REPORT OF SOCIETY MEETING

THE USES AND ABUSES OF THIOPENTONE*

BY

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"It is not the fault of the drugs and methods concerned that a syringe and a hollow needle are so susceptible to clinical abuse." (Gillespie, 1950)

THIOPENTONE has been described in such varying terms as a "godsend" and "too dangerous a drug for routine use". Published figures show that in some centres in America it is used in between one-quarter to one-half of all anaesthetics. In Britain thiopentone is more popular and it is safe to say that an intravenous thio-barbiturate is used for the induction of anaesthesia in more than three-quarters of all cases. In view of Gillespie's statement and our ever increasing knowledge of the action of thiopentone, it is timely to consider some of the uses and abuses of this commonly used drug.

USES

Adriani (1946) has admirably outlined the occasions when thiopentone should be used in anaesthesia:

(1) As an anaesthetic for very brief surgical procedures or induction of anaesthesia.

(2) Basal narcotic to supplement nitrous oxide or other more powerful drugs in low concentrations, or in combination with analgesics.

(3) Anti-convulsant.

(4) In hypnotic doses combined with spinal or local anaesthesia.

In as far as the word "anaesthesia", as conceived by Oliver Wendell Holmes, refers to loss of sensation, thiopentone is a satisfactory anaesthetic. Today the more commonly accepted meaning of this word is a state which will permit surgical procedures to be performed without any reaction from, or any dangers to the patient. While thiopentone is one of the best hypnotic drugs known, by modern standards it is an unsatisfactory anaesthetic agent when used alone. It possesses very little analgesic power and the margin between the dose required for relaxation and that which will result in apnoea is very small.

ABUSES

Many of the complications which have followed the administration of thiopentone can be attributed to the terms "short-acting" or "ultra-short-acting" by which it is described in most of the standard books on anaesthesia or pharmacology. A short period of narcosis generally follows the administration of small doses, but large doses may be followed by prolonged sleep. It is slowly broken down in the body, and a cumulative effect is evident if a dose is repeated within thirty hours. Impairment of mental activity often persists for many hours after the administra-
tion of thiopentone and the deleterious effects on the cardiovascular system or the liver may last for an even longer period of time. A more descriptive term for thiopentone would be “rapidly-acting diffusible” barbiturate.

Only in very special circumstances should thiopentone be used as the sole anaesthetic, except for very minor procedures. No one would use it alone for major procedures such as gastric resection or the repair of herniae, but it is not uncommon to find it being the sole agent for cystoscopic examinations taking half an hour or more. More anaesthetic is required where the stimulus is strong, as for example during distension of the bladder, or where profound relaxation is required as in reduction and plastering a fracture. Large doses are often followed by delayed recovery. The patient may appear to be lightly anaesthetized when the stimulus is present, but on return to the ward may lapse into deep unconsciousness and be exposed to all the dangers of respiratory obstruction.

Thiopentone is a direct cardiac depressant and, while the intact healthy cardiovascular system can accommodate itself to the effects of small doses, one has no way of telling whether the damaged myocardium can stand up to large amounts. The effects on the cardiovascular system depend on, among other factors, the absolute concentration of the drug in the blood stream. While rapid injection produces a short period of good relaxation, the high concentration of the drug has a profound effect on the blood pressure and cardiovascular system in general. The safety of thiopentone is decreased enormously by a rapid rate of injection.

Insufficient use is made of dilute solutions (2–2.5 per cent). With a dilute solution the rate of injection cannot be so quick, the drug will be more diluted in the blood stream and the effects on the heart will be less. It is interesting to note that no severe damage to a limb has been reported following the intra-arterial injection of a 2.5 per cent solution of thiopentone. This does not mean that the precautions taken to avoid this catastrophe when using 5 per cent solutions should be relaxed with the more dilute solutions. Less severe damage is also likely to follow the extravenous injection of a dilute solution of thiopentone.

Judged by views expressed in the literature there seems to be an improper understanding of the contra-indications to the use of thiopentone and the factors which render patients sensitive to the drug. In table I are listed the contra-indications

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<tr>
<th>Contra-indication</th>
<th>No. of appearances in literature</th>
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<tr>
<td></td>
<td>Absolute</td>
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<td>Myocardial weakness</td>
<td>16</td>
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<tr>
<td>Liver dysfunction</td>
<td>14</td>
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<td>Factors interfering with airway</td>
<td>16</td>
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<tr>
<td>Gross respiratory disease with dyspnoea</td>
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<td>Oedema of glottis</td>
<td>16</td>
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<td>Shock</td>
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<td>Renal disease</td>
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<td>Respiratory obstruction</td>
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<td>Children under 10</td>
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<td>Feeble elderly patients</td>
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<td>Severe anaemia</td>
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<td>Sepsis</td>
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<td>Diabetes</td>
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<td>Advanced malignant disease</td>
<td>3</td>
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which appear most frequently in 28 publications on the drug during the past 10 years. In all, 29 conditions were listed in which at least one writer advised against the use of thiopentone. One author lists idiosyncracy to the drug as a contra-indication to its use, but fails to mention how this condition can be detected before the induction of anaesthesia.

It is not a very great exaggeration to say that the absence of suitable veins is the main contra-indication to the use of thiopentone. It is better avoided in patients suffering from porphyria and Addison’s disease, or in severe uraemia. Most of the conditions listed in table I result in patients being sensitive to thiopentone, but it can be safely administered in reduced dosage. Another series of conditions stated as “contra-indications” can be grouped under “inadequate airway”, whether this is present before induction of anaesthesia or is liable to occur during the operation. These conditions or procedures are no more a contra-indication to the use of thiopentone than to any other general anaesthetic agent. If a good airway is established before the induction of anaesthesia or steps taken to see that it will remain patent during the operation, then thiopentone can be administered with safety. As an example of this is the report by Williams and Guribruck (1943) of twenty administrations of the drug to patients suffering from Ludwig’s angina in which no fatalities attributed to its use occurred. Where the subject was using the accessory respiratory muscles, an endotracheal tube was passed under topical anaesthesia or a tracheotomy was performed before the induction of anaesthesia.

Liver or kidney dysfunction are the next most commonly mentioned contra-indications to the use of thiopentone. Recovery from small doses occurs by diffusion to non-nervous tissues and is independent of the liver, but with large doses the detoxicating mechanism is important in recovery and prolonged narcosis may occur in the presence of severe hepatic dysfunction. Apart from this, it is not advisable to administer large doses of a hepatotoxic agent to a patient with an already damaged liver. The kidney only excretes minute doses of unchanged thiopentone and there is no evidence that its breakdown products, whose excretion may be impaired in kidney disease, have any narcotic properties. However, uraemia which is a common accompaniment of renal disease is one of the most important factors met in clinical practice which prolongs narcosis with thiopentone.

Myocardial weakness is a relative contra-indication to the use of thiopentone. In severe cases it is better to avoid the use of the drug if possible, but where necessary small doses of a dilute solution can be injected very slowly. In this type of case the maximum use should be made of non-toxic adjuvants, especially nitrous oxide-oxygen and relaxants.

The ineffective use of nitrous oxide-oxygen as an adjuvant to thiopentone is only too common. One frequently sees it serving only as a vehicle for carrying a volatile supplementary agent, and playing no major part in the anaesthetic sequence. By using a close-fitting face mask or a cuffed endotracheal tube with high flows of the gas immediately after the induction of anaesthesia a concentration of nitrous oxide in the blood sufficient to ensure
narcosis is soon obtained with a corresponding reduction in thiopentone requirements. Pre-oxygenation before the administration of thiopentone also makes any subsequent administrations of nitrous oxide-oxygen more easily effective. It also permits a longer period of respiratory obstruction should any unforeseen accident occur during the induction period.

There is no justification of the use of thiopentone in outpatients if the patients are allowed to leave hospital unaccompanied. Return of consciousness does not mean that the powers of thought and reasoning are normal; subjects may perform automatic actions, such as walking along a quiet street, but when confronted with a situation which requires a certain amount of quick thinking, such as crossing a busy street, an accident may happen. Further complications may arise from the presence of a period of retrograde amnesia which often follows the use of thiopentone.

The mixing of thiopentone with muscle relaxants, and especially the continued use of dilute solutions of this mixture is a practice which is without any scientific basis. The two types of drugs are broken down by different means and conditions which render patients sensitive to thiopentone often cause resistance to relaxants. In this case an overdose of narcotic can be very easily given. At different periods during an operation either more relaxation or deeper narcosis is needed and, with the use of thiopentone-relaxant mixtures, one cannot be produced without the other.

Mixtures of thiopentone and analeptics are likewise not advised. With Lundy’s (1935) mixture of thiopentone and nikethamide one is administering two myocardial depressants to prevent respiratory depression from one of them. Lockett’s (1947) suggestion of mixing thiopentone with d-oxyephedrine (Methedrine) also seems unwise, since the latter drug does not effectively counteract the vasodilatation caused by thiopentone, but only “flogs” the heart depressed already by the barbiturate.

The safe administration of thiopentone necessitates a proper appreciation of the pathological conditions which result in sensitivity to it. In anaesthetic practice “shock”, anaemia and uraemia are the most important clinical entities in this respect. One has only to recall Halford’s (1943) report of its indiscriminate use at Pearl Harbour to appreciate the sensitivity that occurs in injured patients. An “ideal form of euthanasia” was the most complimentary description that he could give to the use of intravenous anaesthesia. Later and more extensive reports from all over the world lead to the conclusion that used judiciously in minimal doses, thiopentone is not in fact necessarily contra-indicated in such patients.

Severe anaemia prolongs thiopentone narcosis (Dundee, 1952), this effect being particularly marked when the haemoglobin level is less than 60 per cent of normal (Haldane standard).

The duration of narcosis is particularly sensitive to alterations in the blood urea level (Dundee and Richards, 1954). With a severe degree of uraemia extremely small amounts of thiopentone will lead to prolonged sleep, and the drug is better avoided.

Other conditions which result in decreased tolerance to thiopentone include
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malaria (where anaemia and liver dysfunction may both be present), malnutrition, myasthenia gravis and intestinal obstruction. Where the drug is used to control the convulsions which follow overdose of a local anaesthetic, the dosage should be kept to a minimum to avoid prolonged narcosis. Whether the latter common result is solely due to the thiopentone is open to question.

In conclusion it is interesting to see how thiopentone stands in relation to the requirements of a perfect anaesthetic as outlined by Morrin at the annual meeting of the British Medical Association in 1933, the year before its discovery.

(1) “Administration should be accomplished without discomfort to either the young or old patient and without complicated apparatus.” This can be done with thiopentone, but to use the drug without means of inflating the chest or controlling the airway is asking for trouble.

(2) “Induction must be agreeable and the anaesthetic should not have any deleterious effects on the respiration or circulation.” Thiopentone is both a respiratory depressant and myocardial poison although these effects can be minimized by proper administration.

(3) “Blood pressure should be maintained at a normal level throughout.” One cannot guarantee this, but again the method of administration is of the utmost importance.

(4) “Elimination should be rapid without producing harmful effects on the hepatic, renal or pulmonary tissues.” Clinically thiopentone is short-acting after small doses but pharmacologically it is long-acting, irrespective of the dose.

(5) “The anaesthetic effect should be induced gradually and it should be at all times under control.” This depends on the method of administration.

(6) “In addition to securing sensory paralysis, complete muscular relaxation should be rapidly and safely obtained.” To attempt this with thiopentone is to increase its toxicity out of proportion to the advantages gained.

The writer in 1933 concludes: “The perfect anaesthetic awaits discovery . . . the anaesthetist has welcomed the products of the analytical chemist with faith and hope.” We shall never find the ideal anaesthetic; rather we shall aim at the ideal anaesthetic combination. However, we owe a lot to the “analytical chemist” for producing a drug, which, if its limitations are appreciated and if it is handled properly can be one of the safest agents available today.

REFERENCES


Halford, F. J. (1943). Anaesthesiology, 4, 47.


DISCUSSION

Dr. G. A. Eason remarked that it was gratifying to find that his clinical impressions of the contra-indications to the use of thiopentone agreed with the scientific evidence presented on the subject. He asked Dr. Dundee if he had any views on hexobarbitone. In his experience it was very useful to “cover” local or spinal analgesia. It is less depressant to respiration, less irritant to the tissues and can be given in a higher concentration.

Dr. H. Garry also voiced agreement with the views expressed on thiopentone. For a long time after its introduction she continued to use hexobarbitone and wondered if it had any place in modern anaesthesia.

Dr. G. J. Rees commented on the remarks concerning the rate of injection of thiopentone. The opener had criticized rapid injection of the drug, but there are equally great dangers associated with too slow an injection. Because of the rapid diffusion of the drug larger doses are required to produce sleep, and the use of large doses is one of the things that Dr. Dundee was criticizing. The term “slow injection” is misleading, and a better description would be a “moderate rate” of injection.

He also doubted whether the absence of reported losses of limbs following intra-arterial injection of 2.5 per cent solution of thiopentone was sufficient evidence to support the view that this concentration could be injected into arteries without danger. One must adopt all the known precautions to avoid intra-arterial injection of thiopentone, irrespective of the concentration of the drug used.

Dr. J. E. Riding expressed the view that thiopentone was the prime factor responsible for regurgitation when it was used in combination with a muscle relaxant in the presence of a full stomach. Morton and Wylie (1951) seemed to blame muscle relaxants for the regurgitation, but O’Mullane (1954) has shown
that the cardiac sphincter is completely competent during full muscular paralysis.

Dr. J. Davidson agreed that it was a dangerous procedure to administer thiopentone to patients who were allowed to go home unaccompanied. He quoted a case in which temporary amnesia occurred following its use.

Dr. S. Lipton suggested that the contra-indications to the use of thiopentone depended on the administrator rather than on the drug itself. In his opinion sepsis below the diaphragm was a contra-indication. Should the patient hiccup the abscess may burst through into the pleural cavity.

The President (Dr. G. R. Hopper), Drs. J. B. Hargreaves, J. M. Marchant, R. J. Minnitt, and B. Solomon, also took part in the discussion.

REFERENCES

ANNUAL MEETING OF THE BRITISH AND CANADIAN MEDICAL ASSOCIATION, TORONTO

The programme for the Section of Anaesthetics at the above meeting, under the Presidency of Sir Robert R. MacIntosh, will be as follows:

Wednesday, June 22.
3.00 p.m. “Antidotes to Curarizing Drugs.” A. R. Hunter, M.D., F.R.F.P.S.G., F.F.A.R.C.S.
4.00 p.m. Round Table Discussion of Questions to be submitted from the Meeting. Chairman: B. C. Leech, O.B.E., M.D., C.M., F.F.A.R.C.S.

Thursday, June 23.
2.00 p.m. “Chlorpromazine.” D. A. Buxton Hopkin, M.D., F.F.A.R.C.S.
3.30 p.m. “Considerations on Recovery Rooms.” Fernando Hudon, M.D., F.R.C.P.(C), F.F.A.R.C.S.