INTRAVENOUS AVERTIN® ANESTHESIA

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WITH the advent of the ultra short acting barbiturates for hypnosis and anesthesia, the use of intravenous avertin® for analgesia and basal anesthesia was discarded. The purpose of our study was to revaluate the intravenous method of administration of this agent to discern its possible place in the anesthesiologist's armamentarium. This report contains our findings and impressions up to the time when we deemed it impractical to continue the study because of untoward local irritative effects of the intravenous solution.

Adams(1) has presented a complete review of the German literature on intravenous avertin anesthesia. Krekeler (2), Holtermann (3), Freienstein (4), Niemann (5) and Kirschner (6) reported favorably on the use of a 3 per cent avertin solution intravenously in a large number of cases, but their reports attracted little attention in the United States. In 1945, Thornton and Rowbotham (7) reported the successful use of a 1 per cent solution in emergency maxillofacial operations on battle casualties. They noted a remarkable advantage over pentothal® sodium in that laryngospasm and other enhanced respiratory tract reflexes were absent. They stated that intravenous avertin was of special value in this type of surgery, but could not claim it was without hazard when used in this way. Bumgarner *et al.* (8) in a preliminary study of 50 cases, reported favorably on the use of 1 per cent avertin solution for endoscopy, endotracheal intubation and for operations about the head and neck.

CHEMISTRY AND PHARMACOLOGY

Avertin is tribromethanol (TBE), a white crystalline substance which is soluble in water at 104 F. (40 C.) up to 3.5 per cent. It is supplied in a concentrated solution with amylene hydrate, each 1 cc. containing 1 Gm. of tribromethanol and 0.5 Gm. of amylene hydrate in dark bottles to prevent decomposition on exposure to light. This preparation remains active for approximately two years. With prolonged storage and temperatures above 105 F. it breaks down into bromacetaldehydes, bromvinyl alcohols and hydrobromic acid. The solution may

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be tested for acid break-down products with aqueous Congo red solution. A blue or violet color signifies that the drug is not suitable for use.

Avertin possesses certain pharmacologic properties that recommend it to the anesthesiologist. Sleep, without movement, is rapidly and quietly induced. The vomiting center is depressed. Nausea and vomiting are usually absent during induction and emergence from narcosis. Intracranial and intra-ocular pressures are diminished. Carotid sinus reflexes are unaltered with average clinical doses (9). In sharp contrast to the barbiturates, pharyngeal, laryngeal and tracheal reflexes are not enhanced but depressed. The cough center is somewhat depressed but the cough reflex is present even in deep hypnosis. The bronchi are relaxed rather than constricted as may be the case with intravenously administered barbiturates or cyclopropane.

Avertin possesses certain undesirable characteristics. Depth of respiration is decreased although usually the rate is not especially affected except with overdosage. Hypotension of a transient nature is a common occurrence with rectal avertin. This may be the result of a depressant action upon the vasomotor center and perhaps upon the heart and blood vessels. The coronary arteries are dilated, the heart rate is slowed and the strength of cardiac contraction weakened (10). Gastrointestinal motility is greatly depressed. Hyperglycemia is present during narcosis and there is a decreased alkali reserve. Renal output is decreased during and increased following its use.

TOXICITY

Tribromethanol is detoxified by conjugation with glycuronic acid. The resultant product is excreted fairly rapidly through the kidneys. The problem of toxic effects of avertin on the liver and kidneys is still unsettled. Anschütz (11) stated that avertin does not produce severe hepatic and renal damage and questioned the importance of the liver in the detoxification process. Bourne and Raginsky (12) considered the interference with hepatic function following its rectal use in dogs mild as tested by the bromsulphalein test. Coleman (13) considered it severe. Tolerance to avertin is decreased by starvation and thiamine deficiency.

Albuminuria and hemorrhagic nephritis following avertin anesthesia have been reported. Kirschner (6) observed transient hematuria with intravenous administration of a 3 per cent solution of avertin but this was obviated by using 5 per cent calorose solution as a vehicle.

Andersen (14) reviewed the literature for cases of hepatic and renal damage with this agent. She described 22 cases in which the use of rectal avertin was followed by symptoms of hepatic and renal insufficiency or both. Seventeen of these cases showed hepatic lesions comparable to those of delayed chloroform poisoning and renal lesions usually diagnosed as nephrosis or tubular degeneration. She believed

that some patients may be unduly susceptible to the toxic effects of the drugs.

CONTRAINDICATIONS

Avertin is contraindicated in patients with hepatic or renal dysfunction, severe cardiac disease or pulmonary insufficiency, extreme old age, shock, dehydration, acidosis, severe toxemia, extensive pulmonary tuberculosis, asthenia, cachexia and perhaps hyperthyroidism.

LABORATORY STUDIES

Because of the paucity of information concerning the properties of avertin solution, we undertook certain basic experiments which we believed of value in this study. The unsterilized concentrated solution is packaged in 25 and 100 cc. bottles. According to the manufacturers it has been tested on occasion and found to be sterile. They stated that the commercial solution is inherently bactericidal but not sporicidal. When diluted to 1 per cent concentration, the bactericidal or bacteriostatic properties, or both, are markedly reduced although not entirely eliminated. We found that a fresh culture of B. subtilis will show growth within forty-eight hours in the commercial solution and within twenty-fours in the 1 per cent concentration in 5 per cent dextrose in distilled water or in normal saline solution.

Although 3 per cent avertin in 5 per cent calorose or normal saline solution is said to be suitable for use up to twelve hours, we found that a fresh 1 per cent solution in 5 per cent dextrose in water or in normal saline solution at room temperature and exposed to light in a clear glass vacoliter bottle will show decomposition after four hours, as demonstrated by the Congo red test. Others (8) found no deterioration after storage of the solution for three weeks.

Although Lundy (15) reported that he had injected the stock solution intravenously for induction of ether anesthesia, we believe this may not to be without hazard. Tribromoethanol is immediately precipitated as visible white crystals when the concentrated solution is added to fresh or banked blood.

Because of the possibility that even a dilute avertin solution might hemolyze erythrocytes and produce toxic symptoms we studied the effects of various concentrations of the agent both in 5 per cent dextrose in water and in normal saline solution on both banked and fresh blood. The 1 per cent solution in 5 per cent dextrose in water or in normal saline solution hemolyzed erythrocytes in about thirty minutes; 0.5 per cent solution in 5 per cent dextrose in water caused hemolysis in about three hours while 0.5 per cent solution in normal saline solution caused hemolysis in 8 to 12 hours. Since the concentration of avertin in the blood for deep hypnosis is given as 6 to 8 mg. per 100 cc., we believe the possibility of intravascular hemolysis is unlikely. However, solutions of avertin should not be left in contact with blood.

TECHNIC OF PREPARATION AND ADMINISTRATION

Vacoliters of 500 cc. capacity containing a solution of 5 per cent dextrose in water were warmed to 40 C. Since these flasks actually contain 550 cc., 5.5 cc. of avertin solution was added by sterile syringe. Solution of the agent was hastened by vigorous shaking for five to ten seconds. Vacoliters of 180 cc. capacity may be employed in preparing small volumes of the 1 per cent solution. If the fluid shows any turbidity, it is unsuitable for injection. Normal saline solution has been used as a diluent but avertin does not readily dissolve in it and may not remain in solution at room temperature as certainly as when 5 per cent dextrose in water is used.

The 1 per cent solution was tested with Congo red. If the test proved satisfactory, the drug was administered through an infusion or transfusion set. Venipuncture was performed with an 18 or 19 gauge needle because the rate of flow must be rapid for induction. The solution was permitted to run in a very rapid drip until the patient was asleep and then the rate was adjusted according to anesthetic requirements. Usually, 75 to 100 cc. of the 1 per cent solution was required to produce sleep in the average patient.

PREMEDICATION

We did not alter our usual premedication. A barbiturate (seconal or nembutal, 0.1 to 0.2 Gm.) was given orally one and one-half hours before operation and morphine sulfate, 11 mg., and atropine sulfate or scopolamine hydrobromide, 0.4 to 0.6 mg., were injected subcutaneously about one hour before the surgical procedure. Although morphine has been blamed for respiratory depression when used with rectal avertin (9), we employed it in standard amounts without difficulty. However, added intravenous morphine or demerol must be administered with caution since respiratory depression of a severe degree may ensue.

There are a number of circumstances under which we believed intravenous avertin might prove of value. We have used it in the following types of procedures:

1) As an induction and basal agent with ether, cyclopropane, nitrous oxide-oxygen, especially in asthmatic patients.
2) As an intubation agent with or without a relaxant.
3) As an hypnotic supplement for spinal anesthesia with or without nitrous oxide-oxygen.
4) As a basal agent in the presence of infections of the neck when irritable carotid sinus reflexes might be a hazard.
5) As a basal hypnotic with local or topical anesthesia for endoscopy.
6) As a basal anesthetic for oral and maxillofacial operations.
7) As a basal anesthetic with weak gaseous agents plus relaxants.

We considered its use as an hypnotic for "sneaking" operations in very nervous patients and as a therapeutic method in the treatment of status asthmaticus and tetanus. Intravenous avertin may prove of value in these conditions when conditions warrant its trial.

TECHNIC FOR INDUCTION

As an intravenous induction agent prior to ether, avertin appeared to be far superior to intravenous pentothal. Kirschner (6) used 3 per cent avertin solution for induction to ether in 590 patients without untoward reaction. Martens (9) has also reported favorably on its use for this purpose. Bosse (16) stated that induction with ether was quieter and smoother than with pernoston (sodium salt of isopropyl-betabromethyl barbituric acid). Holtermann (3) employed it successfully for this purpose in major gynecologic procedures. Freienstein (4) stated that it was an ideal method for induction of anesthesia in which ether by inhalation was to be administered. Waters expressed the opinion that its advantages as a preliminary anesthetic agent were overshadowed by the frequency of venous thrombosis. We employed the 1 per cent solution as an induction agent to ether in 45 cases with excellent results. Sleep was quietly produced without spasmodic movement which may characterize barbiturate or cyclopropane induction. We found the avertin-nitrous oxide-oxygen-ether sequence preferable to avertin-ether-oxygen sequence. A minimal dose of avertin was required when anesthesia with nitrous oxide-oxygen was established to some extent before the addition of ether. The concentration of ether may be rapidly increased and the nitrous oxide quickly omitted. This is in sharp contrast to a barbiturate induction when ether must be added most "gingerly" and maximal use of nitrous oxide analgesia must be made. A pharyngeal airway is tolerated early. A volume of 75 to 100 cc. of the 1 per cent solution was required for induction in the average patient. Volumes up to 300 cc. were necessary on occasion.

OPERATIONS

Forty-one operations such as dilatation and curettage, vein ligations, teeth extractions, lumbar laminectomy, thyroidectomy and open reduction of fractures of the extremities were performed, using 1 per cent avertin-nitrous oxide-oxygen with and without a relaxant when required. We noted that on occasion our maximal dose of 7 Gm. of avertin was insufficient in long traumatic cases such as laminectomy or spinal fusion in large male patients. Added pentothal was given to these patients.

INTUBATION

We used intravenous avertin for intubation both with and without muscular relaxants in 18 cases. We preferred syncurine since curare

may enhance the curariform properties of tribromoethanol. A topical spray of 10 per cent metycaine solution * was applied to the epiglottis, glottis and upper trachea. Although avertin quickly relaxes the masseter muscles, a relaxant cuts down the requirement of avertin and facilitates the placement of the endotracheal tube. About 300 cc. was used without a relaxant and 100 to 180 cc. with a relaxant. We noted that spasm of the pharyngeal musculature on laryngoscopy was usually absent, laryngospasm much decreased and the cough reflex, although present, not troublesome. When laryngospasm and cough did occur from manipulation within the respiratory tract, they were of a transient nature compared to the persistent difficulties encountered with pentothal.

This technic appeared superior to the pentothal-curare or pentothal-syncurine technics for intubation since enhancement of reflexes of the respiratory tract by the barbiturate hypnotic was avoided.

AVERTIN AS A SUPPLEMENTAL HYPNOTIC FOR SPINAL ANESTHESIA

It is our custom to keep most patients asleep while being operated on under spinal or fractional spinal anesthesia. Usually we add pentothal or morphine with scopolamine along with nitrous oxide-oxygen in a 70–30 per cent mixture. In this study spinal anesthesia was supplemented with 1 per cent avertin solution with or without nitrous oxide-oxygen in 80 patients. Sleep was quiet and without muscular movement. The hypnotic effect appeared somewhat longer than with pentothal. An initial dose was often sufficient for a procedure lasting up to one hour. For the average case, 125 to 200 cc. of the solution was used.

RECOVERY PERIOD

Intravenous avertin rarely produced nausea and vomiting. Patients were returned to the ward in possession of active protective reflexes. Postoperative sleep was quiet although an occasional patient exhibited signs of inebriation. We believe sleep was somewhat longer than after use of intravenous pentothal. Avertin, an analgesic combination, may be superior to the barbiturates in the presence of postoperative pain. None of our patients showed clinical evidence of hepatic insufficiency. Urinalysis after operation in 25 cases revealed occasional slight albuminuria without microscopic abnormalities. Such a finding is common after surgery under any anesthetic agent.

UNTOWARD REACTIONS

Hypotension of a transient nature was observed in 2 patients to whom the avertin solution was administered too rapidly. Temporary respiratory depression was produced once from accidental overdosage.

* EDITOR'S NOTE: The maximum concentration recommended by the manufacturer.

In three patients morphine or demerol given intravenously during anesthesia produced respiratory depression lasting fifteen to thirty minutes which necessitated assisted respiration.

There were 2 deaths in the postoperative period. The clinical picture in both instances was that of coronary occlusion coming on about thirty-six hours after surgery. In the first, a cholecystectomy had been performed under endotracheal avertin-nitrous oxide-oxygen-ether sequence in a 68 year old man with known hypertensive cardiovascular disease and coronary insufficiency. Death occurred in forty-eight hours. Permission for autopsy could not be obtained. The second patient was a 60 year old woman with generalized arteriosclerosis who tolerated well a combined abdomino-perineal resection of the rectum under endotracheal avertin-nitrous oxide-oxygen-ether sequence. Death occurred in seventy-two hours. Autopsy was not done.

We discontinued our study in 9 cases because of the development of severe superficial chemical phlebitis in the veins used for the infusion. In 5 cases the veins of the arms and in 4 those of the lower legs were involved. The extremities showed a hard, painful and tender thrombosed vein, 10 to 30 cm. in length. In several instances, the skin was reddened over the affected vessel and in one patient there was mild lymphangitis. Inflammation became noticeable usually during the first postoperative week and 4 patients noted the reaction while at home. In one case the phlebitis persisted for over a month in spite of local treatment.

The incidence of phlebitis in this series of 161 cases was 6 per cent. Adams (1) concluded from the reports of various writers that the incidence of venous thrombosis with 3 per cent avertin solution was 2 or 3 per cent. Bumgarner *et al.* (8) noted 2 cases of "mild venous thrombosis" in their 50 cases. Apparently even the 1 per cent solution is quite irritant to the endothelial lining of the vein. This may help explain the occurrence of proctitis which has followed rectal administration of avertin even when the solution had been tested with Congo red solution.

We attempted to use more dilute solutions of 0.5 per cent and 0.75 per cent avertin but found that often we could not produce hypnosis without extremely rapid flows and excessive volumes of solution which might be hazardous to the patient at the time of operation.

SUMMARY

We have reported the results in a group of 161 patients in whom we employed 1 per cent avertin in 5 per cent dextrose in water, given intravenously, for various anesthetic procedures and operations. The results were promising but the 6 per cent incidence of superficial phlebitis forced us to discontinue the study. In our opinion tribromoethanol with amylene hydrate (avertin) is unsatisfactory for general use as an intravenous analgesic or basal anesthetic agent.

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