URINARY EXCRETION OF ARFONAD BY PATIENTS UNDERGOING "CONTROLLED HYPOTENSION" DURING SURGERY * † §

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THE production of bloodless operative field during surgical intervention, by the deliberate induction of hypotension, has been employed with increasing frequency by anesthesiologists and surgeons during the past few years. The techniques developed to accomplish this end usually have been dependent upon either a reduction of the total circulating blood volume (arteriotomy) (1) or a decrease in the peripheral resistance (sympathetic blockade) (2). In addition to various forms of conduction anesthesia, drugs which possess ganglionic blocking activity when injected systemically have been utilized to produce such sympathetic blockade. Pentamethonium (3), hexamethonium (4), pendiomid (5), and, more recently, arfonad (6), have all been employed for this purpose.

Arfonad, a thiophanium compound with potent ganglionic blocking activity, has provided the anesthesiologist with a controllable and a rapidly reversible method of inducing hypotension. Chemically, this drug is d-3,4(1',3'-dibenzyl-2'-keto-imidazolido)-1,2-trimethylene thiophanium d-camphor sulfonate (fig. 1). Randall, Peterson, and Lehman studied arfonad in 1949 and reported the ganglionic blockade and the subsequent reduction of arterial pressure produced by the drug in the anesthetized dog and cat (7). These workers also noted that, in addition to possessing a high degree of ganglionic blocking activity, arfonad caused histamine to be released in dogs, with the development of a condition resembling hemorrhagic shock. Mitchell and co-workers confirmed the release of histamine, observing that intradermal injections into humans, guinea pigs, and dogs produced typical wheals (8). Holman and Goth obtained evidence of histamine release in human subjects following subcutaneous injections of the drug (9). McCubbin

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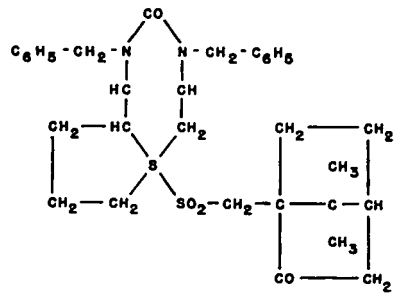
and Page, however, investigating the mechanisms of severe hypotension which occurs in dogs following the administration of large doses of arfonad, concluded that the drug lowers arterial pressure primarily by direct vasodilatation in that species, and that both ganglionic blockade and histamine release play a minor role in the hypotensive responses (10). Profound toxic reactions similar to those occurring in dogs have not been noted in human beings when the drug has been administered intravenously (11–13), and it is now evident that the dog reacts quite differently to arfonad than do the other species tested.

ARFONAD



4-3,4 (1',3'-DIBENZYL-2'-KETO-IMIDAZOLIDO)-1,2-TRIMETHYLENE THIOPHANIUM d-CAMPHOR SULFONATE

FIG. 1. Structural formula of arfonad.

Sarnoff, Goodale, and Sarnoff showed that a single intravenous dose of 0.1 or 0.2 mg. of arfonad per kg. of body weight produced a profound but shortlasting depressor response of the arterial pressure, so that it was possible to give the drug by a continuous infusion technique (11). Arfonad has been administered, therefore, by means of a continuous intravenous drip to induce hypotension during surgery, and by this method a very flexible control of the blood pressure has been made possible (6, 14, 15). Indeed, the basis of the clinical usefulness of arfonad in the production of hypotension during anesthesia and surgery has been its ultra-short action and the minute to minute control afforded by it of both the degree and the duration of the hypo-

tension. Since nothing is known of the fate of arfonad in the body, it has seemed desirable to investigate the possibility of urinary excretion of the drug, with a view toward obtaining a better understanding of its metabolism and the mechanisms of its very brief action.

CLINICAL EXPERIMENTS

Method. Female patients, in good general medical condition but undergoing various surgical procedures, were anesthetized with either nitrous oxide–ether or cyclopropane–ether and positioned on the operating table with meticulous care to place the operative site superiorly, in order to promote venous drainage by gravity from the wound and thus check the amount of bleeding during the surgical procedure. The arterial blood pressure then was lowered by the administration of a dilute (0.1 per cent) intravenous infusion of arfonad, according to the modified technique of "controlled hypotension" previously described (16). Briefly, this technique consists of the administration of the arfonad infusion at a sufficiently rapid rate to evoke a substantial fall in arterial pressure. As the pressure is being lowered, repeated blood-pressure readings may be correlated with the degree of vascular ooze visible in the wound, in order to ascertain the all-important level of pressure which will provide control of excessive bleeding during operation. The infusion rate is regulated to maintain this blood pressure throughout that part of the operation when it is desirable to control the amount of bleeding, and discontinued at the end of such time with a resultant prompt rise to normal levels. It will be noted (fig. 2) that the optimal level of pressure was generally much higher than the dangerously low levels of 50 to 60 mm. of Hg advocated in the past. A relatively bloodless operative field could be achieved in the majority of patients with the blood pressure stabilized within the range of 80 to 95 mm. Hg.

Prior to the induction of anesthesia and the administration of the hypotensive agent, an indwelling catheter was placed in the bladder and a preoperative urine specimen was collected as a control sample. Urine was collected again at the completion of operation, and this specimen was labeled the intra-operative sample. Subsequent urine samples were collected at 6, 12, and 24 hours postoperatively in the first patient in this series, and at 1, 2, 3, 4, 5, 6, 12, and 24 hours in the second patient. In the remaining patients, for reasons to be explained below, the urine specimens were collected preoperatively, at the end of operation, and then hourly for the first 3 postoperative hours.

Estimation of Arfonad. The urinary excretion of arfonad was determined colorimetrically by the method of Mitchel and Clark (17). Essentially, this procedure depends upon the formation of an ethylene dichloride soluble dye complex of bromphenol blue with a quaternary ion. It was noted by Mitchel (18) that tertiary sulfur likewise could be determined by this method.

Certain minor modifications of the original method as developed by Mitchel were found to be necessary. Urine itself had a deleterious effect upon color development, and rendered readings which were too low. This problem was solved by the construction of 3 standard curves, each employing a different urine concentration within the ranges which would be encountered in the actual test procedure; intermediate urine concentrations were then interpolated between curves.

It was also found that very large quantities of arfonad were present in some of the urine samples, so that it was necessary to dilute certain

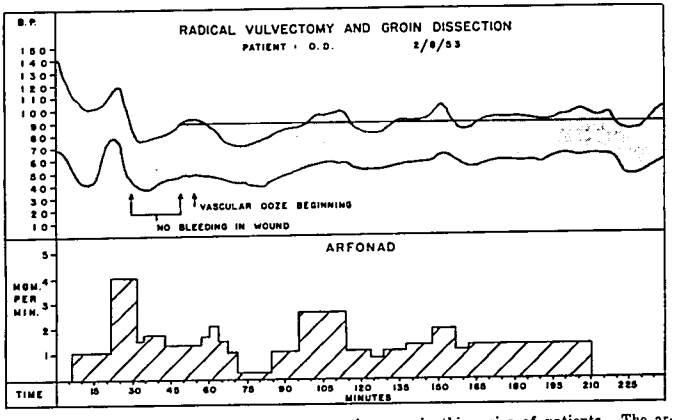


FIG. 2. Anesthetic chart from a representative case in this series of patients. The arfonad infusion was administered at a sufficiently rapid rate to produce a slow fall of blood pressure to that point at which bleeding no longer occurred in the operative wound. This optimal level of blood pressure was then maintained by regulating the flow rate of arfonad on a minute-to-minute basis.

of the specimens in order to carry out the determinations. The amount of dilution that was required varied with the time of collection of the specimen; that is, the intraoperative samples, being the most concentrated, were diluted some 25 times; whereas subsequent samples were diluted only 10 times and the final samples did not require dilution.

An example of a typical determination will be described to clarify the actual details of the procedure. The solid salts ‖ were weighed out

‖ List of Reagents:

Solid Na_2CO_3	0.6 gm.
Solid K_2HPO_4	1.0 gm.
Purified ethylene dichloride	5.0 ml.
Distilled water	1.0 ml.
Bromphenol blue solution (40 mg. in 50 ml. 30% K_2HPO_4)	1.0 ml.
Urine specimen to be tested	1.0 ml.

individually and placed in 30 ml. pyrex reagent bottles with inverted ground glass stoppers. To each bottle was then added 5 ml. of ethylene dichloride, 1 ml. of distilled water, and 1 ml. of the urine sample (diluted, in certain instances, as explained above) to be tested. Finally, 1 ml. of dye solution was added to each bottle, the bottles stoppered, and shaken mechanically for thirty minutes. At the end of this period of time, the contents were transferred to 15 ml. centrifuge tubes and centrifuged for five minutes at 1,500 r.p.m. The ethylene dichloride layer containing the blue complex was decanted into 6 ml. Coleman tubes and read on the Coleman Junior Spectrophotometer at a wave length of 600 Å.

The absolute sensitivity of the method was 25 micrograms of arfonad. The preoperative urine samples were employed as control specimens, since none contained detectable amounts of quaternary ions.

Results. The total dose of arfonad administered to patient No. 1 during a period of fifty-five minutes was 335 mg. Of this total amount, 9.0 mg. were recovered in the intra-operative sample, and 100 mg. were recovered in the sample collected 6 hours postoperatively. No drug could be detected in the samples collected 12 and 24 hours postoperatively. The total amount of arfonad recovered was 109 mg., or 33 per cent of the total dose that had been administered.

In order to verify the supposition that the material containing quaternary ions which was recovered in the urine was indeed arfonad, a diluted sample of urine was assayed biologically (by testing its effect upon the blood pressure of the cat and its influence upon the contraction of the nictitating membrane of that animal) and was shown to bear a 1:1 ratio with known amounts of arfonad.

A total dose of 290 mg. of arfonad was administered to patient No. 2, and the times of collection were varied in order further to delineate the time limits of the urinary excretion of the drug: postoperative specimens were collected every hour for the first six hours after operation, and then at twelve and twenty-four hours postoperatively. The intra-operative sample of urine contained 48 mg. of arfonad; and the samples collected at the end of the first, the second, and the third postoperative hours contained, respectively, 5.5 mg., 1.0 mg., and 0.5 mg. of the drug. No detectable material was found in the samples collected at the end of the fourth, the fifth, or the sixth postoperative hours, or in the samples collected 12 and 24 hours postoperatively.

These results suggested that it was necessary to follow the urinary excretion only for the first three postoperative hours, since no detectable amounts of drug could be recovered in the samples collected after that time. In all subsequent patients, therefore, urine specimens were collected preoperatively, at the end of operation, and then at the end of the first, the second, and the third postoperative hours. Table 1 presents the results obtained from the 7 patients in whom all specimen collections and determinations were completed successfully (a number

TABLE 1

EXCRETION OF ARFONAD IN URINE

Patient	Amount of Arfonad Administered, mg.	Amount of Arfonad Recovered in Urine, mg.	Recovered, per cent	Unaccounted Dose, per cent
1	335	109	33	67
2	290	55	19	81
3	540	250	46	54
4	348	93	27	73
5	590	190	32	68
6	102	32	34	66
7	101	25	25	75
			—	—
		Averages	31	69

of other patients were studied, but difficulties in collections of specimens occurred and these cases are not included in this report). It is seen that 31 per cent of the total dosages of arfonad administered to these 7 patients was recovered in the urine; the remaining 69 per cent of the total dosage could not be accounted for by urinary excretion.

ANIMAL EXPERIMENTS

Methods. To determine whether excretion through the kidney, or possible destruction of the drug by that organ, might account for all or part of the short duration of action of arfonad, the following experiment was carried out. In a cat under dial®-urethan anesthesia, the renal blood vessels were identified and ligatures were placed loosely about them. Then 50 μg. of arfonad were administered intravenously and the effect upon the nictitating membrane and the blood pressure noted. This control was repeated several times, after which the ligatures were tied and the same dose of arfonad administered. The effects of this dose upon the nictitating membrane and the blood pressure were observed. These experiments were repeated on three separate occasions.

In order to determine the importance of the liver in the destruction of the drug, an experiment was carried out in cats similar to that above but involving the liver. Under dial-urethan anesthesia, the vessels to the liver were identified and loose ligatures placed around these vessels. A test dose of arfonad was then administered intravenously, and the effects upon the nictitating membrane and the blood pressure noted. The ligatures then were tied, and the effects of the same dose of drug observed. In addition, the activity of arfonad injected into the portal vein was contrasted with the effect obtained following the injection of the same amount of the drug into one of the jugular veins.

Results. Removal of the kidneys from the circulation caused no change in the duration or the intensity of the action of arfonad. A similar result was obtained in experiments in which the liver was re-

moved from the circulation, although these animals were already in a hypotensive state, and thus the estimation of the effect of arfonad was difficult. No differences in activity were noted between the results obtained following portal or jugular injection of a given dose of arfonad.

DISCUSSION

The studies of the urinary excretion of arfonad in patients undergoing "controlled hypotension" during surgery indicate that a considerable amount of the total dose of drug administered intravenously can be excreted quite rapidly and in a biologically active form, since the material recovered retains its potent and brief ganglionic blocking activity. However, it is also clear that only about one third of the total administered dose can be recovered from the urine, with the fate of the remaining two thirds unknown.

It appears that, in the cat at least, the kidneys do not play a role in the destruction of arfonad, nor does the liver, although the evidence supporting this latter statement is not so clear-cut. It is probable that the drug undergoes very rapid alteration within the body in such a way that its very high degree of ganglionic blocking activity is lost within an extremely short period of time.

The mechanism of this change in the drug is unknown and the very brief duration of arfonad's activity remains a matter of considerable interest. It seems likely from the results obtained in this study that renal excretion does not account for the changes. The question of storage should be considered; however, the observed facts that urinary excretion falls rapidly to zero within three hours after the cessation of the infusion in patients and that subsequent urine samples over a twenty-four-hour period contain no chemically or biologically active material, would tend to negate this as an explanation for the rapidity and the briefness of action. It therefore appears probable that the drug undergoes rapid destruction or at least is rapidly rendered inactive within the body by some as yet undetected mechanism.

SUMMARY AND CONCLUSIONS

The urinary excretion of arfonad was measured in 7 patients undergoing "controlled hypotension" during surgery, and an average of 31 per cent of the total doses which had been administered was recovered from the urine within three hours after operation. No further urinary excretion could be shown during the first 24 postoperative hours, and the fate of the remaining 69 per cent is unknown.

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