Medical Intelligence

Prenarcotic Doses of Barbiturates as an Aid in Localizing Diseased Brain Tissue

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The studies reported here, carried out in collaboration with Dr. Richard Walter and Dr. Martin Lebowitz, concern some uses of sodium thiopental (Pentothal) other than those commonly employed in anesthesiology, and in particular the use of this drug to detect and localize abnormalities of neuronal function in the brains of patients with seizures.

The reaction of the normal human brain's electrical activity to barbiturates has been known well for years. This was first established in terms of the EEG as recorded from the scalp, where light prenarcotic dosages were shown to produce fast frequencies of approximately 20–25 cycles per second, that is, waves considerably faster than the familiar alpha band which centers around 10 cycles per second, and in striking contrast to the very slow waves that develop in the anesthetic stage.

Thiopental, as a diagnostic aid in epilepsy, was first used by Fuster, Gibbs and Gibbs as an activator—i.e., in the attempt to produce spiking. In following up this work, Heuwer, Rémond and Delarue noted that the slow-wave stage was reached in the EEG's of epileptic patients at lower dosages than in those of nonepileptic control subjects. When recorded simultaneously from several locations on the scalp of man, the fast activity of the prenarcotic stage is found to develop first in the frontal regions, progressing gradually more posteriorly. The recovery process proceeds in the opposite direction, the frontal regions being the last to relinquish the effect. Although at first glance this might appear to indicate a reaction of cells in the superficial layers of the brain, later work with deeply implanted electrodes demonstrated that regions of the brain in which the cell bodies of the neurons lie generate the same fast activity as previously had been seen in scalp recordings. These studies made it clear that this effect is at the level of the cell bodies and is a reaction of all normal neurons.

The stage at which this fast activity appears in the EEG is not, in any sense, that of anesthesia, but it is almost certainly one at which the neurons are called upon to react with the agent.

Brain tumors, on the other hand, in general, contain no electrically-active nerve cells, and might reasonably be expected to fail to react to barbiturates in this way. The first investigators to test this hypothesis and prove its correctness were Alema and Sinisi in Bologna, who published their findings in 1950. In contrast to Rémond and his colleagues, Alema and Sinisi specifically advocated the use of the stage of EEG fast activity to detect hemispheric asymmetries, and demonstrated their ability to lateralize, and in some cases to localize, tumors in patients with neoplasms, using as their hypothesis that the metabolic condition of tumor tissue must differ profoundly from that of normal neurons. This early work has since been plentifully confirmed by others, e.g., Pampiglione in the case of lesions which he described as "very large, involving a lobe or more."
Fig. 1. Computer-quantified measurements of the amount of EEC activity in the 20-cps band developing as the result of injection of thio-pental. In this patient the fast activity began to be replaced by slow waves when the dosage passed 200 mg. Left side later resected.

The work described here concerns patients with temporal-lobe epilepsy, a condition in which gross lesions are extremely rare. However, since the days of these earlier workers, a great deal of information which suggests that anomalies at the membrane of neurons are involved in the abnormal electrical discharges of the epileptic brain has accumulated. 5, 6, 9

Intracellular recordings from cortical cells have shown a close relationship between slow membrane changes of the soma and the epileptiform activity recorded at the surface. It seemed possible, therefore, that abnormal functioning of the nerve cell membrane might also manifest itself as a failure to react in a normal way to the impact of barbiturate drugs and thus prove useful in localization not only of non-neuronal tumor tissue, but also of malfunctioning neuronal aggregates.

Direct evidence for the action of barbiturates on the nerve cell membrane cannot, of course, come from studies in man, but the ex-

Fig. 2. Lateralization in a second patient. Right side later resected.
quisite analyses made from intracellular recordings in invertebrates by Chalazonitis and in vertebrates by Somjen made it clear that the site of action is at the membrane of the postsynaptic cell. Changes in membrane conductance are also found with many volatile anesthetics, such as ether, halothane and chloroform, but for a simply-administered diagnostic test, quick-acting thiopental is the chosen agent.

One of the collaborative research programs at this Brain Research Institute concerns a series of patients with temporal-lobe epilepsy whose seizures are resistant to control by medication and who are therefore candidates for unilateral temporal lobe resection as a therapeutic measure. Adequate lateralizing signs are needed to guide the surgeon in his choice of hemisphere. Frequently these patients show no hemispheric asymmetry in scalp EEG’s, for the trouble lies deeper and can be reached only by electrodes inserted deep within the brain in such structures as the hippocampus and the amygdala. In cases such as these, with the hope that it might pinpoint the epileptogenic zones, we have been exploring the use of light doses of thiopental in a search for neuronal tissue that does not react in the normal way by developing fast activity. The effect, of course, can be expected only if electrodes are indeed within recording distance of a malfunctioning zone of neurons.

The procedure is to administer the thiopental extremely slowly in a series of small increments whose timing is decided by the changes occurring in the EEG. The sign looked for is the development of fast waves in the 20-to-28-cps frequency range, though this can be narrowed down to activity in a narrower frequency band in most patients. This can be seen by eye, but for purposes of quantification the amount of this activity has been assessed by computer, and it is this computer measurement that is plotted in the accompany.

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The effect is fleeting, and within two minutes of stopping the infusion the curve returns to normal. However, as is well known, if thiopental is given in larger amounts, the EEG changes even further, the fast activity ceases and slow waves supervene. We have found no lateralizing function of this slow-wave stage—only the stage of fast activity has served this function.

This can be clearly seen in figure 1, from a patient whose maximum fast activity occurred when the thiopental dosage had reached 200 mg, two minutes after the first injection had been given. Increasing the amount to 300 mg replaced the fast activity by slow waves, and the lateralizing signs were lost.

Figure 1 shows recordings from electrodes in the patient's left and right hippocampal gyri. The placement of electrodes was checked by x-ray and found correct in both cases. Later, a left temporal topectomy was performed and histologic examination revealed mesial temporal sclerosis but no neoplasm.

An example from another patient is given in figure 2. These data are from a 21-year-old man who was given thiopental in increasing dosage over a period of 15 minutes. The thiopental dosage was increased progressively by 100 mg at each measurement point, and the amount of fast activity was measured over a period of 5 minutes after the start of the injection.

**Fig. 4.** Localization within the right hippocampus of a fourth patient, which on later resection showed marked atrophy of the pes hippocampi. Note normal reaction of the more posterior zone of the hippocampus and of both sites in the ipsilateral hippocampal gyrus. Increments were given slowly over a period of 24 minutes, but dosages from 600 mg upwards increasingly cut down the amount of fast activity.
man who had had seizures since infancy, un-
controllable by medication, who later had a
right temporal topectomy performed by Dr.
Crandall. A confirmation of electrode place-
ments on the right was therefore available by
both x-ray and histologic examination, and on
the left by x-ray alone.

We have found considerable differences be-
tween patients as regards the "absolute" dosage
at which fast activity is replaced by slow
waves, though this has not been found to a-
ffect the lateralizing potential of this technique.
In addition, the exact frequency band of max-
imum reactivity may differ from patient to pa-
tient. In figures 1 and 2, the frequency band
examined centered on 20 cps. In figure 3,
from another patient, 28-cps activity was
chosen for graphing, and the contrast between
left and right anterior pes hippocampi is
striking.

In the course of our studies of the hippo-
campus of man, it has become clear that there
is electrophysiologic dissociation between the
various zones even in the absence of epilepto-
genic activity. Such dissociations had been
shown in the structurally-very-different hip-
locampi of lower animals such as the rat and
the cat. In man the ongoing electrical ac-
itivity of the hippocampus in the wakening
state has been found to be usually quite in-
dependent in different parts, for example, the
wave-trains recorded from pairs of electrodes
only 7 mm apart have been found to be un-
related in timing and spectral content.

Therefore, it is perhaps not surprising that
in patients with temporal-lobe epilepsy the
EEG may be able to detect circumscribed zones of malfunction within the hippocampus.
In the context of using thiopental to highlight
localization, figure 4 is an illustration. The
graph shows the development of fast activity
in the 20-cps band as recorded by bipolar elec-
trodes in four different electrode sites in the
right temporal lobe. The locations, confirmed
by x-ray, were the anterior and mid zones of
the pes hippocampi and the anterior and pos-
terior zones of the ipsilateral hippocampal
gyrus. With the exception of the anterior pes
hippocampi, the almost immediate increase in
fast activity on injection of 50 mg to 150 mg
thiopental is the normal reaction, falling off
during the lull of four minutes before a booster
dose of a further 100 mg was given. This
stage of fast activity of the EEG is very fleet-
ing and soon declines, but can be reinstated
by a further small dose. When the dosages
reached the higher range of 600, 800 and
1,050 mg, the patient passed the prenarctic
stage and the fast activity began to be re-
placed by the familiar slow waves associated
with loss of contact with the environment.
Noticeable, however, is the failure of the ac-
tivity of the anterior pes hippocampi to react
to the drug. In this patient severe atrophy of
this region subsequently was found at surgical
operation.

To refer briefly to the basic laboratory work
on this problem, the early explorations of the
effects of anesthetic agents on the nerve axon
revealed that, in the concentrations used in
clinical work, it was extremely unlikely that
this was where a block in conduction took
place during general anesthesia. Nerve fibers
are very resistant to interference with trans-
mission of nerve impulses along them, except
by dosages used in laboratory work that have
no parallel in clinical use. Attention then
turned to the much-more-vulnerable link in
the chain of transmission, namely the synapse.
There have been several fine laboratory studies
of the passage of the nerve impulse across the
synapse and its invasion of the membrane of
the postsynaptic cell. There have also been
several detailed studies of how anesthetic agents
impede and delay this action on the postsynap-
tic membrane, as already mentioned.

The mass effect of the behavior of neurons,
such as one sees in the EEG, is just as vul-
nerable as that of the units of which it is com-
posed, and the development of the fast activity
described here (which, incidentally, is also
found in light stages of ether anesthesia) may
be taken as a sign of membrane disturbance.
We have made use of this characteristic to
seek lateralizing signs in our patients with
neurons whose malfunctions reveal themselves
as the epileptic discharge.

In conclusion, in the search for the basic
mechanisms by which different agents affect
cellular membranes, changes in their electrical
activity may be regarded as a promising clue,
even in the difficult circumstances of examina-
tions of human beings.
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References


Obstetrics and Pediatrics

PARACERVICAL BLOCK Paracervical block was performed in 15 mothers in labor and maternal and fetal meperidine concentrations were determined. Blood was obtained from the maternal vein, fetal scalp during labor, and umbilical vessels at birth. Fetal blood also was analyzed for acid–base parameters. Meperidine levels averaged 8.5 μg/ml in the mothers and 7.4 μg/ml in the fetuses. Fetal blood levels were consistently lower than maternal levels. All but one infant had Apgar scores of 8 or 9. Fetal bradycardia was encountered in three cases; two episodes were transient and associated with Apgar scores of 8, and in the third, bradycardia persisted until delivery and was associated with a score of 4. The only significant pH variation was in the infant with persistent bradycardia. The highest meperidine concentrations were found in the three cases with fetal bradycardia. It is probable that a normal fetus can tolerate clinically-induced levels of meperidine, but that infants depressed by acidosis may be compromised. Fetal bradycardia as a result of drug toxicity should be distinguished from that due to fetal asphyxia. Paracervical block is contraindicated when placental insufficiency is anticipated. (Gordon, H. R.: Fetal Bradycardia After Paracervical Block, New Eng. J. Med. 279: 910 (Oct.) 1968.)

ABSTRACTER’S COMMENT: Drs. Sol Shneider and associates, in the correspondence section of the same journal, report significantly higher fetal meperidine levels in infants that had bradycardia than those that did not. Furthermore, meperidine levels in the infants with bradycardia exceeded maternal levels, indicating the drug found its way directly from paracervical tissue to the intervillous space. Objective data such as these will help decide the usefulness of paracervical block with meperidine.