INTERPRETATION OF ULTRA-SHORT ACTION OF THIOPENTONE SODIUM—A REVIEW

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Thiopentone sodium [sodium 5 ethyl 5 (1 methyl-butyl) thiobarbiturate] is one of the ultra-short acting barbiturates which is most frequently employed as an intravenous anaesthetic agent.

Though thiopentone-sodium has been in use for quite a long time and a large amount of work has been done with it, it is only in recent years that, due to introduction of accurate methods of its extraction, estimation in tissues and body fluids the precise knowledge about its distribution, metabolism, excretion and duration of action has been acquired.

The first barbiturate-barbitone, was introduced into medicine by Emil Fischer and Von Mering (1903), under the trade name of Veronal. Since then several barbiturates with varying degree of potency and duration of action were prepared, presented to the medical profession, and usually employed as hypnotics by mouth.

But Prodet and Perlis (1924), showed that general anaesthesia could be produced by intravenous injection of a combination of different derivatives of barbituric acid. They used a compound called "Sumnifene", a 10 per cent solution of diethyl barbiturate of diethyamine and allyl-isopropyl barbiturate of diethylamine. This opened up a new line of approach in the field of anaesthetics. Intravenous injection of Sumnifene produced surgical anaesthesia without excitement but the recovery of consciousness was prolonged and the subject slept for a very long time afterwards, and as such it did not present appreciable advantage over the other older barbiturates. However, its introduction gave an impetus to the synthesis of barbiturates which could be effectively used as anaesthetic agents by the intravenous route for short periods of anaesthesia.

Weese and Sharpff (1932), introduced in Germany a new barbiturate which was considered to be an improvement on the previously used intravenous anaesthetics in potency and in the duration of its action. It was N-methyl cyclohexenyl-methyl barbituric acid, known under various names, as, Evipal, Evipan,Cyclural or Hexobarbitone. It produced rapid anaesthesia, lasting for a short duration after intravenous injection; an average therapeutic dose in human subjects produced unconsciousness for a period of 10 - 20 minutes and the degree of anaesthesia produced by it was fairly deep (Lancet 1933), Due to thevery short duration of action it was called an "ultra-short acting" barbiturate.

At the time when Hexobarbitone was in use in Germany, another barbiturate with a short period of action similar to it, was introduced in America by Tabern and Volwiler (1924). This new barbiturate differed from Hexobarbitone and the other older barbiturates by the presence of a sulphur atom in the position of the barbituric acid ring in place of oxygen. It was chemically known as 5 Ethyl-5 (1 methyl-butyl) thio-barbituric acid, commonly known as thiopentone, or thiopental. The sodium salt was called Thiopentone Sodium (Pentothal Sodium). The barbturates with the sulphur atom in the 2 position of the barbituric acid ring became known as thiobarbiturates.

Though the thiobarbiturates came into prominence only from 1935, they were not new in the field but were as old as the first member of the barbituric acid compound, barbital. Emil Fischer and Dilthey (1904), prepared 5-5 diethyl thiobarbituric acid and Emil Fischer and Von Mering (1904), tried it on a dog weighing 7 kg. giving one gramme of the drug by mouth. This produced deep sleep with loss of response to stimuli followed by death eight hours after its administration. As a result of this fateful experiment they concluded that the presence of the sulphur atom in the barbituric acid nucleus made the compound too toxic to be of value for therapeutic use.

After them Einhorn and Diebach (1908), investigated the sulphur derivatives of the various substituted barbituric acids and observed the unstable nature of the thiobarbituric acid ring. They also considered that the thiobarbituric acid compounds were very toxic which was confirmed again by Dox and Hjort (1927).

Dox and Plaisence (1916) and Dox and Yoder (1921) prepared several derivatives of thiobarbituric acid but these compounds were not given any pharmacological trial. A few 5-5-di-substituted-thiobarbiturates were used as intermediaries in preparing their oxygen analogues by the removal of sulphur atom from them.

However, although 5 (ethyl 5 (1-methyl - butyl) thiobarbituric acid was mentioned in the old German patents, no serious attempts were made to evaluate the pharmacological properties of the thiobarbiturates till 1932.

In the meantime the possibility of producing anaesthesia in man by intravenous administration of barbituric acid compounds was made evident and need was felt to secure a barbiturate possessing a quick and short period of action. As none of the available barbiturates met the requirements of an ideal anaesthetic, the attention of the chemist was directed to the thiobarbiturates.

Tabern and Volwiler (1934), synthesised several thiobarbiturates and from the results of their preliminary experiments it become apparent that certain members of this group of compounds possessed powerful hypotic action of very short duration; when given in proper dosage intravenously they produced immediate sleep and surgical anaesthesia for a varying period, after which the animal became normal again.

They also observed that of all the compounds that were tried, sodium 5 ethyl 5 (1-methyl-butyl) thiobarbiturate was found to be definitely more active and in general less toxic than its oxygen analogue (Nembutal).

After experimental trials with sodium 5 ethyl 5 (1 methyl-butyl) thio-barbiturate Lundy (1935), concluded that it was a quick acting anæsthetic agent. When used intravenously it produced short period of anaesthesia associated with a fair amount of muscular relaxation followed by rapid recovery without excitment. He named this compound sodium thio-nembutal due its structural resemblance to Nembutal (pentobarbitone sodium) - and published the preliminary reports of its early clinical trials on 700 cases in 1935. Since then it has been in use as an intravenous anaesthetic agent, having a quick intense action of short duration. Though it is not an entirely ideal anæsthetic (in fact, such an agent has never been produced), it is capable of producing a satisfactory form of anæesthesia which could be considered desirable by the anæsthetist, the surgeon and the patient when judiciously used under proper conditions. The short duration of anæesthesia followed by quick recovery after an intravenous dose of thiopentone-sodium was attributed, in the beginning, to the low stability of the compound attributable to the substitution of oxygen in the 2 position of the barbituric acid ring by sulphur. Owing to its very short duration of action it was designated as an 'ultra short-acting barbiturate to distinguish it from other barbiturates known as 'short-acting' ones, viz. Nembutal, Sodium Amytal, etc.

Werner and his associates (1937), from the result of the experimental work with thiopentone-sodium on rabbits, believed that the drug was very rapidly

detoxicated and concluded that it was safer than the other short-acting
barbiturates, as this compound produced relatively short period of depression
of central nervous system. Moreover, even a slight overdose could be
detoxicated in comparatively short period when the respiration was
maintained. They estimated the Minimum Lethal Dose, Minimum
Hypnotic Dose and the period of sleep produced by a specefic dose of the
thiobarbiturates and Pentobarbitone Sodium.

Drugs.	In Rabbits M.L.D. M.H.D.		Period of Sleep	Period of narcosis produced by 60 per cent of M.L.D.
(1) Thiopentone sodium i.v.	35 mg/kg.	7 mg/kg.	5 minutes.	28 minutes.
(2) Thio-analogue of Amytal i.v.	80 mg/kg.	15 mg/kg.	7 minutes.	45 minutes.
(3) Pentobarbitone Sodium i.v.	45 mg/kg.	10 mg/kg.	21 minutes.	130 minutes.

The results of the experiments showed that, of the drugs tested, thio-
pentone-sodium was the shortest-acting one.

Warner et al. (1937), also believed that the substitution of oxygen in the
2 position of Pentobarbituric acid, by sulphur, resulted in the shortening of
the duration of action, probably due to the decreased stability of thiopentone
in the body of animals.

Gruhzit et al. (1937), studied the pharmacological effects of a number
of thiobarbiturates, compared their effects with those of their oxygen analo-
gues and concluded that the anæsthetic effect of thiopentone-sodium on intra-
venous injection was produced instantaneously and the depth of anæsthesia
was proportional to the amount used beyond the level of the effective dose.
The induction of anæsthesia was always associated with respiratory depres-
sion and the ease with which respiratory centre became depressed by it
constituted a drawback as in the case of other barbiturates.

They also investigated the anæsthetic potency and toxicity of thiobarbit-
urates, using albino rats of both sexes and starving them for 18 hours before
the experiments. The results are shown below :

| Drugs. | In Rats | | | Ratio $\frac{M.T.D.}{M.A.D.}$ |
	M.L.D.	M.T.D.	M.A.D.	
Sod. ethyl (1-methyl-butyl) thiobarb. i.v.	70 mg/kg.	65 mg/kg.	15 mg/kg.	4.3
Sod. Iso-amyl thiobarb. i.v.	160 mg/kg.	150 mg/kg.	20 mg/kg.	7.5
Sod. Diethyl thiobarb. i.v.	210 mg/kg.	200 mg/kg.	100 mg/kg.	2.0

From the result of the investigation in rats and similar comparative studies on the effectiveness and toxicity of thiobarbiturates in rabbits and dogs Gruhzit *et al.* were of the opinion that sodium ethyl (1-methyl-butyl) thiobarbiturate and sodium iso-amyl thiobarbiturate possessed highest anæesthetic potency and of the two, sodium ethyl (1-methyl-butyl) thiobarbiturate was found to be more toxic and twice as effective.

Although the results of the preliminary animal experiments and the early clinical trials showed that thiopentone-sodium injected intravenously acted as an 'ultra short-acting' barbiturate, it became subsequently evident that it behaved as an ultra short-acting drug, when it was administered in a small dose and only for the first initial dose. It, however, lost the property of 'ultra short-action' when given in a long continued intravenous injection (i.e. in a total large dose) or small doses repeated at some intervals, in which case the effect became progressively prolonged. This altered phenomenon of thio-pentone-action brought about a change in the conception of the manifestation of its effects. At one time it was suggested that thiopentone, in all probability, was changed in the body into substances with longer duration of action in a way similar to N-methyl-barbitone (1939). However, it was not possible to show the presence of such a compound in the blood or in the tissues by the then available analytical methods.

By 1950, when accurate and specific methods of detection and estimation of barbiturates in tissues and in body-fluids were evolved, Taylor and his associates (1950), using radio-active (S35) thiopentone in rabbits, observed that the fat depots of the body were capable of taking up the drug in fair amounts. They also noted that the threshold of consciousness (in terms of the concentration of thiopentone) in cats was between 13 to 16 micrograms of thiopentone per gramme of brain tissue and about 10 micrograms per ml. of plasma.

In the same year Brodie *et al.* (1950), working on the distribution of thiopentone in man and laboratory animals, using ultra-violet spectrophoto-metric methods, arrived at conclusions which opened up a new line of approach in the interpretation of the effects of thiopentone in the body. They observed that after the injection of a small dose (viz. 0.4. gram. in normal subjects), the concentration of thiopentone in plasma fell rapidly for a duration of about 15 minutes which was associated with the lightening of anæsthesia and subsequent recovery. The initial rapid fall in the level of the drug in plasma, according to them, was not due to the rapid transformation of thiopentone into ineffective substances, as was previously supposed, but was due to the transference of the drug from the plasma to the tissues in the process of its distribution in the body. Once the equilibrium in the concentration between the plasma and the tissues was established, the rate of fall in the concentra-tion became slower, and was said to represent the rate of metabolism of the drug. They also found that the greater proportion (in terms of percentage) of the administered thiopentone became deposited in the fat depots. As regards the metabolism of thiopentone, they observed that it was completely changed into some other compounds and only 0.3 per cent of the total dose was excreted unchanged in the urine. They isolated one of the metabolic products, which they named thiopentone carboxylic acid.

This compound was considered to be an oxidation product of one of the methyl groups in the alkyl side chain of thiopentone. It was excreted in the urine to the extent of about 10 to 25 percent of the total dose and was devoid of anæsthetic effect in dogs and mice. In this connection, it was interesting to note that Maynert and Van Dyke (1949), during the study of metabolism of Pentobarbitone, detected in the urine a metabolite which they described as hydroxy-pentobarbituric acid. This compound also possessed no pharmacological effects.

Shideman and Gould (1951), studying the distribution of thiopen-tone in rats, at different intervals an intravenous injection of 30 mg. of thio-pentone-sodium per kilogram of body weight, found that the equilibrium in the concentration of thiopentone between blood, brain and liver occurred within one minute after the injection, whereas adipose tissue took one to two hours to attain it. By the time the thiopentone concentration reached its maximum limit in adipose tissue, it was about 6.6 times and 3 times more than that in blood and liver respectively.

They also observed that the rate of metabolism of thiopentone in rats was on an average about 10 per cent of the administered dose, per hour, up to the first six hours, after which it became slower.

They also noted the important role played by the liver and the kidneys in the metabolism of this drug. The partial removal of the liver (70 per cent) resulted in the conversion of only 27 per cent of thiopentone with a period of 12 hours as compared with approximately 90 per cent in normal animals. In animals with bilateral removal of the kidneys, only 58 per cent of the drug was metabolised in the next 12 hours after the administration of thiopentone.

Brodie and Burn (1952), presented a new interpretation of the action of thiopentone under different dosage levels based on the knowledge of the distribution of thiopentone in the body. The difference in the behaviour of a small intravenous dose and a large or repeated small doses at certain intervals, was, according to them, due to the variation in the concentration of thiopentone in plasma. They explained that after the intravenous injection of a small dose of thiopentone-sodium its concentration in the plasma fell very rapidly, in the process of its distribution, resulting in the quick recovery of the subject from anæsthesia but once the equilibrium in the concentration of the drug in different tissues was established, the decline in the plasma concentration became very slow. The early rapid fall was considered to be due to its rapid distribution in the tissues (with the exception of fat where its entry was slow) and consequent lowering of its concentration in the plasma below the anæsthetic level associated with the quick recovery of the subject from anæsthesia.

After intravenous injection of a large dose or repeated small doses of thiopentone-sodium, its concentration in the plasma remained much above the anæsthetic threshold level even after the attainment of equilibrium in the concentration in different tissues including fat. As the actual rate of transformation of thiopentone into ineffective metabolities was slow, a large amount of the drug remained in the plasma, resulting in the producting of a longer period of anæsthesia in the treated subject.

Brodie *et al.* (4) also observed that the body fat played an important part in controlling the duration of the action of thiopentone by taking it up in considerable amounts. They also found that thiopentone readily passed through the 'blood-brain barrier' and became uniformly distributed throughout the various parts of the brain without showing any tendency for selective localisation.

Various other workers e g. Gould and Clark (1953), Philip *et al.* (1952), etc. also expressed identical views concerning the role of the body fat in regulating the thiopentone action as laid down by Brodie and Burn (3).

Brodie (1952) studied the relationship between the clinical effects of thiopentone and its concentration in the plasma in men. Subjects receiving

4 grammes of the drug were unconscious for 4 to 6 hours and even after regain-
ing consciousness remained in a state of drowsiness for period of over 10 hours,
during which time the plasma level of the drug showed a slow fall. In men,
two hours after the administration of 1 to 4 grammes of thiopentone-sodium,
the rate of decline in the concentration in the plasma was found to be
between 10 to 15 per cent of the dose per hour; this was considered by him
as the index of the true metabolic rate of thiopentone in the body.

In dogs, Brodie (1952), noticed that the maximum concentration of thio-
pentone in plasma, brain and liver was reached immediately after the intra-
venous injection, in muscles a short while later.   The level of drug in these
tissues dropped rapidly in an identical manner for a period of about one hour,
after which time the rate in the fall of concentration became progressively slower
for the next $2\frac{1}{2}$ to 3 hours. In fat, however, the concentration of thiopentone
which was negligible at first, showed a rapid rise during the first hour,
gradually reaching the maximum level in about $3\frac{1}{2}$ hours, after which it
declined slowly. From these observations he was of the opinion that thiopen-
tone was not quickly destroyed but remained in relatively stable form in the
body. He also studied the distribution of other 'ultra short-acting' barbi-
turates, such as Surital, (5 Ethyl 5 (methyl-butyl) 2 thiobarbituric acid :
Kemithal, 5 (2-3 cyclohexenyl) 5 allyl 2 thiobarbituric acid; and Hexobarbi-
tone (N methyl-cyclohexenyl-methyl barbituric acid) in dogs. He found that
these drugs were distributed roughly in the same way as thiopentone with
some localisation in fat depots some time after their administration.

This led him to conclude that these so-called 'ultra short-acting' thio-
barbiturates behaved as such only after a small dose, owing to their rapid
distribution in the various tissues and their high localisation in the body fat.
Brodie (1952), also observed that, the brain in spite of its high lipid content,
showed only a slightly higher concentration of thiopentone than that of
plasma, suggesting that it was only the neutral fat, that was capable of taking
up considerable amounts of the drug. Thiopentone was found in plasma in
two forms, a free diffusible form to the extent of about 25 per cent and the
rest in a form bound to the plasma proteins.

Shideman *et al.* (1953), also noticed in laboratory animals that while
most of the tissues showed maximum concentration within one minute
after administration of thiopentone, the body fat took one to two hours in
rats, 4 hours in dogs and $1\frac{1}{2}$ to 2 hours in man, to attain the same. They
found that the rate of metabolism of thiopentone was approximately 10 per
cent of the administered dose per hour, during the first 6 hours, after which
it became still smaller. Thus their findings were almost the same as those of
Brodie (1952).

Brodie *et al.* (1953), compared the duration and the plasma concentration of thiopentone and pentobarbitone by injecting into normal men 12 mg. of these drugs per kilogram body weight. They observed that the duration of anæsthesia produced by the dose of thiopentone-sodium and pentobarbitone-sodium were 20 to 40 minutes and $1\frac{1}{2}$ to 3 hours respectively. The plasma concentrations of these drugs showed a rapid fall at the beginning, but became slower afterwards, when the diffusion equilibrium was established.

The slow fall in the concentration of the drugs, which represented the rate of metabolism, was found to be, an average, 15 per cent for thiopentone and 5 per cent for pentobarbitone, thus explaining the difference in the duration of their action. Pentobarbitone, was found to be distributed roughly in the same pattern as thiopentone in most of the tissues except the body fat, where it was not extensively localised like thiopentone. The fat/ plasma concentration ratio for pentobarbitone was found to be only 1/6 as compared with the corresponding ratio for thiopentone which was as high as 6/10.

They also studied the partition ratio of pentobarbitone and thiopentone in vitro, using a buffer at pH 7.4 and pea-nut oil and observed that while most of the thiopentone was in the oil phase, only 50 per cent of pentobarbitone was in the same, showing its relatively low affinity for fat.

It was also interesting to note that the replacement of oxygen in the 2 position of the barbituric acid ring by a sulphur atom, altered the physico-chemical character of the substance and also brought about changes in the pharmacological effects in the body.

The information gathered from the literature clearly showed that thiopentone was not quickly destroyed in the body; the shorter period of its action after a small dose was due to its rapid fall in concentration in the process of diffusion into various tissues and its special localisation in fair amounts in the body fat. The body fat thus played an important role, regulating the duration of its action under different dosage levels.

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