EFFECT OF AZOTEMIA UPON THE ACTION OF INTRAVENOUS BARBITURATE ANESTHESIA

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The use of new and sensitive analytical techniques has contributed considerably to our increased knowledge of the distribution and fate of drugs in the body. Such procedures have also greatly increased our understanding of the mode of action of barbiturates. The fate of these drugs has recently been reviewed (1). A study of the available data indicates that considerably more effort has been devoted to the role of the liver as a site of detoxification for the short acting barbiturates than to any other organ. Today the predominant role of the liver in the metabolic degradation of the clinically important barbiturate derivatives as, for instance, thiopental or hexobarbital is sufficiently assured. On the other hand, it has often been assumed that the kidneys are of no special importance in the detoxification of these drugs. Only a limited amount of pharmacologic investigation has been directed to this subject. Masson and Beland (2), working on rats, did not consider the kidney of great importance in the detoxification of either thiopental or hexobarbital. However, more recent work in our laboratory (3–5) as well as by Dorfman and Goldbaum (6) and by Kelly and Shideman (7), casts some doubt upon this as far as thiopental is concerned. A review of prior work on this subject indicates that one of the standard procedures used to elucidate the role of the kidney as a limiting factor for the duration of action of ultra-short acting barbiturates was to determine sleeping time with a standard dose before and after bilateral nephrectomy. The in-

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jection of the barbiturate in such studies was usually made as soon as the animal had recovered from the effects of the operative procedure. Thus the effect which the removal of kidney tissue exerted directly upon the destruction of the barbiturate could be estimated but what influence the metabolic disturbance which followed the removal of the excretory function of the kidneys may have upon the action of the drugs in question could not be determined.

In a series of experimental studies we have investigated the effect of hexobarbital and thiopental in experimental animals immediately after the removal of the kidneys and at various intervals following this operation during the development of increasing azotemia. Corresponding clinical studies were undertaken in suitable patients who had either an endogenous azotemia or in whom the blood urea level was artificially raised.

Pharmacological Investigations

Results of the pharmacological investigations which in part have been reported at other occasions (3–5) can be summarized in the following manner.

Groups of rabbits and rats were given thiopental (pentothal® sodium) or hexobarbital (evipal sodium®) intravenously in doses that produced about the same duration of sleep. Several days later bilateral nephrectomy was performed in the same or comparable groups of animals, under light ether or spinal anesthesia; in other animals a sham operation was done. Injections of the barbiturates were given at various intervals up to twenty-four hours after the operative procedure. The effect of hexobarbital remained unchanged when the drug was injected three hours after the operation, and only a moderate prolongation was noted in rats but none in rabbits after twenty hours had elapsed. With thiopental, however, a marked and increasing prolongation of the effect was noted in rabbits and even more so in rats. This effect was slight and inconstant when the barbiturate was given within one hour after the operation, but amounted to several times the original sleeping time beginning six hours after nephrectomy, especially in rats. Ligation of the ureters instead of nephrectomy led to similar results, but the effects came on more gradually. No change was noted on sham-operated animals.

Experiments on a large number of rats proved that the prolongation of anesthesia increased in a straight line relationship with the time after nephrectomy and also with the resulting increase in urea. In fact, rats or rabbits that were given injections immediately after nephrectomy of an artificially prepared solution of urea, designed to raise the plasma level far above normal, reacted to it with a marked prolongation of the thiopental sleep, similar to the reaction of animals whose plasma urea was permitted to reach the same level by passage
of time. We were not able to produce this phenomenon by injection of such urea solutions in normal rabbits.

The course of the thiopental plasma level was followed in normal rabbits and a few days later in the same animals about twenty-four hours after bilateral nephrectomy. Statistically proven results indicate that there is no significant difference in the plasma levels before and after operation for the duration of the thiopental effect for

**Fig. 1.** All animals were given intravenous injections of thiopental, 25 mg. per kilogram. The figures inside of the first twin columns refer to sleeping time in minutes; inside the second and third twin columns to micrograms of thiopental per cubic centimeter of blood plasma.

normal animals. In other words, at the time when the normal rabbits awoke, the plasma level in the nephrectomized animals had fallen to the identical level, but the operated animals remained asleep and awoke much later. During this period of prolonged sleep, the plasma level of operated animals dropped at a significantly slower rate than in the normal rabbits which were already awake. The results of such an experiment conducted on the same 6 rabbits before and twenty-three
hours after bilateral nephrectomy are illustrated in figure 1. This indicates that at least two factors probably are responsible for the increased thiopental effect, namely, a greater sensitivity to a given barbiturate level and a slower metabolism of this drug. Careful checks of hemoglobin, hematocrit, hydrogen ion concentration of the blood, circulation, and so forth, showed that no marked changes had taken place within twenty-four hours after nephrectomy, during which period these experiments were carried out.

It was shown in separate studies (5) that a prolonged effect of thiopental was noticed in nephrectomized rats as soon as the threshold doses were exceeded.

Attempts to obtain prolongation of sleep with thiopental in nephrectomized cats and dogs were less successful. In cats no certain prolongation was obtained while in dogs a definite effect was noted only after twenty-four hours had elapsed. It should be mentioned that the animals were still in fairly good condition at that time.

Although there were occasional unpublished observations of an unexplained prolonged duration of thiopental anesthesia in patients with renal complications, no systematic study of this subject came to our attention. In view of the experimental results reported above, it appeared desirable to study this problem clinically both in patients suffering from azotemia attributable to disease and in normal individuals with artificially increased blood urea, which is the main constituent of the plasma nonprotein nitrogen.

**CLINICAL OBSERVATIONS**

Clinical data available to support these views can be divided into two parts: (1) observations on patients with a pathological rise in blood urea and (2) observations on a small number of subjects in whom an elevated level of blood urea was induced by oral ingestion of urea and curtailment of fluid intake.

(1) **Observations on Patients with a Pathological Rise in Blood Urea**

In the anesthetic technique for prostatectomy described by Marcus and Gray (8) spinal anesthesia is induced with dibucaine (nupercaine®), blood pressure is supported with an intravenous epinephrine or nor-epinephrine drip, a light level of anesthesia is maintained by intermittent injection of 2.5 per cent thiopental and nasal oxygen is administered. It is not unusual to find a raised blood urea among subjects with long standing prostatic obstruction. Consequently, a sufficiently large number of persons whose thiopental requirements are observed with the above technique will form an ideal group of subjects in whom to observe the effects of a raised blood urea. Such observations were made on 46 subjects, 35 of whom had a preoperative blood urea of between 28 and 42 mg. per 100 cc. and in the remaining 11 it was over
50 mg. per 100 cc. Subjects with complications, other than a raised blood urea, that might alter the response to thiopental were excluded in the series. Such complications included severe anemia (Dundee, 9), hepatic dysfunction (Shideman et al., 10; Dundee, 11), any excessive acute blood loss or prolonged period of hypotension. All subjects were premedicated with 10 mg. of morphine sulfate and 0.65 mg. of atropine sulfate subcutaneously one hour before operation and the

**Fig. 2. Requirements of thiopental in patients undergoing prostatectomy.**

- • Average requirements of 35 patients with blood urea between 28 and 45 mg. per 100 cc.; average age 63 years.
- ▲ Average requirements of 8 patients with blood urea of 51 to 80 mg. per 100 cc.; average age 66 years.
- —— Individual requirements of 3 patients in the latter category in whom the operation was of too short duration to include in the average.

Vertical lines show three times standard error of mean.

The amount of thiopental administered was noted at induction and at fifteen minute intervals thereafter.

Figure 2 illustrates the results obtained on the 35 subjects with "normal" blood urea and on 8 of the subjects with raised blood urea. Since the majority of the patients for prostatectomy fall within the former category it was possible to exclude all from this group for whom the operation lasted under ninety minutes and yet obtain a series large enough for statistical analysis. This was not possible for
patients whose blood urea was over 50 mg. per 100 cc., but an average was obtained from 8 persons for operations lasting seventy-five minutes and over. Figure 2 also shows individual requirements in 3 subjects whose operation was of too short duration to be included in the average.

Figure 2 reveals a marked diminution in thiopental requirements in subjects whose blood urea was over 50 mg. per 100 cc. compared with those whose range was within 28 to 42 mg. per 100 cc. The difference is too great to have arisen by chance.

![Diagram](image)

Fig. 3. Relation between thiopental requirements and blood urea level in 2 patients operated on at two different occasions. See text.

The following patients were subjected to thiopental anesthesia at varying intervals on two different occasions for similar operations—in each patient the blood urea was within normal limits at one time and on the other occasion there was a marked pathological rise. Requirements of thiopental were noted on each occasion.

**Case 1.** Two operations for transplantation of the ureters were performed on this subject. The interval between operations was three weeks. Anesthesia consisted of d-tubocurarine chloride-thiopental-nitrous oxide and oxygen at both operations. On the first occasion the blood urea was 26 mg. per 100 cc. and at
the second it was 94 mg. per 100 cc. Requirements of thiopental on each occasion are shown in figure 3, revealing a markedly increased sensitivity to the drug associated with the raised blood urea.

**Case 2.** Details are similar to those of case 1, except that at the first operation the blood urea was 149 mg. per 100 cc. and at the second it had fallen to 35 mg. per 100 cc. Requirements of thiopental are shown in figure 3, revealing a diminution in thiopental requirements associated with the raised blood urea.

**Case 3.** A man, aged 45 years, was admitted to the hospital with a history of passing blood clots through the urethra for nine months. Cystoscopy was performed on two occasions within one week. Each time the patient was extremely resistant to thiopental and required between 1 and 2 Gm. for the procedures lasting not longer than twenty minutes. On discharge from the hospital the blood urea was 34 mg. per 100 cc.

Three months later the patient was re-admitted to the hospital with clot retention. Only 90 ml. of urine had been passed during the preceding forty-nine hours. Blood urea was 175 mg. per 100 cc. Thiopental, 500 mg., produced satisfactory anesthesia for bouginage and cystoscopy lasting for more than one hour and the corneal reflex had not returned at the end of the operation.

**Case 4.** A man, aged 51 years, had a nephrolithotomy performed for removal of a large staghorn calculus. The preoperative blood urea was 37 mg. per 100 cc. Before a skin incision could be made a total of 1.0 Gm. of thiopental and 30 mg. of d-tubocurarine chloride was administered, and the operation was completed using nitrous oxide, cyclopropane and ether.

Following the operation the blood urea rose steadily and by the fifteenth day was 230 mg. per 100 cc., when a ureterolithotomy was carried out to re-establish flow of urine. For the whole procedure, which lasted thirty-five minutes, a total dose of 500 mg. of thiopental and 20 mg. of d-tubocurarine chloride, combined with nitrous oxide-oxygen, was sufficient.

**Case 5.** A urethral stricture was dilated in a 26 year old man; 1 Gm. of thiopental provided anesthesia to which the patient’s response was described as “lively.” This patient was subsequently admitted to hospital with a diagnosis of retention of urine owing to infection. Ten days after the initial procedure the blood urea was 128 mg. per 100 cc. Laparotomy was performed and a small perforation was found at the base of the bladder. Thiopental (400 mg.) d-tubocurarine chloride (25 mg.) and nitrous oxide were given during the operation which lasted eighty-five minutes, and the patient did not regain consciousness for a considerable time after its completion.

Two weeks later the blood urea had returned to normal and 500 mg. of thiopental was administered for further dilatation of the urethra. This procedure lasted fifteen minutes, at the end of which time the patient was moving vigorously.

These case reports further substantiate the view that tolerance to thiopental is greatly decreased in the presence of a pathological rise in blood urea. In all of these patients the elevated blood urea was only one manifestation of renal insufficiency, and many of them had biochemical disturbances of more serious import. It might be thought that these, and not the raised blood urea, could have been responsible for the sensitivity to thiopental which they exhibited. That an eleva-
tion in blood urea is at least in part responsible is shown by the following experiments.

(2) Observations on Subjects in Whom a Raised Blood Urea Was Induced by Ingestion of Urea and Deprivation of Fluids

Eight healthy volunteer subjects who were to undergo ligation of bilateral varicose veins were deprived of fluid for twenty-four hours before operation. Urea, 15 Gm. dissolved in 75 to 100 cc. of water, was given orally between 110 and forty minutes before operation. The fluid restriction was necessary in order to prevent too rapid clearance of urea from the bloodstream. Blood urea was estimated before the solution of urea was given and immediately before induction of anesthesia; it ranged from 21 to 30 mg. per 100 cc. before the urea administration of urea and rose to 42 to 66 mg. per 100 cc. after the medication.

![Graph showing dose of thiopental in mg/kg vs. duration of operation in min.](image-url)

**Fig. 4.** Average requirements of thiopental, in milligrams per kilogram of body weight, in two series of patients undergoing ligation of bilateral varicose veins under thiopental-nitrous oxide-oxygen anesthesia.

- Average of 48 normal subjects (blood urea 21–30 mg. per 100 cc.).
- Average of 8 subjects who received 15 Gm. of urea before operation (blood urea 42–62 mg. per 100 cc.).
- Individual requirements of subjects to whom urea was administered.

Vertical lines show two times standard error of mean.
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just before anesthesia. All subjects received a hypodermic injection of 10 mg. of morphine sulfate and 0.65 mg. of atropine sulfate about one hour before induction of anesthesia. Intermittent injection of thiopental supplemented by 6 liters of nitrous oxide and 2 liters of oxygen was the technique used for all cases. As a control, observations were made on 48 normal subjects undergoing the same operation, subjected to the same preoperative preparation and the same anesthetic technique employed by the same anesthetist. Only patients having operations of seventy-five minutes’ duration and over were included in the control series.

The results of this experiment are summarized in figure 4, giving the average requirements of thiopental in fifteen minute intervals for the control experiment as well as after the administration of urea. The illustration also shows the individual requirements for this barbiturate of the 8 patients under the influence of urea.

### Table 1

<table>
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<th>No.</th>
<th>Thiopental (mg.)</th>
<th>Duration of Anesthesia (min.)</th>
<th>Dose of Urea Administered (gm.)</th>
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<td>400</td>
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The difference between the two series is very similar to the results shown on figure 2 and strongly suggests that an elevation in blood urea, even without the coincidental biochemical upset of uremia, is capable of markedly reducing the tolerance to thiopental in man.

The following case further substantiates this view.

Case 6. A man, age 49, was admitted to hospital at weekly intervals for dilatation of urethral stricture. On two occasions it proved difficult to obtain satisfactory anesthesia for the procedure with thiopental-nitrous oxide-oxygen owing to the patient’s resistance to the barbiturate. He was then requested to take no fluid for twenty-four hours before coming to hospital and on admission 20 Gm. of urea was given orally. This procedure, carried out on two occasions, markedly increased the duration of the thiopental effect. Lest this be the result of the increasing ease of dilatation and hence reduction in the stimulus, the urea was omitted on two subsequent occasions and the original resistance to the barbiturate again became manifest. Details of anesthesia, and duration of thiopental effect on seven occasions in this patient, three with and four without previous administration of urea, are shown in table 1; events are recorded in
chronological order. Duration of anesthesia was reckoned from the end of the injection of thiopental to the first movement by the patient. At the fourth and seventh administrations several estimations of blood urea were carried out and figure 5 shows the degree and duration of elevation of blood urea that occurred.

In this last case in particular, and to a lesser extent in most of the previous ones, an undue degree of postoperative somnolence was observed. This was more apparent in those who received urea by mouth than in patients with a pathological rise in blood urea. In all cases (unless recorded to the contrary) consciousness was regained within thirty minutes of completion of the operation, and questions could be answered with a reasonable degree of accuracy. Although a tendency to fall asleep again when not being stimulated is common after the use of thiopental, an impression was formed by the nursing staff that in these patients this was more prone to happen than usual. Postoperative amnesia was also greatly increased. Only 2 of the 8 subjects who had urea by mouth remembered anything until the morning after operation, or an incidence of amnesia of 75 per cent. In
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comparing this with the control series of 20 patients, amnesia was present in only 8 (40 per cent).

Discussion

The above cited experimental and clinical evidence focuses the attention upon the role of kidney function as related to the duration of action of thiopental anesthesia. Although the results of animal experimentation and clinical observations differ in some aspects they are in essential agreement in the most important points. Significant increase in sensitivity to a standard dose of thiopental, evidenced by marked increase in sleeping time or, vice versa, the need for smaller doses for a comparable duration of anesthesia, could be demonstrated in animals in experimental azotemia and correspondingly in human beings having an increased blood urea level owing to obstruction of the urinary passages. Since, in animals, such an effect is only moderate and inconstant when this barbiturate is injected immediately after bilateral nephrectomy, the role of the kidney as a directly detoxifying organ appears to be of only moderate importance. Consequently, the impairment or loss of normal kidney function must be held largely responsible for the rapidly increasing sensitivity to the action of thiopental.

Of the experimental animals studied the rat seems to be most likely to show prolongation of thiopental action after nephrectomy. This applies both to the speed with which increased sensitivity developed following nephrectomy and to the degree of prolongation which may reach more than ten times the normal sleeping time. The mouse and the rabbit also demonstrate this phenomenon while the dog and cat react less in this respect. As we have reported earlier, we could produce a marked prolongation of sleeping time with thiopental in rabbits immediately after nephrectomy when the blood urea of the animals was acutely raised by intravenous injection of an artificial solution of urea. This could not be done in normal rabbits. The clinical experiments reported here, however, show that in the healthy human being the temporary increase of the blood urea level following oral administration of urea produces an effect upon thiopental anesthesia similar to that of endogenous azotemia. Since animal experimentation proved that similar, though quantitatively less pronounced, effects could be obtained by the injection of equally hyperosmotic amounts of sodium chloride or sucrose solution instead of the urea solution in freshly nephrectomized animals, it appears that physical-chemical changes which accompany artificial as well as endogenous azotemia play an important part in this phenomenon. Here one has to think of the changes of osmotic pressure in the body fluids and especially with regard to urea of its effect upon cell permeability. Other factors which may contribute to the prolonged action of thiopental in azotemia.
are still being investigated. The work on animals cited above gives evidence of a greater sensitivity of the azotemic animal toward thiopental; this is in agreement with the clinical findings. The decreased speed in the fall of the thiopental level in nephrectomized animals after equilibrium between blood and tissue has once been reached indicates a somewhat impaired rate of detoxification, probably partially attributable to metabolic disturbances resulting from the azotemia and partially to the loss of kidney tissue, which has some ability to destroy thiopental.

Newer experimental data reveal (12, 13) that the albumin fraction of the plasma proteins decreases after nephrectomy. Since thiopental is to a considerable extent bound on albumin the decrease of this protein fraction leaves a larger part of the injected drug unbound in the plasma. Only this free barbiturate is able to penetrate the blood-brain barrier; consequently, an azotemic animal has more active thiopental in his blood stream than a normal one given the same dose per kilogram. The fact that hexobarbital is much less bound to plasma proteins and also much less affected by experimental azotemia is in agreement with this viewpoint. It is not yet possible to quantitate the role that these and other factors may play in the over-all effect.

The clinical data show consistently a significant reduction of the dose of thiopental necessary to maintain anesthesia in patients with urinary obstruction as well as in normal individuals after administration of urea. For the first group, the average dose necessary to induce sleep was 73 per cent of that used in patients undergoing the same type of surgical procedure but having a normal blood urea level. Determinations of the additional amount needed to maintain anesthesia in the pathological group calculated in fifteen minute intervals showed these to be 60 to 73 per cent of the normal requirements. This is in agreement with the experiments in which thiopental requirements were determined in systemically healthy persons with and without oral administration of urea. Here, the urea treated group required 90 per cent as much of the drug for induction as did normal persons, probably not a significant difference, but only 55 to 64 per cent, very significantly less than the untreated ones, for the maintenance of an equally long sleep. The case reports further illustrate the remarkable correlation between blood urea level and thiopental requirements. This is particularly evident in case 6. The occurrence of long postoperative drowsiness in the above group of patients has been commented on occasionally by other observers.

Although it is obvious that much remains to be done in the elucidation of the pathophysiological and pharmacological mechanisms of these observations, certain clinical conclusions may be drawn. Additional observations of this type appear highly desirable and such studies should be extended to the action of the other anesthetic agents under
similar conditions. The present findings suggest that the anesthetist should expect a greater sensitivity of patients in azotemia to thiopental. The drug appears to be a safe and desirable anesthetic when its use is indicated and if properly administered, and no increased incidence of untoward reactions was noted during the course of the anesthesia.

SUMMARY

Although for some time the kidneys generally were not considered involved in the degradation of short acting barbiturates, recent work reveals that they possess some ability to destroy thiopental. New observations, however, appear to be of greater importance; these observations indicate that experimental animals, especially rats and rabbits, react with increasingly prolonged sleep to injections of thiopental as the time interval after nephrectomy or ligation of the ureters and the concomitant azotemia increases. Hexobarbital shows this change to a markedly lesser degree. Under appropriate conditions an acutely increased sensitivity to thiopental as measured by prolongation of sleeping time can be obtained by the injection of an artificial urea solution, leading to sudden azotemia.

Clinical studies are in essential agreement with these experimental findings. Patients undergoing prostatectomy and suffering from azotemia attributable to urinary obstruction required significantly less thiopental for induction and maintenance of anesthesia than a comparable group with normal blood urea level. Several patients subjected to thiopental anesthesia at different times with and without increased level of blood urea needed less of the drug during the azotemic stage. In normal human beings in whom the blood urea level was artificially raised by fluid restriction and oral administration of urea, anesthesia could be maintained with considerably smaller doses of thiopental than in a control group. The factors involved in these phenomena and their clinical significance are discussed.

REFERENCES


THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.
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OCTOBER 28–29, 1954

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