4-1-1938

The Short-Acting Barbiturates as Intravenous Anesthetics

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IN 1875, Oré[1] successfully employed chloral hydrate intravenously in the production of general anesthesia. Since that time various other hypnotics, such as methyl-propyl-carbinol-urethane (Hedonal), trichlorisopropyl alcohol (Isopral), isoamyl-ethyl (Amytal), secondary-butyl-bromallyl (Pernoston), ethyl-1:methyl-butyl (Nembutal), and cyclohexenyl-ethyl (Phanodorn) barbituric acid, and even ether in Ringer's solution have been employed.

The use of the barbiturates dates back only to 1929. It was in that year that Zerfas[2] and his co-workers, at the Indiana University School of Medicine and Hospitals, found that Sodium Amytal was capable of producing surgical anesthesia. However, it was soon found that this and the other barbiturates named above exhibited definite disadvantages when employed as general anesthetics. Patients subjected to them were prone to sleep unduly long postoperatively, and about 25 percent showed extreme hyperexcitability, either during induction or following the operation. As a consequence, their use was restricted to the field of basal anesthesia.

In 1932, methyl-cyclohexenyl-methyl barbituric acid (Evipan) was synthesized. Used as the sodium salt, this barbiturate quickly gained favor as a general anesthetic, first in Europe and later in America, for use in operations of short duration (15 to 20 minutes). It was characterized by the production of rapid induction, good somatic and visceral relaxation, seldom an alarming fall of blood pressure, satisfactorily short postoperative narcosis, and usually no postoperative gastric disturbances. Patients who have been anesthetized with it have expressed satisfaction.

Following in the wake of Evipal, there have appeared sodium ethyl-1:methyl-butyl-thio-barbiturate (Thio-Nembutal, or Pentothal Sodium), sodium allyl secondary-butyl-thio-barbiturate (Thiosebutal), and 1:methyl-(5-5) allyl-isopropyl barbiturate (Narconumal). These compounds manifest a striking similarity of dynamic action, excepting the fact that Pentothal is approximately one-third more toxic than Evipal; and Thalheimer[3], who has used Narconumal more than Evipal, prefers the former, claiming for it an absence of the factor of excitement. Although I have used them all, I have had widest experience with Evipal and prefer it to the others solely on that account. My discussion will be confined to Evipal Soluble, though I would have it understood that whatever is said of Evipal applies equally as well to the other members of this particular group.

Discussion

Every anesthetic agent has its peculiar disadvantages and limitations. In the study of any therapeutic agent it is imperative to know its particular limitations and disadvantages. This is the best safeguard against bringing a good agent into disrepute. Among the limitations and disadvantages of this group of barbiturates, used for intravenous anesthesia, should be mentioned the following:

1.—*Toxicity and Absorption:* From the results of an extensive experience with laboratory animals, and a somewhat more limited clinical experience with Evipal, I have been able to make some interesting observations regarding the question of the toxicity of this compound. The problem of toxicity, within reasonable limits, is a function of the rate and mode of administration, rather than the size of the individual dose. This is due to the fact that absorption plays a more dominant role than the quantity administered. Thus, when Evipal is given by mouth or subcutaneously, the rate of absorption may be so slow that detoxification within the system may run almost parallel with absorption. In this event the amount actually administered over a period of time could reach startling figures. As the equation shifts from the side of absorption, the end-point of an otherwise surely fatal dose might be expressed merely in terms of stupor, dizziness, or incoordination.

Two years ago, Maloney and Hertz[4] reported on this point as follows: "The hazard of toxicity is inherent, not in the drug *per se*, but rather in its absorption constant in the system in any unit of time." When administered intravenously, in which case absorption is immediate, Evipal presents a

distinct problem in toxicity. If the rate is too rapid, it may produce sudden paralysis of the respiratory center, resulting in death or profound respiratory embarrassment.

2.—*Anesthetic Inefficiency and Tissue Damage:* Under the caption of toxicity and absorption, the dangers at both extremes, incident to the rate of injection, were stressed. But here is another problem associated with slowness of injection rate. This problem is two-fold: (1) Failure to produce anesthesia due to the fact that detoxification may run parallel to absorption. In this case the drug is likely to be blamed when, in fact, the anesthetist is at fault; and (2) the detoxifying mechanism may break under the severe strain of the large dose required and permanent liver damage result from an irreversible toxic cellular reaction.

3.—*Non-volatility:* Anesthetists and pharmacologists are agreed on the point that an acceptable anesthetic is one that is easily controllable. By their very nature the volatile anesthetics meet this criterion. Regarding the barbiturates used for general anesthesia there are conflicting opinions. Without any pretentions at settling the question, I am prepared to state that picrotoxin, the most effective antidote for barbiturate intoxication, serves as a good control in Evipal anesthesia, both prophylactically and antidotally. I use picrotoxin prophylactically as a routine measure to protect the respiratory center from the paralyzing action of Evipal in an overdose.

Unsuitable Cases

Evipal is not suitable for every case. As with other anesthetic agents, a judicious selection is imperative, in which complicating factors and contraindications are to be recognized. On the question of complicating factors, Heard[5] mentions early bronchiectasis, diabetes, hypertension, endocarditis, and advanced carcinoma. Of course, this list, with the possible exception of hypertension, would constitute "complicating factors" with virtually every sort of anesthetic. If careful pre- and postoperative management of individual cases falling within these categories is exercised, there is no reason why Evipal could not with safety be employed. It is well tolerated in cases exhibiting hypertension, provided there is no significant associated impairment of hepatic function. Two cases in our series (Maloney[6]), with hypertension, showed marked diminution of pressure (240 to 200, and 160 to 88 systolic).

The major contraindication to Evipal anesthesia is direct impairment of liver function or any morbid condition which would tax heavily the detoxifying capacity of the liver. I cannot stress too strongly the importance of hepatic dysfunction. Evipal is almost wholly detoxified by the liver. If liver function is definitely impaired, a normal therapeutic dose of Evipal might prove fatal. Two cases in point have come to my attention: The first had a positive Fouchet test, indicative of hepatic dysfunction. In spite of this finding, Evipal was employed, contrary to routine instructions. The patient had a very stormy postoperative experience. The second case was a patient with burns over a wide surface of his body. Evipal was given illadvisedly. The result was a fatal toxemia.

Duration of Anesthesia

Opinion is unanimous that Evipal makes an ideal anesthetic for operations of short duration. While I am in hearty accord, it is but fair to point out the triteness of this statement. It holds true for all anesthetics. My claim is that, with Evipal, shortness of duration of anesthesia is not definitive. Within reasonable limits (such as are allowed for any other anesthetic agent), it makes no difference how short or long a time the anesthesia under Evipal is to last. Safety of induction is the problem of first consideration. When once induction has been successfully obtained, duration becomes a matter of fractional injection, as required to maintain a given level of anesthesia with smoothness. Provided that the respiratory center is given adequate protection by the prophylactic employment of picrotoxin, any ordinary operation may be performed, regardless of time. I found, in our first series of 40 cases, that the average duration was 58.85 minutes; 18 lasted 60 minutes or more; 3 lasted 125, 125, and 133 minutes, respectively.

Technic of Administration

The patient is prepared in the usual manner on the night preceding operation. Morphine, with scopolamine or atropine, may be given, if necessary, to insure psychic or nervous stability and an adequate amount of restful sleep. However, I would strongly urge that no sedative be given just before the anesthetic, because it complicates the general picture by potentiating the depressant action of Evipal in a way that cannot be measured with accuracy, and thereby prevents a correct estimation of the effective anesthetizing dose. Avoidance of these factors of danger is of greater importance than lessening the initial amount of the anesthetic agent.

Upon a signal of readiness from the surgeon, 1 to 2 cc. of a 0.3-percent solution of picrotoxin is injected intramuscularly. The patient is then asked to count audibly as soon as the needle delivering the Evipal solution is in the vein and the injection started. The injection is made fairly rapidly until

the patient's voice fades away. Undue slowness of the injection rate serves to increase the induction time and the initial amount of the anesthetic required. In man, the injection rate must be more rapid than in laboratory animals, because of the relatively longer course of the systemic circulation in man. Using the same caliber syringe and needle at all times, the technician quickly learns to gauge the optimal rate of injection.

With the fading off of the patient's voice, an additional one-third of the amount already delivered is then given. The administration is now stopped, the needle being held in position in the vein for subsequent fractional injections. The signal is now given the surgeon to begin. No special apparatus is necessary, though there is a simple device available for use in intravenous anesthesia. This apparatus is described by Jarman and Abel[7], in *The Lancet* for March 4, 1936.

Dosage

The amount of Evipal necessary to produce surgical anesthesia varies with the individual. In our series the average dose per patient happened to be 1.875 Gm., the largest single dose being 4.7 Gm. The prime consideration here is, not the total amount, but rather the distribution of that amount. Our fractional doses are characterized by smallness and frequency rather than quantity, ever bearing in mind the maintenance of a constant level of anesthesia. In this connection I take the quality of the respiration as my cardinal guide. Under Evipal anesthesia the respiration closely resembles deep physiologic sleep, with a gentle stertor of definite depth and rhythmicity. The minutest detectable deviation from an established rhythm and depth is taken as a sign for either giving or withholding the anesthetic.

It is imperative to call attention at this point to the necessity of keeping the airway clear at all times. An obstruction may serve to disturb the depth and rhythm of respiration. It is good procedure to use a mechanical airway (Cornell's), unless it causes gagging. Should postoperative restlessness occur, morphine furnishes prompt relief (Maloney[6]).

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