condemn thousands of times without once inflicting the slightest injury, and I should not doubt such statements; no more should I doubt my own conviction that as long as such a method is generally adopted, so long shall we continue, rarely it may be, to meet with examples of this grave and easily avoidable injury.

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PHARMACOLOGICAL PROPERTIES OF ISO-AMYL ETHYL BARBITURIC ACID (AMYTAL) *

BY

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Nearly thirty years ago veronal was first introduced as a hypnotic. Since then the derivatives of barbituric acid have found progressive favour as hypnotics, and, in more recent times, as premedication drugs in anaesthesia, and even as general anaesthetics.

One of the more recent derivatives is amytal (iso-amyl ethyl barbituric acid). This drug was first described by Shonle and Moment¹ in 1923, and was promptly used by Page² in pharmacological experimentation. At first the difficulty of preparing the soluble sodium salt of amytal delayed the use of this drug as an anaesthetic for human beings. Very recently, however, the presence on the market of the sodium salt of amytal in stable form has permitted its wide application as an anaesthetic in man.³ A full description of the clinical use of the barbituric acid group of drugs, both in surgical and in non-surgical cases, may be found in the *Proceedings* of the staff meetings of the Mayo Clinic.⁴ Amytal, since its introduction, however, has been widely used in physiological and pharmacological laboratories as an anaesthetic for animals. Although the direct application of information derived from animals to man is notoriously unsafe, yet the data from the clinical use of amytal resemble so closely the findings in the laboratory that a description of my own experience and that of other laboratory workers may be not irrelevant.

ROUTE OF ADMINISTRATION

In laboratory animals, at least, oral administration of the drug is unsatisfactory. The action is slow and uncertain. Subcutaneous or intramuscular injection of a 10 per cent. solution of sodium amytal is much to be preferred. The injection itself causes no distress, the onset of anaesthesia is quiet, but it is somewhat slow, being sometimes delayed for one hour or more. Intraperitoneal injection of the 10 per cent. solution is equally painless; there is subsequently no sign of peritoneal irritation, and the onset of anaesthesia is rapid—ten to fifteen minutes. Frequently there are signs of nasal irritation, the animal sneezing repeatedly and rubbing its snout with its fore-paws. Beyond this there is no disturbance and no distress. Intravenous administration of the same strength of solution causes very rapid onset of anaesthesia, but the injection must be carried out very slowly, because of severe circulatory disturbances.

In animals the subcutaneous or intraperitoneal is the route of election.

DOSAGE

In the cat and in the dog the basic dose for complete surgical anaesthesia is 50 mg. per kilogram of body weight. In the rat and in the rabbit the dose is somewhat greater.

* A communication to the Section of Anaesthetics, British Medical Association, Eastbourne, 1931.

A slightly larger dose is necessary by the subcutaneous than by the intraperitoneal or intravenous route. Twice the minimum effective dose may usually be given with safety, even by the intravenous route. In man a smaller dose seems to be effective; 20 to 25 mg. per kilogram of body weight, given intravenously, is adequate for complete surgical anaesthesia, and 12 to 20 mg. per kilogram of body weight is sufficient to lower the dose of such volatile anaesthetics as ether, or N₂O and O₂, to one-quarter of the usual amount required.⁴ Stormont, Lampe, and Barlow,⁵ working on rats, showed that premedication with amytal or other barbituric acid derivatives permitted the production of full anaesthesia with a lower percentage of N₂O and a higher percentage of O₂ than is usually necessary. All danger of oxygen deficiency during the anaesthesia was thus eliminated.

DURATION OF ANAESTHESIA

In the cat and in the dog complete anaesthesia lasts two to three hours, using the basic dose of the drug for anaesthesia. The period of surgical anaesthesia is followed by an interval of drowsiness and sleep, which may last from twenty-four to thirty-six hours. In the rabbit all the phases are very much shorter. In man, according to the dose, there is post-anaesthetic sleep and drowsiness for twelve to seventy-two hours. This considerably increases the necessary nursing attention. Neither in animals nor in man are there signs of post-operative distress.⁶

EFFECTS ON METABOLISM

The statement by early workers that carbohydrate metabolism is unaffected by amytal made this drug the anaesthetic of choice during the wave of experimental investigation into carbohydrate metabolism which followed on the discovery of insulin. This sweeping claim for amytal as a true "physiological" anaesthetic has not stood the test of time. Glucose injected intravenously is not removed from the blood at the usual rate, presumably due to inhibition of the storage of glycogen in the liver.^{7 8} Many workers claim that the blood sugar level remains unaltered under amytal anaesthesia, and that the level of the sugar in the blood responds normally to the injection both of adrenaline and of insulin.^{2 9 10} It is possible that the abnormal blood sugar levels which have been reported under amytal anaesthesia may have been due to disturbance of the animal, but this is denied by Weiss.¹¹ However this may be, there seems to be a general consensus of opinion that amytal anaesthesia has a less disturbing effect on carbohydrate metabolism than the majority of other anaesthetics in general use. This may be not without significance in anaesthesia in man if damage to the liver is feared.

As is to be expected, amytal lowers the body temperature, certainly by enforced inactivity and possibly by a direct depressor action on metabolism. Shivering is very apt to occur.¹²

Respiratory System.—All barbituric acid derivatives are respiratory sedatives. Amytal, however, in anaesthetic dosage, does not greatly diminish the minute-volume of respiration, and the respiratory centre remains sensitive to CO₂.¹³

Circulatory System.—Amytal has a definitely toxic action on the heart, and this is more marked the more rapid the administration.¹⁴ For this reason rapid intravenous exhibition of the drug is fraught with danger. The blood pressure falls rapidly, and one hour or more may elapse before it regains its previous level. This fall in blood pressure is due both to dilatation of the heart, with reduction in minute-output, and also to vaso-dilatation.^{15 16} Large doses administered rapidly may cause heart-block, ventricular fibrillation, and death. In clinical use amytal

lowers the systolic and diastolic pressure, and this fall in blood pressure may be alarming if the administration be rapid.⁴

Nervous System.—Barbituric acid derivatives have a specific affinity for the nervous system, but amytal, even in deep anaesthesia, leaves the bulbo-spinal reflexes of animals but little affected. The action of amytal on the involuntary nervous system is peculiar. The inhibitory action of the vagus on the heart is abolished, and may not be restored to its previous vigour, in the cat at least, for several hours.^{14 17 18} This action of amytal is not comparable to that of atropine, because amytal does not inhibit the action of acetylcholine.¹⁴ If this action on the vagus is present in human beings it may be of no small importance in connexion with vagus inhibition of the heart during the induction stages of anaesthesia with the more common volatile anaesthetics. Several workers have suggested that amytal may have a specific paralysing action on the parasympathetic system in general,^{17 19} but this is not of universal application.¹⁴ The true sympathetic system seems to be unaffected by amytal.

Gastro-Intestinal System.—Amytal causes a definite decrease in intestinal motility, and the pylorus is tightly closed. This is possibly due to an action on the parasympathetic system. Thus absorption of glucose, when given by the mouth, is negligible and is greatly delayed, even when injected directly into the duodenum.¹⁹

Reproductive System. *In vitro*, amytal, even in high concentration, has no effect on the movements of the guinea-pig uterus, and the response to "pitocin" is unaffected.²⁰ Amytal has been used successfully in obstetrics.

Excretory System.—Barbituric acid derivatives do not all react in the same way; they are excreted in variable amounts and with variable speed. Amytal does not appear as such in the urine of dogs, whatever the route of administration.²¹ There appears to be no detrimental effect on the kidneys. Like other anaesthetics, amytal inhibits water diuresis.²²

SUMMARY

The known effects of amytal (iso-amyl ethyl barbituric acid) on laboratory animals are correlated with the more recent experiences of amytal as an anaesthetic in human beings. Although amytal has been definitely disappointing as an anaesthetic in physiological research work, yet, when properly used, its pharmacological actions may be of no hindrance to its use as an anaesthetic in man.

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SOME INTERESTING DRUG ERUPTIONS*

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Almost all active drugs are liable to cause cutaneous eruption, and as new ones are introduced into medicine the list of drug eruptions grows longer. These cutaneous manifestations are really only evidence of the activity of the medicine, and it may almost be said that a drug which *never* causes an eruption is one which is not of much use. The chief exceptions to this generalization are to be found among the aperients and among the various hormones. One reason for the importance of diagnosing these eruptions as they occur is that if their true nature is not recognized they are quite likely to be mistaken for a manifestation of the disease which is being treated, with the result that the very drug which is really causing the mischief is pushed with still greater vigour, and to the increasing detriment of the patient.

The mechanism of production in drug rashes is obscure, and their distribution is often very capricious. In some cases only those parts which are exposed to light suffer, while in others the eruption appears to follow with some exactitude the distribution of the blood vessels in the skin. Many drugs only affect a very small percentage of patients, and can be given to the vast majority with impunity. It is amusing to speculate as to the nature of the factor producing susceptibility. To some extent this is a family characteristic. I like to imagine that susceptibility to drug eruption depends on some chemical peculiarity of the protoplasmic molecule of the individual. The modern conception of the protein molecule is that of a central nucleus, more or less stable in character, to which are attached an indefinite number of side chains with unsatisfied chemical affinities. Protoplasm, which may be regarded as the protein molecule endowed with life, must likewise possess similar affinities. Chemists tell us that there are about twenty-five different amino-acids that may be concerned in the structure of the protein molecule, and the permutations and combinations of these are quite sufficiently numerous to account for all the different varieties of protein and protoplasm met with in the world of life. I think it is legitimate to imagine that there is a characteristic chemical formula for the protoplasm of every separate individual as well as of every different species; but there will be slight variations in the chemistry of the protoplasmic molecule even between individuals of the same species. The side chains of the protein molecule will have different unsatisfied affinities, upon which the susceptibility of the individual to various drugs may well depend.

To return to the more practical aspects of the subject, is there any satisfactory classification of drug eruptions? The drugs can, at all events, be separated into several different groups according to their peculiarities of action. There are: (1) drugs which are applied almost exclusively to the surface—for example, oil of turpentine, sulphur, and various rubefacients. These are all irritants, and, if persisted in, will sooner or later cause a traumatic dermatitis in almost all patients. There is, however, a wide individual variation in susceptibility. (2) Drugs which, when administered internally, cause cutaneous manifestations in most patients, if used for a sufficiently long time. These are arsenic, iodine, bromides, belladonna, etc. Here again it must be remembered that there are the widest possible differences in susceptibility between various patients. (3) Drugs which, when administered to the vast majority of patients

* A lecture given to the London School of Dermatology, St. John's Hospital, Leicester Square.