THE USE OF ELECTROENCEPHALOGRAPHY TO MEASURE RECOVERY TIME AFTER INTRAVENOUS ANAESTHESIA

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SUMMARY

Depth of anaesthesia and tendency to sleep were assessed by means of electroencephalography in healthy volunteers following the administration of different intravenous anaesthetics. Graphs of sleep depth were constructed from the records. Characteristic differences were observed in the postanaesthetic course between methohexitone, thiobarbiturates, neuroleptanalgesics, and propanidid. Whereas the effects of propanidid rapidly diminished, this was not the case with the other drugs, and even after 12 hours the potentiating effect of a small quantity of alcohol was discernible after methohexitone, thiopentone and thiobutobarbitone. The results suggest that after intravenous barbiturate anaesthesia for out-patient procedures the patient should be cautioned against driving or drinking alcohol for 24 hours, but after propanidid a 2-hour period is sufficient.

Many authors have followed the course of anaesthesia by electroencephalography (Faulconer and Bickford, 1960; Kugler and Doenicke, 1964, 1965; Schneider and Thomalske, 1956) but they have not carried their studies into the postanaesthetic period. In this period clinical observations and simple psychic tests (Doenicke and Sigmund, 1964; Klebelsberg and Steinbereithner, 1963) have been partly contradictory and have provided no guidance on the medico-legal problem of the patient's fitness to leave hospital after an anaesthetic. Doenicke and his colleagues (1965) showed that psychological tests did not reflect adequately the variations in cerebral function during the hours and days following anaesthesia. Such tests are significant only if prolonged study is carried out using a combination of several tests (Doenicke and Sigmund, 1964). The difficulty inherent in this method is that variations in cerebral function of short duration are insufficiently noted. Prolonged psychological tests cannot be repeated as often as desired within 24 hours; training, habituation and fatigue can lead to spurious results. Electroencephalography has the following advantages:

1. It appears to be a sensitive indicator of the presence of full consciousness, reliably recording even brief variations.
2. It does not require external stimuli by which wakefulness can be modified.
3. It can be continuously recorded and analyzed by simple methods.

In order to differentiate the specific effect of an anaesthetic agent from that of postoperative stress, clinical testing and electroencephalography were combined on healthy volunteers. The results of pre-anaesthetic control examinations were compared with those obtained after administration of intravenous anaesthetics to gain information on the duration and degree of postanaesthetic sedation and the intensity of mental concentration.

METHOD

139 anaesthetics were administered to 38 healthy volunteers. The following preparations were used:

- Thiopentone or thiobutobarbitone (Inactin) in three doses, 1,000, 500 or 250 mg (74 times).
- Methohexitone 150 mg (10 times).
- Propanidid 500 mg (36 times).
- Dehydrobenzperidol 25 mg and fentanyl 0.5 mg (Thalamonal) (18 times).
- Dehydrobenzperidol 25 mg (once).

At intervals of not less than six weeks each volunteer was given one of the above anaesthetics.
under strictly controlled conditions. Before each experiment the subject was requested to adhere to a standard living and eating schedule for several days. In every instance anaesthesia was commenced at 8 a.m. The close similarity of each study justified statistical analysis of the findings.

Anaesthesia was induced by the rapid administration of the preparation into an antecubital vein after previous intravenous injection of atropine 0.5 mg. A cannula was inserted in the free arm for withdrawal of blood samples for serum barbiturate estimations and liver function tests.

One subject was given half a litre of beer following both thiobutobarbitone and methohexitone to ascertain the possible modification of the clinical and electroencephalographic effects.

Electroencephalographic tracings were begun before anaesthesia to record the initial pattern and were continued during, and for the first few hours after, anaesthesia. Thereafter, the electroencephalogram was recorded for 15 minutes, at intervals of one hour. Eight and twelve channel Schwarzer and Hellige apparatus was used.

The electrical activity of the right parieto-occipital region was led to a second apparatus, the writing systems of which recorded with a paper speed of 0.2 mm/sec. One channel recorded the electroencephalogram at this slow speed as a control for electrical changes and artefacts. The second channel recorded the transformation of the electroencephalogram by a Schwarzer integrator. The variations in voltage induce, through a direct current amplifier, a rise of the writing pen proportional to the integrated surface of the electroencephalogram. The pen was returned to the zero line every 10 seconds. A condensed survey of the integral of the record was obtained and was a measure of the degree of synchronization of the electroencephalographic activity and variations in it which lasted longer than 10 seconds. More rapid fluctuations and details of the shape of the waves cannot be seen. Comparison with the simultaneously recorded electroencephalogram is an indispensable safeguard against misinterpretation of artefacts. In the visual evaluation of the electroencephalogram, depth of sleep or anaesthesia was estimated according to Loomis's classification, at intervals of 20 seconds with 15 mm/sec paper speed (Loomis, Harvey and Hobart, 1938).

Depth of sleep was classified according to the following criteria: slowing and decrease in amplitude of alpha activity (stage A) was rated as drowsiness; flat diffuse slow waves (B0) and transition into higher 4–5/sec waves (B1) as onset of sleep; small sharp waves and so-called sigma-rhythms (B2) as light sleep. Sleep of medium depth was recorded as higher 4–5/sec waves, repeated sharp waves, more distinct 12–14/sec spindles, and K complexes evoked by psychosensory stimuli (stage C). High irregular series of 1–2/sec waves and broad K complexes following acoustic stimuli were classified as deep sleep (stage D). Anaesthesia was similarly classified, beginning with the initial stages showing irregularities, followed by accelerated activity, as stages A and B, the analgesic stages with increase in high slow waves, as C and D, deep anaesthetic sleep with very sluggish delta waves as E, distinguishing the coma stages with periods of electrical silence as stage F. Within these stages various degrees of characteristic waves were quantitatively estimated.

Comparison of integration values with electroencephalograms and sleep depth graphs reveals that paying attention, or apprehension (e.g. before an injection or before anaesthesia), results in acceleration and flattening of the pattern and reduction of the curve integrals. A similar effect appears during stages of early sleep from A to B1, and during certain sleep stages with slow eye movements. On the other hand, during stages of medium and deep sleep there is considerable increase in the amplitudes observed, as well as in the surface integrals. The course and temporal fluctuations of the integrator values otherwise agree well with the sleep depth graph visually determined from the electroencephalogram. Isolated high deviations of the integrator, standing out from comparatively regular flat activity, usually occur as artefacts due to swallowing or other movements.

The serum level of barbiturates was estimated by spectrophotometry (Goldbaum, 1952).

RESULTS

Comparison of propanidid and barbiturates.

Considerable differences between the various anaesthetic preparations were evident even at the onset and during the first few minutes of anaes-
thetic effect. These differences are, for example, especially marked if methohexitone is compared with propanidid (fig. 1). The electroencephalog-raphic patterns differ in their content of rapid activity, which is especially strong and of relatively long duration in the emergence phases after propanidid. The electroencephalograms and the amplitude integrals show, by their content of high slow waves, persistence of anaesthesia for 10 minutes or more after methohexitone. On the other hand, there is rapid emergence after the second minute following propanidid. The increase in depth of anaesthesia is more rapid after propani-did than after methohexitone.

Comparison of the sleep-depth graphs for the period after methohexitone anaesthesia shows short interruptions in wakefulness and a prolonged tendency to sleep, reaching a maximum about 3-4 hours postanaesthetically, while no measurable tendency to sleep was present in most subjects after propanidid. The analysis of evoked potentials following photic stimuli showed 3 to 8 minutes after the injection of propanidid in one case a considerable increase in amplitude, surpassing the initial level (Kugler and Doenicke, 1965).

An activating effect of propanidid similar to bar-biturates on the electroencephalographic anomalies of epileptic patients, probably with slow injection, has been reported by Bushart (1964).

The same differences in tendency to fall asleep were found in other subjects after anaesthesia (fig. 2). The patterns show that the stages of drowsiness and light sleep after methohexitone do not differ from the stages of physiological sleep, presenting flat slow waves and irregular flat K complexes after arousing stimuli (5th hour) and small spontaneous vertex spikes (6½ hours). After propanidid, however, this volunteer also did not
FIG. 2
Eight-channel electroencephalogram and sleep-depth graphs following injection of methohexitone 150 mg (upper part) compared with propanidid 500 mg (lower part) in the same subject (G.U., male, 25).
Electroencephalogram and sleep-depth graphs in the same subject (G.U., male, 25) following injection of thiobutobarbitone 250 mg (upper part) compared with propanidid 500 mg (lower part). At 11 hours 20 minutes after injection on both occasions 0.5 l. of beer (ale) was taken by the subject.
Fig. 4
Electroencephalogram and sleep-depth graphs in the same subject (H.W., male, 25) after dehydrobenzperidol 25 mg and fentanyl 0.5 mg (upper part) compared with propanidid 500 mg (lower part).
exhibit recognizable sleep stages. Decreases of alpha waves and flattening, seen in the electroencephalogram (2nd hour) did not exceed the degree of fleeting tiredness.

During the afternoon hours, the electroencephalographic records showed characteristic differences after anaesthesia induced with thiobutobarbitone and propanidid. Figure 3 demonstrates the different tracings in a person after anaesthesia induced with thiobutobarbitone 250 mg intravenously and anaesthesia induced with propanidid 500 mg intravenously. The pre-anaesthetic initial patterns did not essentially differ. One minute after beginning the injection the maximal effect of thiobutobarbitone showed as small rapid activity of about 16/sec, while with propanidid there was high irregular slow activity. Eight minutes after the injection, some rapid activity was still present with thiobutobarbitone, whereas the propanidid graph had approximated to the initial pattern. Six hours after the barbiturate anaesthesia there were varying sleep stages with sigma rhythms and slight small vertex waves. On the other hand, after propanidid, the pattern of activity continued to resemble the initial tracings for the whole period of further observation. The waveform 8 hours after the barbiturate anaesthesia showed stages of light sleep with higher waves of 4-5/sec. Eleven hours and 20 minutes after thiobutobarbitone (20 minutes after drinking half a litre of beer) clinical signs of complete drunkenness were associated with paroxysmal short groups of generalized theta waves, while after propanidid the brain electrical activity remained unchanged. After thiobutobarbitone, this person again fell asleep several times and 12 hours after the anaesthetic became completely intoxicated and unable to walk after drinking less than half a litre of beer (Doenicke, 1962). In contrast to this, only a few minutes after the injection of propanidid 500 mg, subjective well-being had been regained, the electroencephalogram did not indicate any drowsiness during the afternoon hours, and nothing abnormal was noted after drinking half a litre of beer.

Neuroleptanalgesia.
In contrast to studies carried out with other anaesthetics, the electroencephalogram after dehydrobenzperidol and fentanyl showed little...
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alteration during the injection and during the following 20 minutes (fig. 4). During the tests, the persons were at all times reactive and rousable, although at the same time insusceptible to pain, and they were affectively and emotionally depressed if not completely indifferent. The subjects were frequently asked to overbreathe to avoid going to sleep during the first 10 to 20 minutes after injection. After the critical phase of possible hypoxia with an arbitrary reduction of environmental stimuli, the subjects fell asleep. The clinically established sleeping states were accompanied by patterns of physiological sleep lasting several hours until the evening. They could be interrupted at any time by arousal stimuli. The graph of sleep depth was similar in all 19 test persons. In one volunteer who received only 25 mg droperidol, clinical signs of sleep and the graphs conformed with those induced by dehydrobenzperidol with fentanyl (fig. 5). Usually, sleep states and waking states alternated for a period of 10 hours after injection (Doenicke et al., 1964).

Comparison of thiobarbiturates.

Considerable differences in sleep depth graphs and serum concentrations were apparent even between the two very similar substances, thiopentone and thiobutobarbitone. Comparisons of two

![Graph](https://example.com/graph.png)

FIG. 6

Mean serum concentrations (above) and sleep-depth graphs (below) of twelve subjects after thiopentone 500 mg (—) compared with thiobutobarbitone 500 mg (—).
or more barbiturates have been mainly based on
the duration of anaesthesia, since not enough is
known about the distribution of the drugs within
the body several hours after administration. After
the same dose of these barbiturates it was ob-
served that thiobarbiturate was present in the
serum in a higher concentration during the first
24 hours (fig. 6).

The electroencephalographic control tracings
confirmed that there were stages of electrical
silence at the point of maximum depth after
thiopentone injection, while thiobarbiturate
anaesthesia developed more slowly and was less
deep. This difference is also apparent in the
records representing average depth of anaesthesia
(fig. 6).

DISCUSSION

Electroencephalographic records permit assess-
ment of postanaesthetic states in man and, as
stated earlier, they are more reliable than psycho-
logical tests. Postanaesthetic states cannot be
reliably investigated in patients for a variety of
reasons. Postoperative stress and modifications of
sympatho-adrenal regulation influence the activity
of the reticular formation of the brain stem and
the cerebral cortex. Anxiety and pain before and
after the surgical intervention can also affect
behaviour. It is, therefore, understandable that
certain clinical features in the postanaesthetic
state, for example, after dehydrobenzperidol with
fentanyl, while barely noticeable on operated
patients can be observed on normal volunteers
(Doenicke et al., 1964). It has been shown above
that the postanaesthetic effects of this combination
are of longer duration than previously stated in the
literature. A tendency to sleep is demonstrable in
the electroencephalogram until the 12th hour
and clinical signs of autonomic effects even per-
sist until the 3rd or 4th postanaesthetic day.

We have no means of estimating the concentra-
tions of the substances dehydrobenzperidol and
fentanyl in body fluids. A comparison of the
electroencephalographic tracings and the con-
centrations of barbiturates determined by spectro-
photometry suggests that a correlation exists
between the actions on the central nervous system
and certain physicochemical properties (lipid
solubility and protein binding) of barbiturates.
The postanaesthetic effects of thiobarbiturates
have been ascribed to desulphuration and detoxi-
cation by side-chain oxidation, the longer side-
chain of thiopentone being more readily oxidiz-
able compared with the relatively stable side
chain of thiobutobarbitone (Frey, 1959; Frey,
Doenicke and Jäger, 1961).

Dundee and Barron (1962) also pointed out
that thiobutobarbitone, having the shorter side
chain (one CH₃ group less), is less active than
thiopentone. This weaker action holds true for
the duration of anaesthesia and the first half-hour
of the postanaesthetic period. The anaesthetic
potency of a preparation varies with its lipid
solubility. The greater the lipid solubility, the
faster the substance can pass the blood-brain bar-
er. The desired anaesthetic stages can thus be
reached more quickly (Brodie, Kurz and
Schanker, 1960; Brand et al., 1963; Doenicke,
1964; Gaudette and Brodie, 1959). The distinct
differences in lipid solubility (thiobutobarbitone
0.531 compared with thiopentone 1.800) and in
protein binding (thiobutobarbitone 68.68 per cent
thiopentone 85.0 per cent) certainly have a bear-
ing on postanaesthetic effects.

High lipid solubility results in a more rapid
passage into tissues during subsequent hours.
Our comparison of thiopentone and thiobarbi-
tone in the same volunteers has revealed
significantly lower barbiturate concentrations in
serum after thiopentone with its greater lipid
solubility. The rate of protein binding also plays
an important part in postanaesthetic effects
(Richards and Taylor, 1965; Taylor et al., 1954)
and Kurz (1964) showed that only the unbound
portion of the substance is pharmacologically
active. In our example, due to the lower lipid
solubility of thiobutobarbitone, the serum con-
centrations are higher after anaesthesia, and
according to its lower rate of protein binding, a
greater proportion of substance is pharmacologi-
cally active. Brand and associates (1963) found
that the degree of plasma binding of methohexi-
tone and thiopentone is about the same, while
methohexitone is less fat soluble than thiopentone
due to its slightly lower oil-to-water partition
ratio. Therefore, compared with thiopentone,
smaller amounts of methohexitone will be
deposited in the body fat.

Taking into account both our results and those
of Brand and colleagues it appears that, compared
with thiopentone, more thiobutobarbitone and methohexitone is circulating in the plasma during the first 12 hours after injection (fig. 6, upper part). These cause more profound sleepiness during this period.

The average graphs of sleep depth calculated from the individual graphs show statistically significant differences in peak values. In the electroencephalogram there is, at certain times (2–12 hours postanaesthetically), more drowsiness after thiobutobarbitone than after thiopentone (P<0.05 by the symbol test, which was used instead of the Student test because the same volunteers with similar initial conditions were employed). The partition ratio of thiobutobarbitone is lower and the serum concentration significantly higher (fig. 6). Both subjective postanaesthetic effects and stages of drowsiness in the electroencephalogram were significantly stronger (P<0.01) after thiobutobarbitone, which has a lower protein binding rate and lower distribution coefficient (higher serum barbiturate concentrations).

This study has attempted, by comparing the prolonged electroencephalographic effects of single doses of two closely related thiobarbiturates to show the deficiencies of using the duration of primary anaesthesia as a guide to the similarity of such drugs for outpatient anaesthesia. If the whole pattern of effects is observed for 24 hours, it appears unjustifiable to refer to these substances as short-acting anaesthetics.

Electroencephalographic records after the intake of a small quantity of alcohol confirmed that potentiation of action still occurred 12 hours after 150 mg methohexitone and after 250 mg thiobarbiturate, as well as 24 hours after 500 mg thiobarbiturate. On the other hand, 12 hours after anaesthesia induced with propanidid, alcohol intake did not evoke any change in electroencephalographic tracings.

A member of the profession may be at risk of legal action arising from the early discharge of a patient from hospital if he has been responsible for the administration of an anaesthetic, in the event of an accident befalling the patient. The results of this investigation emphasize the need for caution and the authors have issued (with the co-operation of Abbott GmbH) a form embodying recommendations for the reduction of risk to both patient and doctor.

Although recovery after propanidid is very much more rapid it is recommended that the rules of conduct be observed strictly for 2 hours.

These results have led us to use propanidid exclusively for induction of anaesthesia for the past year. In 3,000 patients in whom it was followed by halothane, no complications referable to the method were encountered and it is believed that propanidid confers real advantages over barbiturates, both for in- and out-patient anaesthesia.

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REFERENCES

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L'ELECTROENCEPHALOGRAPHIE COMME MOYEN D'APPRECIER LE TEMPS DE RECUPERATION APRES UNE ANESTHESIE INTRAVEINEUSE

SOMMAIRE

Les auteurs ont apprécié chez des volontaires en bonne santé la profondeur de l'anesthésie et la tendance à dormir, au moyen de l'electroencephalogramme, après l'administration de diverses anesthésiques intraveineux. D'après les enregistrements, ils ont établi des graphiques de la profondeur du sommeil. Ils ont observé des différences caractéristiques dans le temps post-anesthésique après administration de méthohexitone, de thiobarbiturates, de neuroalgalésiques, et de propanidid. Alors que les effets du propanidid diminuent rapidement, ceux des autres médicaments persistent, et on peut constater l'effet potentialisateur d'une petite dose d'alcool encore douze heures après l'administration de méthohexitone, de thiopentone, et de thiobutobarbitone. Ces résultats suggèrent qu'après une anesthésie intraveineuse aux barbituriques faites ambulatoirement, il faudrait recommander au malade de ne pas conduire une voiture ou boire de l'alcool pendant vingt-quatre heures, alors qu'après l'administration de propanidid deux heures d'abstinence suffisent.

DIE MITTLSES EINES ELEKTROENZEPHALOGRAPHEN GEMESSENE AUFWACHZEIT NACH INTRAVENESEN NARKOSEN

ZUSAMMENFASSUNG