NEWER ANAESTHETIC AGENTS IN CHILDREN, WITH SPECIAL REFERENCE TO TRICHLORETHYLENE AND KEMITHAL

C. R. STEPHEN, M.D.C.M., D.A.,† AND H. M. SLATER, M.D.

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It has been postulated that the ideal anaesthetic is one which is safe and complete, and from which the subject can recover quickly. It should be associated with the minimal amount of psychic trauma during and after induction, and be followed by the least possible number of postanaesthetic and postoperative complications (1). With such ideals to strive for, the anaesthetist of this day is not always happy in carrying on his work with the agents and combinations of drugs now available. He realizes certain shortcomings in the field of anaesthesiology, and is ready to evaluate new narcotic agents as they are presented by the pharmacologist.

The modern trend in anaesthesia is toward the employment of small doses of various drugs which may be given by several routes and excreted in different ways. This “balanced anaesthesia,” as it is called, is another method of attempting to obtain the ideal. The argument is presented that small amounts of many agents are less toxic to the patient than a large amount of a single agent. The safety factor to the patient is widened, and the balanced anaesthesia induced keeps him close to the physiologic normal during operation. These trends are a healthy sign in the specialty. They indicate that the anaesthetist, unlike his patients, is not sleeping quietly, content with the knowledge which has been accumulated. He is looking forward and upward, in the realization that only the fringe of potential possibilities has been explored.

† From the Department of Anaesthesia, Children’s Memorial Hospital and McGill University, Montreal, Canada.

† Associate Professor of Anaesthesiology, Duke University School of Medicine, Durham, North Carolina.
TRICHLORETHYLENE

The first of the newer anaesthetics to be considered is trichlorethylene.† This drug was first employed as an anaesthetic agent in the human being in the United States in 1934 (2, 3). This is rather surprising, in view of the fact that most of the knowledge concerning its use has been relayed to us from England. There are perhaps two reasons to explain this apparent anomaly. The first is a report from the Council on Pharmacy and Chemistry of the American Medical Association, which appeared in 1936 (4). In this report it was stated that the available evidence does not justify acceptance of trilene as an agent for general anaesthesia. It was suggested that more investigation should be carried out with reference to the toxicity of decomposition products and that there should be substantiation of its clinical value from other sources. The second deterrent to its popularization in America came in 1943 when Waters, Orth and Gillespie (5) in Madison published an analysis of the cardiac arrhythmias seen with this drug. They concluded that trichlorethylene was “capable of producing undesirable effects on the automaticity of the heart.” This statement from such an influential centre is proving still to be a damper to the utilization of this agent in North America.

In England, the use of trichlorethylene as an inhalation agent was reported and recommended first in 1941 by C. Langton Hewer (6). Since his authoritative publication, its employment in Great Britain has spread rapidly and widely, until today it is estimated that well over one million patients have been anaesthetized with the vapour of trichlorethylene. In England its utilization is on the increase (7). On this continent, and especially in Canada, interest in this agent is being revived. One cannot disregard any drug in anaesthesia which one investigator reports using 40,000 times without serious mishap (8).

Chemistry.—In appearance trichlorethylene is a colourless liquid with a pleasant, fruity, chloroform-like odour. Its boiling point is 87 C. The American product, “trelene,” is colourless, but the English product “trilene” is coloured with waxoline blue, 1:200,000, to distinguish it from chloroform. To the latter product is added also traces of thymol which act as a preservative. Both these preparations are pure and suitable for inhalational use. It is important to emphasize this factor of purity because the agent as employed commercially has certain impurities or degeneration products which, if inhaled over periods of time, may produce giddiness, vomiting, optic neuritis or debilities of the cranial nerves. For this reason, only specially prepared trichlorethylene should be used for anaesthesia.

Moreover, care should be taken not to anaesthetize patients with trilene which has been left exposed to air and sunlight for more than

† We are indebted to Imperial Chemical Industries, London, England, for supplies of this drug.
three or four days. The drug will oxidize in such situations, with the possible production of dichloracetyl chloride, carbon monoxide, hydrochloric acid and phosgene. It may be the first-named of these breakdown products which has been responsible for the nerve palsies in industry.

In chemical structure trilene is nothing more nor less than ethylene with three hydrogen atoms replaced by chlorine. Its properties, however, are such that it more closely resembles its methane analogue, chloroform. In potency it is on a par with, if not greater than, chloroform. It requires a concentration of only 0.75 to 1.25 per cent in the inhaled atmosphere to produce surgical narcosis (9). These are figures which command the respect and restraint of every anaesthetist employing the drug. Recent work indicates that trilene is not eliminated entirely through the lungs. A small portion of its undergoes metabolism in the body to trichloracetic acid. This compound is apparently innocuous to the body and is excreted in the urine slowly over several days (10).

Before passing along to pharmacologic reactions, three other points should be stressed. The first is that trichlorethylene must never be used in a closed system with soda lime. There is a chemical reaction between these two substances with the production of dichloracetylene. This latter compound is definitely toxic to the nervous system and has resulted in serious nerve lesions and death (11). The second relates to the fact that this is a noninflammable agent, and may be used with safety in the presence of a cautery. The other point of lesser significance is that trilene will react with the rubber parts of an anaesthetic machine, resulting in their decomposition.

Pharmacology.—Before its adoption by the anaesthetic fraternity, trichlorethylene was thought to exert some peripheral analgesic effect of a specific nature on structures such as the trigeminal nerve. Krantz and his co-workers, however, have indicated that the pain-relieving properties of this agent are central in action, possibly at the level of the basal ganglia (12). The most outstanding characteristic of this compound in clinical anaesthesia is the analgesia which it produces. Its narcotic power is not great. Indeed, there are cases on record in which resistant individuals, such as alcoholics, have successfully opposed the attempts of the anaesthetist to depress them to the third stage of anaesthesia (3). We have personal knowledge of one such patient. Moreover, it is well-nigh impossible to produce narcosis sufficiently profound to be accompanied by muscular relaxation. There seems little doubt that its present popularity in some quarters stems primarily from the potent analgesia provided.

Effects on respiration are sometimes disturbing. Tachypnoea is a frequent occurrence if one tends to push the administration of the drug. The rapid shallow respirations are believed to be the result of increased sensitisation of the nerve endings in the lung which partici-
pate in the Hering-Breuer reflex. This disturbance can be overcome by reducing the concentration of the drug or by changing to another agent (13).

It is the alterations in the cardiovascular system accompanying the inhalation of trichlorethylene which have aroused the greatest controversy regarding its use. Everyone agrees that it markedly increases vagal tone (14), thereby inducing a definite bradycardia. By the same virtue it increases the irritability of vagal reflexes and thus allows various types of cardiac arrhythmias to be established. At this point clinical opinions have been divided into two camps. The first group claims that the arrhythmias are not dangerous to the patient and probably of no greater significance than those seen with cyclopropane (7). The second group warns that the cardiac irregularities may be serious (15), and to prove it, show electrocardiographically the development of multifocal ventricular tachycardia, the precursor of ventricular fibrillation, in 5 out of a series of 14 patients (9, 5, 16). In rebuttal, the first group claims that the reported cardiac deaths with this agent are extremely rare (17). There is common agreement, in any event, that epinephrine should never be used with trilene.

Good evidence has been accumulated that metabolism is disturbed but little with this agent. According to the cephalin flocculation test, liver function is disturbed less than with ether (18). There is little rise in the blood sugar, and animals subjected to deep anaesthesia for two hours have shown no specific changes in the liver cells (2). Clinically, renal function is not altered to any significant degree (9).

From much of the foregoing, one may conclude that because of the deleterious effects on the respiratory and cardiovascular systems, the value of this agent is open to question. Experience derived from its employment in over 600 children, however, leads one to believe that it does have some place in the armamentarium of anaesthetic drugs.

**Technique of Administration.**—Because of the high boiling point already mentioned, trichlorethylene does not volatilize sufficiently to be employed on the open drop mask. Therefore in the series under consideration the liquid has been vaporized by having nitrous oxide and oxygen pass over it in greater or lesser amounts as required. The agent is placed in the standard Heidbrink wick ether bottle or in the small amber vinethene bottle adaptable to Foregger machines. Since very small amounts of the agent are used, it is never necessary to put more than 1 ounce into the bottle. A partial rebreathing technique is employed, using high flows of gases to prevent accumulation of carbon dioxide in the system. The child is usually rendered unconscious by blowing pure nitrous oxide over the face with the mask held some distance off the face. The mask is gradually lowered, and as it makes contact with the face oxygen is flowed in to prevent hypoxia. At the same time a small amount of trilene is turned into the circuit. The flow of gases is adjusted so that nitrous oxide and oxygen are given in
a 75 to 25 ratio and sufficient trilene is used to produce the required amount of analgesia. Such an induction is pleasant and rapid. Although premedication is of sedative value, it is not necessary with this combination as trilene does not stimulate the production of salivary secretions. Very rarely is any excitement stage seen during such inductions. In children it is never necessary to turn the indicator on the Heidbrink ether bottle over the 3 or 4 mark to obtain satisfactory operating conditions. After three to five minutes, adequate anaesthesia can be maintained with the indicator at the 1 or 1.5 mark. This is to be expected because of the low volatility of the drug. It is always possible to use at least 25 per cent oxygen in the inhaled atmosphere. With induction and maintenance as described, it is possible to perform dental extractions, circumcisions, reductions of fractures, orthopaedic manipulations, incision and drainage of abscesses and other short procedures with a light degree of narcosis and yet with excellent analgesia. A diminution in the oxyg/.1 flow to achieve better operating conditions is never necessary. The patients awaken completely within two to five minutes of the time the mask is removed. Nausea and vomiting are extremely rare, unless too much trilene has been given. If an out-patient, the child can walk out of the hospital within twenty minutes. There are few other combinations in present use where such is possible.

One will properly ask, "What about the harmful effects which have been mentioned?" To prevent the possibility of danger from decomposition products, trilene is discarded after being in the bottle for four to five days, and the wick is thoroughly dried. Tachypnoea can be avoided by not trying to make the agent perform feats for which it is not meant. For example, one should not try to obtain abdominal muscular relaxation by increasing its percentage in the inhaled atmosphere. Cardiac arrhythmias have been extremely uncommon clinically when the drug has been used in the manner just described. Bradycardia is frequent and indeed is to be expected, but occasional extrasystoles have been the only irregularities noted in children. Possibly the paucity of arrhythmias seen is owing to the fact that the cardiovascular system in children possesses an inherent automaticity not evident in adults.

There have been two experiences which indicate that this agent should not be used in children under 2 years of age. In one infant 5 months old and in another of 12 months, generalized clonic convulsions began suddenly after about ten minutes of anaesthesia. Oxygen was administered immediately under pressure, and no difficulty was encountered in inflating the lungs. In each case the convulsions ceased after one minute and spontaneous respirations were resumed in another two minutes. Neither infant suffered any sequelles. Convulsions with trilene have been reported only once in the literature (19). This complication is the only serious one which has been encountered, either during or after anaesthesia, in the entire series.
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It is not suggested that trichlorethylene will replace other anaesthetic agents which are now in use, but any drug which provides a pleasant induction, almost unbelievable analgesia and a rapid awakening devoid of nausea and vomiting is bound to be a useful adjuvant. In addition, any agent which is noninflammable is an asset to the operating room. As long as the anaesthetist respects its potency, and therefore is conscious of its hazards, he will find it a useful agent to add to his armamentarium.

Kemithal

The statement is found commonly in textbooks that ultra-short acting barbiturates should not be given intravenously to children under 10 or 12 years of age. The reasons given are that these drugs are too depressant to the respiratory centre, they are somewhat unpredictable in their action and once administered they cannot be withdrawn. These arguments are all true, and yet it has been found that these ultra-short acting barbiturates can be safe and are proving very useful in anaesthesia for children. In the last two years these agents have been used intravenously in over 1000 patients coming to the operating room. No serious complications have resulted from the use of these compounds.

Proper usage of intravenous barbiturates implies realization of the fact that these drugs are primarily hypnotics, and exert an analgesic and anaesthetic effect only by the depth of hypnosis induced. Therefore, except in rare instances, their employment should always be combined with some additional agent which has analgesic, narcotic or relaxant properties. It is in such a form of balanced anaesthesia that they have been utilized with success in children.

Until a few months ago pentothal was the only ultra-short acting barbiturate employed. When used in its proper manner, this agent was quite satisfactory, but frequently produced sufficient depression of respiration to warrant assisting the child’s breathing. The amount of depression involved might not be considered important in the adult, but in the child even a small degree of anoxia and its associated carbon dioxide accumulation is not well tolerated. Then a supply of kemithal § became available, and because it was reported to depress respiration less than pentothal, we thought it was worth a trial (20, 21, 22). To the present time we have employed it in 300 cases and are coming to the conclusion that in children it has definite advantages over pentothal.

Chemistry.—Kemithal is a pale yellow powder which dissolves easily in distilled water. In solution it has a pH of 10.6, which is the same as that of pentothal. It has an odour distinctly similar to that emitted by a certain much-respected animal who carries black and

§ Again may we thank Imperial Chemical Industries, London, England, for trial supplies of this agent.
white stripes. The patient, however, does not appear to taste it! A 5 per cent solution will begin to precipitate if left in a syringe for longer than four days. Up until that time it has been used without ill effect. Pentothal in 2.5 per cent solution will remain unprecipitated in a syringe for ten days. In chemical structure kemithal bears some resemblance to evipal and also to pentothal. Many of its properties appear to be a modification of one or the other of these compounds. It is broken down almost completely in the body in about the same time as pentothal.

Pharmacology.—It has been shown in mice that the ratio of the median hypnotic dose to that of the median lethal dose is almost twice as high for kemithal as it is for pentothal. In other words the safety margin of kemithal is considerably higher. Although results in mice are not directly applicable to human beings, such information is of significance in evaluating the drug.

Technique of Administration.—For injection in children a 5 per cent solution is usually employed. This is equivalent in potency of action to 2.5 per cent pentothal. It has been estimated that gram for gram kemithal is about one-half as powerful as pentothal and about equal in strength to evipal. This decreased potency in itself is of some advantage in children. When curare and kemithal are mixed in the same syringe, according to the technique described by Knight and Baird for pentothal, an opalescent colloidal-like solution results. This can be injected intravenously with safety, and produces satisfactory relaxation and hypnosis. Extravascular injection of the 5 per cent solution has occurred accidentally on several occasions, but in no instance has there been any evidence of irritation of the involved tissues.

Induction with this agent is similar to that seen with pentothal. It is rapid, pleasant, not associated with any unpleasant taste in the mouth and not accompanied by an excitement stage. A good many children are terrified of needle punctures, however, and in these unconsciousness may be produced with nitrous oxide prior to the puncture. The remarkable difference between pentothal and kemithal during induction is that respiratory depression is much less pronounced with kemithal, and apnoea is rarely seen. For example, we have given 1.0 Gm. of kemithal to a normal-sized boy of 4 years over a period of two minutes without alarming depression of the respiration. In the same boy 0.25 Gm. of pentothal produced apnoea which was followed by respirations so shallow that manual aid from the anaesthetist was necessary. This lack of respiratory depression with kemithal has led us to evolve a variation of technique whereby a large dose of the intravenous agent is given at the beginning of operation, and then anaesthesia is continued by giving nitrous oxide and oxygen in a 75 to 25 ratio. Seldom is it necessary to give more of the intravenous drug for at least an hour. At the conclusion of the operation the patient usually wakens while still on the table.
We have been able to add a certain amount of objectivity to the clinical impressions that respiratory depression is less with kemithal by using the oximeter to observe the arterial oxygen saturation in some patients. The arterial oxygen saturation always falls to a greater degree with pentothal than it does with equivalent doses of kemithal.

Laryngospasm during induction in uncommon with kemithal. We have seen it only twice in 300 cases. Perhaps the fact that all the patients received morphine and scopolamine preoperatively aided in reducing the incidence of spasm, but it is our clinical impression that spasm is seen more frequently with pentothal, even when adequate premedication is given. Likewise, fairly good relaxation of the jaw accompanies administration of kemithal in children. In a number of cases intubation was possible without the addition of other agents. Such a procedure, however, is not practiced or recommended as a routine.

Clinical Results.—Kemithal has been employed in a large variety of operative procedures. Most frequently it has been used in conjunction with nitrous oxide and oxygen, with or without curare added. The youngest infant receiving it was 1 month old, and he was given 100 mg. for a forty-five minute herniorrhaphy. The longest procedure, a plastic operation, was in a 5-year-old youngster who received 1.4 Gm. over a three and a fourth hour period. The largest dose which we have given any one patient is 3.0 Gm. over a two and a half hour period to a 9 year old boy. Blood pressure, pulse and respiratory rates remain remarkably constant using this intravenous anaesthetic associated with a partial rebreathing technique employing nitrous oxide and oxygen. As with pentothal, there may be a fall in blood pressure for a short period immediately after induction. This is never alarming, however, and it returns to its preoperative level rapidly and without specific therapy.

The postoperative course of patients receiving kemithal has been free of major complications. Postanaesthetic respiratory depression has not been a problem. Invariably these patients are in possession of all their reflexes before leaving the operating table, and frequently they are awake. If they fall asleep on their return to the ward, it is always a light slumber from which they can be fully aroused on stimulation. Nausea and vomiting are the exception in these cases, and there have been no respiratory complications.

There is one phenomenon seen frequently during the period of awakening which should be mentioned. If these patients are stimulated strongly at the conclusion of operation, about 60 per cent of them, in addition to phonating and moving about, suddenly become stiff as a board. It becomes almost impossible to flex or extend their limbs. Some patients have intense shivering movements, as if they were beginning a severe chill. Rectal temperatures are normal, however, and no alterations in blood pressure or pulse have been seen. Respiration
are not affected, and there is no associated laryngospasm. If the patients are left alone and not moved or stimulated further, the limbs will relax in two or three minutes. This condition is seen occasionally after pentothal administration, and very frequently after evipal is given. We do not know of any explanation for this occurrence. It has never been seen to persist and has not caused any harmful sequelae in the patient.

The question may be asked: "Will kemithal ever replace pentothal?" Such an empirical question is difficult to answer, but one believes the reply should be "No." Pentotal has been proved to be a satisfactory agent, and another drug would have to be of superlative value to supplant it. It is doubtful whether kemithal is that much superior in quality and properties. It is a useful agent in anaesthesia, however, and has, we believe, certain advantages when used in the younger age groups.

**Summary**

The chemistry and pharmacology of two newer anaesthetic agents, namely, trichlorethylene and kemithal, have been outlined.

Technics of administration of these agents to children are presented.

Clinical observations are noted and evaluated with special reference to the safe use of trichlorethylene and kemithal for anaesthesia in children.

**References**


NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The third regular meeting of the New England Society of Anesthesiologists for 1950–1951 will be held on Tuesday, April 10, 1951, at 7:30 p.m., in the Auditorium of Bishop McAuliffe Lying-In Pavilion at St. Francis Hospital, Hartford, Connecticut.

Dinner: 5:30 p.m. at the Bond Hotel
Business Meeting: 7:30–8:00 p.m.
Scientific Meeting: 8:00–9:00 p.m.

"Methohexamine and Relation to Anesthesia," William K. Bannister, M.D.

"The Use of Relaxants for Intubation," David Little, M.D.

"Present Status of Intravenous Procaine," Stevens J. Martin, M.D.

The final meeting of the year of the New England Society of Anesthesiologists will be held on Tuesday, May 8, 1951, at 7:30 p.m., in the Amphitheater, Building A, Boston University Medical School, 80 East Concord Street, Boston.

Dinner: 5:30 p.m. at the Somerset Hotel
Business Meeting: 7:30–8:00 p.m.
Scientific Session: 8:00–9:00 p.m.

Leo V. Hand, M.D., Moderator, Anesthesiologist, New England Deaconess Hospital, Boston.
Richard H. Sweet, M.D., Surgeon, Massachusetts General Hospital, Boston.
Norman Wilson, M.D., Surgeon, Overholt Thoracic Clinic, Boston.
Myer Sakkal, M.D., Anesthesiologist, Rhode Island Hospital, Providence.
Philip D. Woodbridge, M.D., Anesthesiologist, Greenfield, Massachusetts.

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