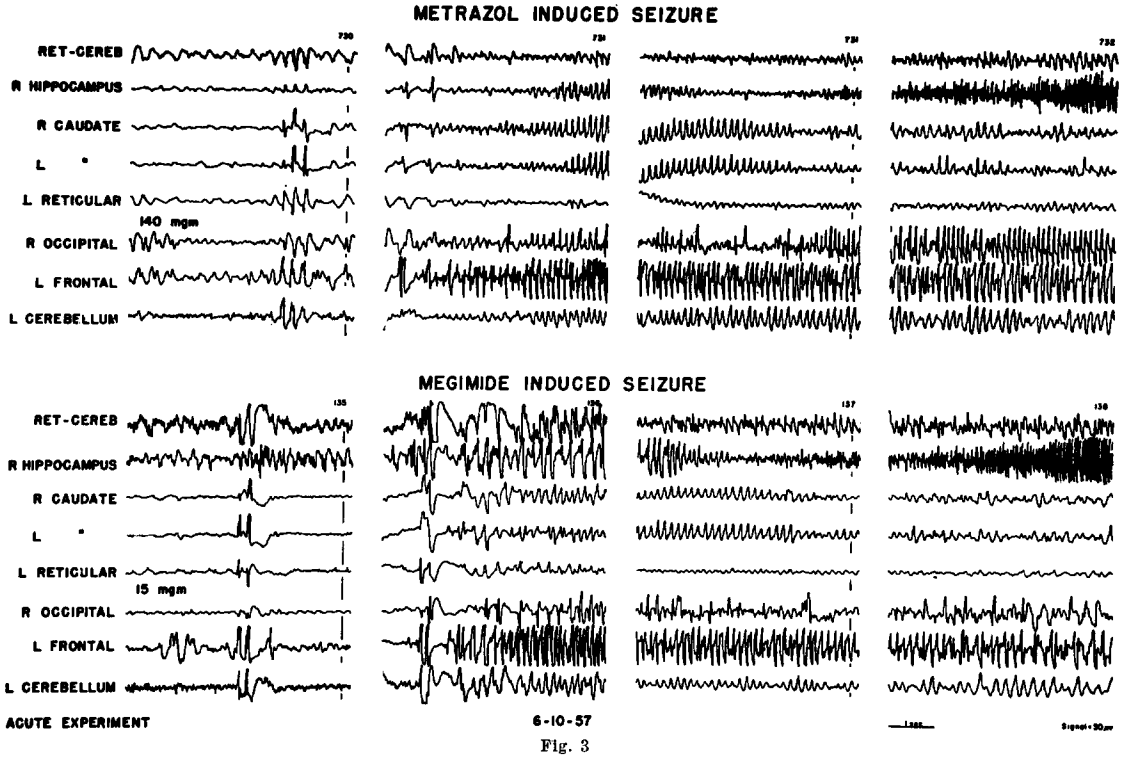

Fig. 3

Comparison of Metrazol and Megimide seizures in the acute cat preparation. The tracings on the first channel reflect recordings between the midbrain reticular formation and the left cerebellar hemisphere. The other channels record bipolar from the structures indicated. The large dose of Metrazol is due to extremely slow drug administration. The calibration signals represent 50 μV. Please note the different amplifications used.

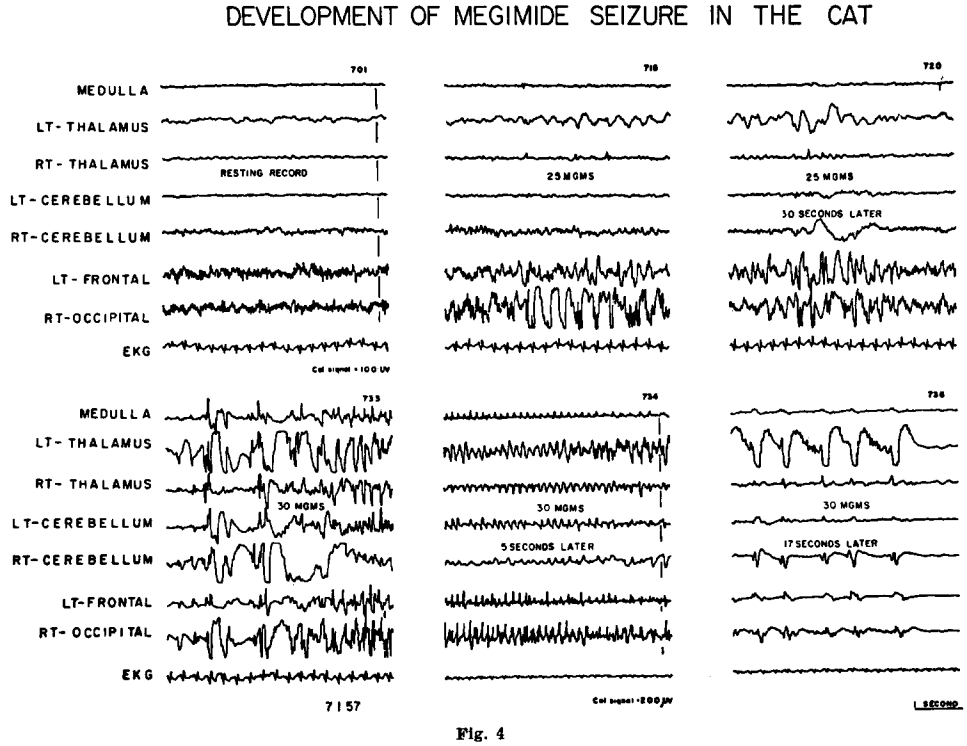

Fig. 4

Acute cat preparation, bipolar recordings. The nuclear structures of the thalamus sampled were not identical on the two sides. The tip of the left electrode was found to be in n. ventr. post. lat., the tip of the right electrode in n. ventr. post. med. Calibration signals 100 and 200 μV. respectively.

Megimide in the cortex. The subcortical structures studied fired only after there had been seizure activity established in the cortex. This effect was also observed with slow i.v. injection of Metrazol and is in agreement with Starzl *et al.* (1954). A further similarity between Metrazol and Megimide was the observation that status epilepticus which was induced at the end of 3 experiments with Megimide could be promptly controlled by intravenous administration of a 5 per cent solution of Tridione.

Drug comparisons in the cat were extended to 3 chronic preparations with permanently implanted screw type electrodes in frontal, auditory, and visual areas of the cerebral cortex, and in both cerebellar hemispheres. The pre-seizure buildup and the seizures themselves were similar under both drugs in spite of the fact that Metrazol was given subcutaneously while Megimide had to be administered intraperitoneally because of its weak concentration. A convulsant dose of Megimide was found to be between 17 and 20 mg/kg., whereas that of Metrazol was 40 to 50 mg/kg. In one animal the electrical seizure activity was slightly more lateralized to one side of the brain under Megimide while it appeared more symmetrical with Metrazol. The voltage of these seizure discharges was about one-third less during the Megimide convulsion. All 3 cats evidenced qualitatively similar behavior during the preseizure buildup with both drugs. Initial meowing was followed by urination, defecation, panting, piloerection, twitching. salivation, and finally massive jerking. Although all of these responses also occurred with Megimide, there appeared to be a quantitative difference, *i.e.*, the meowing was in general not as loud and as persistent, the panting was less vigorous, and there was more twitching rather than massive jerking. In these respects the observations suggest that Megimide may have a milder action than Metrazol.

CONCLUSIONS

The results obtained in this study confirm the observations reported in the literature, that Megimide and Metrazol produce essentially comparable effects clinically and electroencephalographically. There is also a suggestion that Megimide gives rise to somewhat less intense subjective sensations than is the general rule with Metrazol and it may be in some instances milder in its electroencephalographic effect. When Megimide is used for diagnostic purposes in patients suspected of having convulsive disorders it will, however, be necessary to employ the same caution in interpreting the findings that one has to use in regard to Metrazol findings, since it is quite apparent that some non-epileptic "normal" volunteers, may also show electroencephalographic activation at low levels of the drug.

Megimide was kindly supplied for this investigation by A. and G. Nicholas Inc., N.Y. The project was in part supported by USPHS Grant No. 1379 and B-1068.

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