THE EFFECT OF ARFONAD ON THE MONKEY

JOSE A. AGUILAR, M.D., AND EDWIN B. BOLDREY, M.D.

IN 1949, Randall, Peterson and Lehmann [15] demonstrated the ganglionic blocking action of Arfonad * and later a direct vasodilator property was demonstrated by other investigators.[10] Subsequent reports of clinical trials attested to the effectiveness of Arfonad in achieving controlled hypotension. The carefully titrated administration of Arfonad in humans, in which dosages ranging from 12 mg. to 1,500 mg.[9] were used, were of little value in determining its margin of safety. The degree of hypotension induced in humans never approached the level of 32 mm. of mercury (mean arterial blood pressure) believed to be critical for maintaining circulation in the capillary bed.[7, 8] Many fundamental questions about Arfonad-induced hypotension remained unanswered, and the safety of its continued use in humans has been uncertain. The experimental work which followed clinical trial was concerned with its mode of action and with the renal and cerebral hemodynamics of a limited hypotensive state.[13, 14]

Although hypotension has to some extent been supplanted by hypothermia as an adjuvant to the handling of vascular intracranial problems, there are still many occasions in which hypotension may have value either alone or in combination with lowered temperature. This study was undertaken, therefore, to shed further light on the hypoxic effect, particularly on the brain, of the greatest degree of hypotension obtainable in the monkey by use of Arfonad. The experiment also yielded information concerning other toxic effects of the drug and its elimination by the kidney.

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* Arfonad is *d*-3, 4(1',3'-dibenzyl-2'-keto-imidazolido)-1, 2-trimethylene thiophanium *d*-camphor sulphonate (trimethaphan camphorsulfonate).

METHOD AND MATERIALS

The experiments were conducted on 44 Macacus rhesus monkeys, weighing from 2 to 6 kg. Pentobarbital and Arfonad were given intravenously while the head of the animal was kept at the level of the heart. The anesthetic was administered carefully to abolish movement and corneal reflex and to preserve respirations and the cough reflex. Endotracheal intubation was facilitated by cocaine applied locally. After a period of mechanical ventilation all animals were permitted to breathe without the respirator in order to test the depth of anesthesia. When the animals started breathing spontaneously the respirator was restarted to relieve them of respiratory effort and to provide ventilation during the hypotensive period. Body temperature was maintained with a warmed woolen mattress and was recorded by intrarectal thermocouples. The femoral artery was cannulated with needles no smaller than no. 22 gauge which were connected to a Statham strain gauge.[20] A direct-current amplifier system † projected a continuous quantitative reading of the pulse curve onto a cathode-ray oscillograph equipped with a calibrated photographic recording system. The mean blood pressure was charted graphically from short segments of the photographed arterial pulse pressure. Intermittent injections of a dilute solution of heparin prevented clotting of blood in the needle. Blood pressure was recorded continuously until the animal awakened. At the termination of the procedure the arterial perforation was sutured.

Simple supportive therapy was given to help the animals during the immediate postoperative period. Long-term survival of the animals in order to make a fair assessment of functional damage was the principal objective of the experiment and their deliberate sacrifice was avoided. Complete autopsies were obtained

† Consolidated Electrodynamics Corporation, Pasadena, Calif.

of the animals that did die, and sections of all the major organs were studied microscopically.

Only in female animals was it possible to catheterize atraumatically for urinalysis. Otherwise, urine for analysis came from random spontaneous voidings and care was taken to include only clean, fresh specimens. The centrifuged specimens were studied microscopically and the fluid was examined qualitatively for *p*H, albumin, acetone and sugar.

In eight preliminary experiments Arfonad, in a solution of 0.1 to 1.0 per cent, produced moderate and inconstant hypotension. More concentrated solutions were necessary to maintain a constant blood volume. Studies involving extensive sampling were abandoned and the total fluid administered was restricted to less than 50 ml. to avoid overhydration.

In the principal study 36 experiments were carried out on 31 animals (5 animals participated twice since they had received very small doses of Arfonad in the first experiment). The duration of hypotension was usually from one to two hours. The principal objective in every experiment was to maintain a systolic blood pressure of less than 40 mm. of mercury in order to impose a significant level of hypotension.

Group 1 (13 Animals). In these experiments the dosage was increased gradually to determine the total hypotensive effect that could be achieved with the least amount of the drug. The maximum hypotensive response was found to consist of an initial sudden fall in pressure which lasted for about ten minutes, followed by a recovery to a slightly higher blood-pressure plateau which resisted large doses of Arfonad. A quantitative discussion of this response will be made later. The degree of the initial fall in blood pressure could not be repeated and could only be achieved with the initial dose of at least 10 to 15 mg. (3.0 to 4.0 mg./kg. of body weight). When a predictable response was established the routine of giving additional Arfonad after the initial dose was modified with respect to the expected development of the drug-resistant plateau, as follows:

Group 2 (Eight Animals). After the initial hypotension, further Arfonad was withheld until the first sign of a rise in blood pressure. The beginning of the recovery was clearly shown in the oscilloscope by an improvement in the pulse pressure.

Group 3 (Six Animals). Additional administration of the drug did not start until five to ten minutes after the rise from the initial dip was established.

Group 4 (Six Animals). In this group of experiments, amounts of Arfonad were administered at rapid intervals throughout the initial fall in blood pressure.

Group 5 (Five Animals). These animals were tuberculous and their sacrifice was anticipated by giving them large doses of Arfonad in a 5.0 per cent stock solution in total doses ranging from 33 to 229 mg./kg. of body weight. Administration of large doses was started immediately to test the possibility of continuing the maximum hypotensive value that was possible only with the initial rapid dose.

Group 6 (Three Animals). These animals were tested using the same experimental conditions and the same type of anesthetic, but without the use of artificial respiration.

Group 7 (Four Animals). In the light of the experience with Arfonad in the normothermic monkeys, it was decided to test the drug's hypotensive property in animals after they had been made hypothermic. Four animals were cooled to 26.0 C. with ice packs. Arfonad was then given to assure a quick, complete hypotensive action. Hypotension was ended by allowing the animals to breathe by themselves. They were then warmed gradually in a tepid bath.

Miscellaneous Considerations. In eight animals taken at random from the group of 36, drainage of cerebrospinal fluid failed to change the degree or pattern of the hypotensive response. The fluid was collected intermittently by an indwelling cisternal puncture needle. Blood pressure was recorded from the brachial artery after the animals had been placed in a horizontal lateral decubitus position. Total protein and volume of fluid formation were recorded during periods of spontaneous respiration, ventilation, hypotension and recovery, but there was no consistent trend, even in the control values, which would justify proceeding with qualitative cerebrospinal fluid changes.

TABLE 1

COMPLICATIONS OCCURRING IN 36 EXPERIMENTAL ATTEMPTS TO INDUCE STRESSFUL HYPOTENSION WITH THE MAXIMUM HYPOTENSIVE EFFECTS OF ARFONAD

Experiments are arranged in order of increasing dosage to show the progressive severity of the complications with toxic amounts of the drug.

Animal (no.)	Weight (kg.)	Total Amt. of Arfonad (mg./kg.)	Duration of Administration of of Arfonad (minutes)	Mean Blood Pressure, First 10 min. (Maximum Hypotension) (mm. Hg)	Results
			Group 1		
			Experiments with Trial of Progressive Increase in Total Dosage		
31	4.0	4.2	120	60/40	Recovery. Normal urine.
875	3.1	6.4	110	36/28	Recovery. Casts, albumin in urine —3 days.
32	3.5	6.7	120	56/45	Casts—24 hours and albumin in urine—3 days.
33	4.5	10.2	100	50/42	Recovery. Albuminuria 2 days.
6	3.5	14.3	50	55/43	Recovery. No urinalysis.
27	3.0	20.0	45	36/28	Recovery. Albumin and casts.
429	8.0	25.0	90	35/25	Recovery. Casts in urine.
26	3.5	27.1	100	38/32	Died 4 to 6 hours postop. Autopsy negative. Possible circulatory failure.
60	4.0	50.0	40	36/29	Recovery. No urinalysis. Death from tuberculosis 6 weeks later. No renal disease.
10	4.0	62.5	40	35/29	Died—4 days. Anorexia, debility, oliguria. Recurrent hypotension and hypothermia.
848	3.5	87.5	70	38/28	Died—2 days. Anorexia, debility, oliguria. Recurrent hypotension and hypothermia.
9	3.5	107.0	125	39/30	Recovery after 4 weeks of anorexia, debility, weight loss, casts in urine.
963	3.0	166.7	100	36/28	Died—4 days postop. Anuric. Blood-urea nitrogen—183. Severe renal damage.
			Group 2		
			Experiments in Which Additional Arfonad Was Withheld Until Early in the Recovery from the Initial Fall in Blood Pressure		
2	3.6	5.5	50	36/30	Recovery. Normal urine.
830	6.0	21.0	85	36/25	Recovery. Normal urine.
327	3.5	71.0	90	36/30	Died. Unable to breathe unassisted when respirator failed.
4	2.6	115.0	30	35/25	Died—4 weeks postop. Anorexia, debility, weight loss. Tuberculosis. Severe resolving renal damage.
8	2.8	125.0	122	38/30	Died—6 hours postop. Circulatory failure.
631	4.2	125.0	100	36/28	Recovery. Recurrent hypotension. Anorexia, debility, weight loss for 3 weeks. Autopsy 4 weeks later. Severe resolving renal damage.
21	3.8	198.0	60	36/30	Died 2 hours postop. Circulatory failure. Acute renal damage.
6	2.8	214.0	65	37/27	Died—6 hours postop. Circulatory failure. Acute renal damage.

TABLE 1—*Continued*

Animal (no.)	Weight (kg.)	Total Amt. of Arfonad (mg./kg.)	Duration of Administration of of Arfonad (minutes)	Mean Blood Pressure, First 10 min. (Maximum Hypotension) (mm. Hg)	Results
			Group 3		
			Experiments in Which Additional Arfonad Was Withheld Until Later in the Recovery from the Initial Fall in Blood Pressure		
881	5.0	3.39	110	45/35	Recovery. Casts in urine—2 days.
25	3.3	38.0	36	36/28	Recovery. No urinalysis. Death from tuberculosis 4 months later. No renal damage.
875	4.8	52.0	60	36/30	Recovery. Casts in urine.
30	2.8	75.0	95	39/29	Died—12 hours. Circulatory failure. Casts in urine.
29	3.0	83.0	120	36/28	Died—3 days postop. Anuric. Blood-urea nitrogen 189. Severe renal and hepatic damage.
22	3.0	191.0	120	35/25	Died—2 hours. Circulatory failure. Severe, early renal and hepatic damage.
			Group 4		
			Experiments in Which Arfonad Was Continued Immediately After the Initial Fall in Blood Pressure		
9	3.0	30.0	30	32/26	Recovery. Normal urine.
632	2.8	56.0	120	36/28	Died—6 hours postop. Circulatory failure.
933	4.0	96.0	100	39/30	Recovery. Recurrent hypotension. Anorexia, debility and weight loss.
2	4.5	155.0	75	32/25	Died—3 hours postop. Circulatory failure.
			Group 5		
			Experiments in Which Excessive Administration of Arfonad Was Continuous With the Initial Fall in Blood Pressure		
830	6.0	33.0	111	36/28	Recovery. Casts in urine. Autopsy 7 weeks later. No renal damage.
861	3.2	86.0	30	35/25	Died 5 hours postop. Circulatory failure. Albumin, casts in urine. Acute renal and hepatic damage.
857	4.2	101.0	80	38/30	Died 2 days. Anuria. Acute renal and hepatic damage.
869	4.0	187.0	100	36/27	Died 3½ hours postop. Circulatory failure. Acute renal and hepatic damage.
23	2.4	229.0	50	35/25	Died 7 hours postop. Circulatory failure. Acute renal and hepatic damage.

Results

Table 1 summarizes the results in 36 experiments when large doses of Arfonad were given with restricted amounts of fluids in an attempt to induce stressful hypotension. It proved impossible to produce the low blood pressures desired with the maximum hypotensive properties of Arfonad. An example of the blood-pressure record is shown in figure 1, a composite record made during one experiment (in which a no. 22 gauge needle was used). The characteristics of the response to total vasodepression induced by Arfonad are as follows:

Group 1 (13 Experimental Trials of Increasingly Larger Doses of Arfonad). When Arfonad was given slowly the fall in blood

pressure was gradual, irregular and never very pronounced. The fall in pressure occurred when solutions of up to 0.2 per cent were given to animals 6, 32 and 33. In animal 10, the drug was given rapidly during the first ten minutes and the concentration was increased from 0.05 per cent to 0.8 per cent. The fall in blood pressure was gradual but was complete after a total dose of 15 mg. (approximately 3.0 to 4.0 mg./kg.). The remaining 8 animals each received an initial dose of at least 10 mg. (approximately 3.3 mg./kg.) in the first 30 to 60 seconds. This resulted in an abrupt fall in blood pressure which was consistent in each animal and was the lowest fall in blood pressure that could be achieved. The initial fall lasted 8 to 12 minutes and averaged 33 mm. of mercury (mean arterial blood pressure) for the eight animals. A rise in mean blood pressure of 8 to 13 mm. of mercury regularly followed until a plateau was reached which resisted subsequent dosages as high as 30 to 40 mg./kg. of body weight. The degree of the initial fall could not be repeated but a rise in blood pressure from the drug-resistant plateau was easily prevented with additions of 5 to 10 mg. of Arfonad given every ten minutes.

Groups 2, 3 and 4 (Three Groups of Experiments in Which Different Techniques of Administration of Arfonad Were Used During the Early Part of the Hypotensive Period). There was no effect on the development of the rise in blood pressure after the immediate maximum fall when the schedule of adding Arfonad to the initial dose was changed in these three groups. The rise of from 8 to 13 mm. of mercury occurred at the expected time in spite of the variable dosages within the wide range of safety (up to 30 to 40 mg./kg.) that were tried on the drug-resistant plateau.

When larger doses of Arfonad were given during the drug-resistant plateau an irreversible hypotension resulted. Cardiac arrhythmias developed and the blood pressure gradually fell as pulmonary edema and cardiac standstill developed. The electrocardiograms often revealed second-degree heart block and Wenckebach phenomenon, or, in some cases, frequent ectopic systoles that progressed to a bundle-branch block and low voltage. Curiously, the heart rarely showed ventricular fibrillation when examined by direct vision in the terminal stages. Manual massage and large doses of vasopressors would often restore a period of regular pulsations which would gradually diminish in vigor and proceed to cardiac arrest. Dilatation of the right side of the heart occurred and the bronchioles were filled with foamy moisture.

Group 5 (Five Animals to Whom Arfonad Was Given in Excessive Dosages During the Effect of the Initial Maximum Fall). In three animals the drug-resistant rise in blood pressure was blocked by giving, during the first ten minutes, amounts of Arfonad that caused irreversible circulatory failure. The fourth animal survived a dosage of 33.0 mg. per kilogram

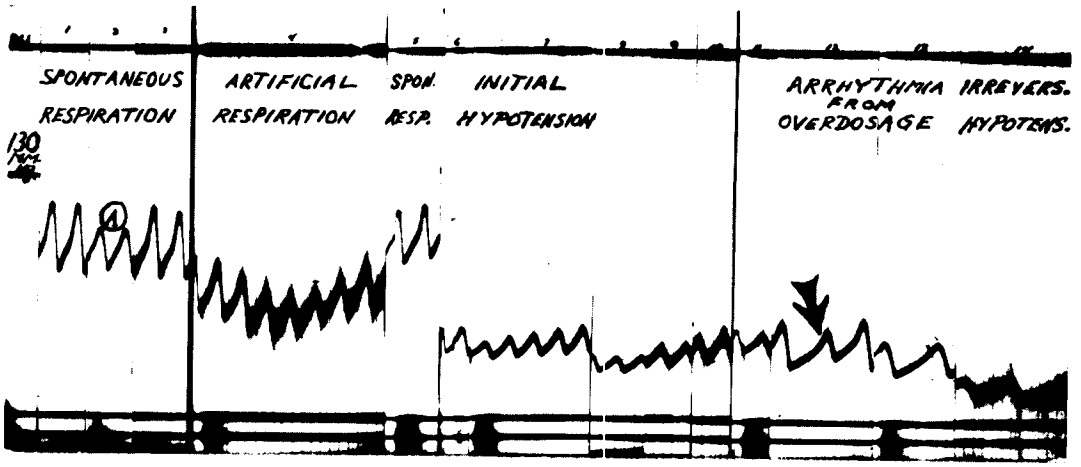

FIG. 1. Composite of the blood pressure record during one experiment. Segment A shows the damping effect of smaller needles. The arrow points to cardiac arrhythmias.

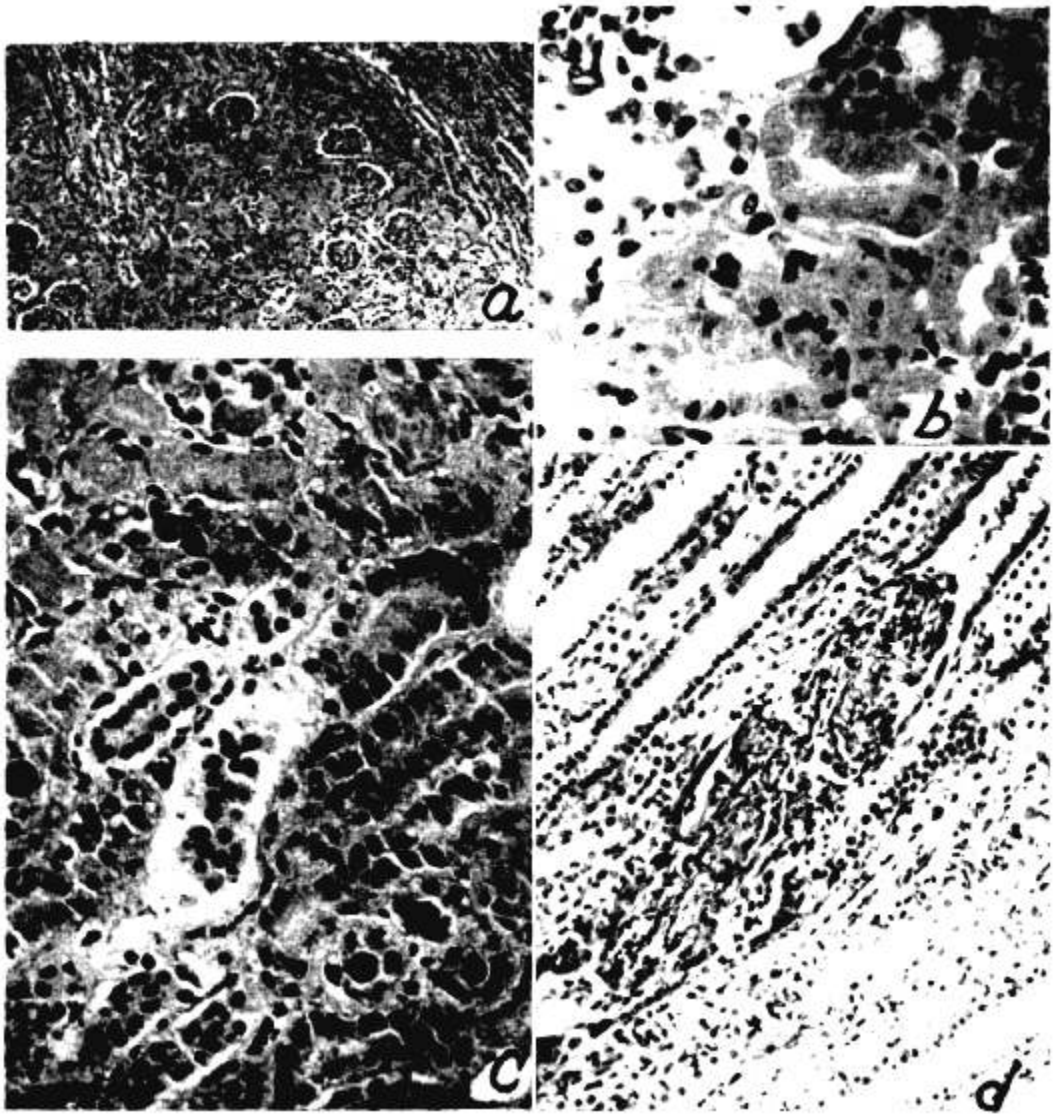

FIG. 2. The lesions in the kidney following large doses of Arfonad. (a) Damage in the proximal convoluted tubules (H & E, × 35). (b) Early changes in the tubular epithelium three hours after administration of the drug was stopped (H & E, × 240). (c) Transformation of nuclei to a dark material that also appears in the lumens of the tubule (H & E, × 240). (d) Cellular cast in a distal tubule (H. & E, × 120).

of body weight. The fifth died after two days of anuria.

Relation Between the Dosage of Arfonad and Its Toxicity. A survey of the experiments, arranged in order of increasing dosage in each group (table 1) shows that dosages of up to 20 to 30 mg. kg. of body weight were well tolerated but that death usually occurred whenever the total dose of Arfonad exceeded 50 mg. kg. of body weight. Eleven of the 31 animals survived for periods varying from one day to more than three weeks. They awakened from anesthesia but continued to be debilitated, anorexic and in a curiously poikilothermic state, the temperature often being from 28–32 C. Some of the animals died 48 to 72 hours after the onset of persistent hypotension and circulatory failure, but no evidence of damage to the

brain or of visual disturbance was found. The monkeys awakened promptly and recruited strength to resist examination. Animals 60, 9, 4 and 631 survived a two to three week period of anorexia, debility and weight loss.

Urinalysis. Attention was focused on the urine when gross hematuria occurred in one monkey who was given the drug during anesthesia without artificial respiration. The appearance of albumin, well-molded casts of proximal tubular epithelium, and often red blood cells became consistent. These were routine findings whenever the dose of Arfonad exceeded 10 mg./kg. of body weight, but were also found in two monkeys that had received only 3.3 and 6.4 mg./kg. respectively. The development of casts during the actual period of hypotension was recorded in four female monkeys studied by catheter drainage. Each was oliguric during the period of hypotension and one showed an impressive linear decrease in urinary output. When doses did not exceed 40 to 50 mg. the casts disappeared in three to seven days, but albuminuria continued indefinitely. Rhomboid crystals were commonly observed. Three animals died after two, three and four days respectively, following complete renal shutdown and a rising blood-urea nitrogen.

Autopsy. Twenty-one postmortem examinations were performed. Grossly, the only abnormality was the frequent occurrence of moderate gastric dilatation and retained secretions. The most important microscopic finding was selective damage to the proximal convoluted tubules of the kidney (fig. 2a). The greater the dose of Arfonad, the more severe was the damage. Conspicuous cellular damage occurred in the proximal tubules as early as two to four hours after the administration of the drug ceased. Figure 2b shows karyorrhexis of nuclei and dissolution of cytoplasm in one animal that died within three hours. In the collecting tubules epithelial casts could be clearly identified (fig. 2d). In one instance of large dosage the nuclei were transformed into a homogeneous dark blue (hematoxylin and eosin); a similar material was also present in the tubules (fig. 2c). In the animals surviving for three to five days the proximal tubular epithelium was completely necrotic, and cells were transformed into brightly eosinophilic, finely granular coagulum. Animals surviving for three to six weeks showed severe unresolved renal damage but each had groups of tubular units that were seemingly spared. The glomeruli and distal tubules showed no noticeable changes. Central lobular necrosis occurred in the liver only when very high dosages were administered.

Arfonad-Induced Hypotension During Spontaneous Respiration. The 3 monkeys who were given the drug while breathing without assistance were uniquely similar in the development of acute respiratory failure. The profound initial drop in blood pressure and complete mydriasis did not occur as they did in the animals on whom the automatic respirator was used. Undiluted Arfonad was given rapidly in increments of 25 mg. until respiratory difficulty developed manifested by weak body movements and swallowing gestures. An abrupt expulsion of air followed a deep inspiratory effort as a slow, vigorous pulse developed. Administration of Arfonad was continued until cyanosis appeared and respiratory arrest developed. The animals were then promptly relieved with the mechanical respirator, at which time a moderate fall in blood pressure occurred. Within 10 to 20 minutes all three monkeys were able to resume spontaneous respirations. Recovery was uneventful, although all the animals had casts in the urine for several days after the procedure. Two of the animals were autopsied one month later and both had many damaged renal tubular units.

Arfonad-Induced Hypotension During Hypothermia. Administration of the drug to animals in the hypothermic state gave a gratifying level of hypotension with relatively small doses of Arfonad. Mean blood pressure was stable and sustained at the levels indicated in table 2. Arfonad abolished the shivering mechanism and facilitated hypothermia with a minimum amount of anesthetic. All four animals were taken off the automatic respirator at the depth of their hypothermic and hypotensive state and each began spontaneous respirations promptly. Three of the animals recovered rapidly and completely from a one-hour period of hypotension in the hypothermic state. The fourth was hypotensive for two hours and was breathing well during the warming period. He never recovered a normal blood pressure

TABLE 2

ARFONAD-INDUCED HYPOTENSION DURING HYPOTHERMIA

Animal (no.)	Weight (kg.)	Temperature Before Hypotension (C.)	Duration of Hypothermia (hours)	Total Amount of Arfonad Given (mg.)	Mean Blood Pressure During Hypotension (mm. Hg)	Duration of Hypotension (hours)
631	5.0	26.4	5	100	30	2
834	3.0	23.8	3	100	40	1
881	3.1	26.5	5	100	30	1
875	3.1	26.1	4	100	29	1

and was found dead shortly after his body temperature had been restored.

DISCUSSION

In these experiments on monkeys, the demonstration of a blood pressure level that resisted doses of up to 50 mg. per kilogram of Arfonad has precluded the need for careful titration against a dangerous hypotension. It is apparent that a critical hypotension exists which will not cause physiologic damage in the dormant man and anthropoid in a horizontal position.[1] This level will be tolerated when the pressure-regulatory mechanisms for the postural changes of normal activity are not at play, insofar as the hypotension is not provoked by blood-letting. Even in shock, the paralysis of vasoconstriction with ganglionic-blockers is protective against circulatory collapse and death.[2, 4] The existence of a resistant "blood-pressure floor" promises a new concept of safe levels of hypotension, at least with respect to the controlled hypotension of ganglionic-blocking agents.

The observations in the present study are consistent with the experience with Arfonad in humans. Mazzia, Ray and Artusio,[9] and others [19] observed an initial drop in blood pressure, imperceptible by cuff manometer, which lasted for 10 to 20 minutes after Arfonad-induced hypotension. A similar experience has been described with the use of Hexamethonium.[19, 23] In 39 patients Scurr and Wyman [16] reported a "pressure floor" of 60 to 80 mm. of mercury systolic that resisted increased doses of Arfonad.

The mechanism of the rise in blood pressure to the drug-resistant plateau is explained by increase in plasma volume resulting from an interchange of fluid from the extracellular space through the capillary membrane. The reduced intracapillary hydrostatic pressure during the acute phase of hypotension causes a shift of fluids into the capillaries from the tissues due to plasma-protein osmotic pressure until an equilibrium is restored. The "denervated" vascular bed is thus distended to capacity, sustaining a critical pressure. The rapid development of this process of autoinfusion has been shown experimentally [6, 21] and its role has been stressed as a more efficient system when a greater surface for infusion is afforded by preventing vasoconstriction.[22] The humoral substances occurring with hypotensive states described by others [3, 17] may also play a role. Of more direct relation to Arfonad with respect to humoral substances that affect the blood pressure is its histamine-liberating activity.[11]

There was no evidence to incriminate hypoxia as the sole cause of the damage to the kidneys and liver. Other investigators have shown that the kidney is relatively resistant to hypoxia.[12] The severity of the tubular damage was related to the amount of Arfonad given rather than to the degree of hypotension. These lesions must be explained by the combined effect of drug toxicity, low glomerular filtrate fraction, and whatever hypotensive hypoxia exists. The observation of selective toxicity of Arfonad in the proximal convoluted tubular epithelium of the kidney under the conditions of this project appears significant in relation to observations in the human. During the hypotension that is incidental to the administration of Arfonad, it is unlikely that a sufficient glomerular filtration is occurring to allow its excretion by this route.[13] Yet it is known that in humans Arfonad appears in

large amounts in the urine very rapidly after its intravenous administration.[5] One must assume, therefore, that active tubular excretion is responsible for the rapid clearance of Arfonad and that it is this site which is selectively damaged by toxic amounts of the drug.

The dose of 50 mg./kg. of Arfonad that uniformly caused serious toxicity or fatality was three to four times greater than dosages that are considered to be moderate (15 mg./kg.) for humans during an average period of hypotension under anesthesia. Clinically, renal complications are known to be foremost among the serious consequences directly related to the drug itself or to the associated hypotensive state. Oliguria was a major postoperative complication in three of the 98 cases reported in 1956 by Mazzia, Ray and Artusio.[9]

Evidence of damage due to hypoxia occurred in a single experiment in which the animal showed an unusual response to a single initial dose of 50 mg. His blood pressure dropped to 4 to 10 mm. of mercury for 10 minutes and stayed below 16 mm. of mercury for 20 minutes before given vasopressors. This monkey showed no damage in other organs. The damage from hypotension, however, signifies that the protective drug-resistant plateau in monkeys is not completely reliable and that unusual responses can occur. A case of death from cerebral hypoxia in the human has also been reported.[9]

Respiratory failure with large doses of Arfonad in cats and monkeys through a mechanism exclusive of a curare-like action on the muscles of respiration was initially reported by Randall, Peterson and Lehmann.[15] Respiratory failure was repeated in the present study in an identical and consistent pattern in three monkeys with doses of 53, 56 and 89 mg./kg. of body weight. Respiratory failure occurred at 33, 35 and 39 minutes, respectively, after the administration of the drug was begun. The mechanism of this action is as yet unexplained.

A limited exploration of the maximum hypotensive effect of Arfonad in conjunction with hypothermia was conducted on four animals. This small group is mentioned for three reasons. First, the degree of hypotension obtained was gratifying and was the only way in which blood pressures below 30 mm. of mercury could be sustained. Secondly, the effect of the drug in blocking the shivering mechanism, stabilizing cardiac irritability, and rendering the animal more truly poikilothermic with minimal anesthesia was impressive. The protective action of Arfonad against ventricular fibrillation in hypothermic dogs undergoing cardiotomy has been demonstrated by Shumacker *et al.*[18] This aspect of the potential use of Arfonad should be explored further. Lastly, the animals rendered hypotensive while in a hypothermic state recovered much more promptly from the effects of hypotension. They appeared to be more alert on the first day and urinated more promptly.

Summary

Forty-four anesthetized monkeys were subjected to a wide dosage range of Arfonad in order to determine quantitatively its maximum hypotensive action. A histopathological search was made for evidence of anoxic damage at these hypotensive levels. The drug was administered by careful titration and by addition of massive supplementary doses at varying intervals following the initial hypotensive response under conditions of spontaneous respiration, artificial respiration (normothermia), and hypothermia.

The total action of Arfonad in the Macacus rhesus monkey consists of a profound initial hypotension of brief duration followed by a rise to a mean blood pressure of 40–45 mm. of mercury, which resists additional doses of the drug. The maximum hypotensive effect of Arfonad may be achieved with amounts that are within a wide margin of safety. This degree of hypotension is easily tolerated by the monkey during anesthesia and artificial respiration without toxic reaction. Larger doses of Arfonad have a toxic effect upon the proximal convoluted tubules of the kidney. Death from Arfonad intoxication results from respiratory failure or, when artificial respiration is employed, from renal damage. Still lower levels of hypotension can be achieved with a combination of Arfonad and hypothermia.

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REFERENCES

1. Best, H. C., and N. B. Taylor: The Physiological Basis of Medical Practice, ed. 5. Baltimore, Wilkins & Williams, 1950, p. 169–171.
2. Boba, A., and Converse, J. G.: Ganglionic blockade and its protective action in hemorrhage: review, ANESTHESIOLOGY **18**: 559, 1957.
3. Bromage, P. R.: Effect of induced vascular hypotension on liver; alterations in appearance and consistence, Lancet **2**: 10, 1952.
4. Converse, J. G., and Boba, A.: Experimental study of Arfonad in hemorrhagic shock in dogs, Am. Surgeon **23**: 420, 1957.
5. Gertner, S. B., Little, D. M., Jr., and Bonnycastle, D. D.: Urinary excretion of Arfonad by patients undergoing "controlled hypotension" during surgery, ANESTHESIOLOGY **16**: 495, 1955.
6. Glasser, O., and Page, I. H.: Experimental hemorrhagic shock; study of its production and treatment, Am. J. Physiol. **154**: 297, 1948.
7. Griffiths, H. W. C., and Gillies, J.: Thoracolumbar splanchnicectomy and sympathectomy; anesthetic procedure, Anaesthesia **3**: 134, 1948.
8. Landis, E. M.: Micro-injection studies of capillary blood pressure in human skin, Heart **15**: 209, 1930.
9. Mazzia, V. D. B., Ray, B. S., and Artusio, J. F.: Use of a thiophanium derivative for controlled hypotension in intracranial operations, Ann. Surg. **143**: 81, 1956.
10. McCubbin, J. W., and Page, I. H.: Nature of hypotensive action of thiopanium derivative (RO 2-2222) in dogs, J. Pharmacol. & Exper. Therap. **105**: 437, 1952.
11. Mitchell, R., Newman, P. J., MacGillivray, D., and Clark, B. B.: Evaluation of histamine liberator activity, illustrated by thiophanium compound RO 2-2222, Fed. Proc. **10**: 325, 1951.
12. Moyer, J. H., Heider, C., Morris, G. C., Jr., and Handley, C.: Renal failure; effect of complete renal artery occlusion for variable periods of time as compared to exposure to sub-filtration arterial pressures below 30 mm. Hg for similar periods, Ann. Surg. **145**: 41, 1957.
13. Moyer, J. H., Livesay, W. R., and Seibert, R. A.: Effect of blood pressure reduction with Arfonad on renal hemodynamics and the excretion of water and electrolytes, Am. Heart J. **49**: 322, 1955.
14. Moyer, J. H., and Morris, G. C., Jr.: Cerebral hemodynamics during controlled hypotension induced by continuous infusion of ganglionic blocking agents (Hexamethonium, Pendiomide and Arfonad), J. Clin. Invest. **33**: 1081, 1954.
15. Randall, L. O., Peterson, W. G., and Lehmann, G.: Ganglionic blocking action of thiophanium derivatives, J. Pharmacol. & Exper. Therap. **97**: 48, 1949.
16. Scurr, C. F., and Wyman, J. B.: Controlled hypotension with Arfonad, Lancet **1**: 338, 1954.
17. Shorr, E., Zweifach, B. W., and Furchgott, R. F.: On occurrence, sites and modes of origin and destruction, of principles affecting the compensatory vascular mechanisms in experimental shock, Science **102**: 489, 1945.
18. Shumacker, H. B., Jr., Riberi, A., Boone, R. D., and Kajikuri, H.: Ventricular fibrillation in hypothermic state; role of extrinsic cardiac innervation, Ann. Surg. **143**: 223, 1956.
19. Stephen, C. R., Woodhall, B., Odom, G. L., Reynolds, D., Bourgeois-Gavardin, M., Martin, R. C., and Bloor, B. M.: Induced hypotension for neurosurgical procedures: critical analysis, Ann. Surg. **143**: 143, 1956.
20. Van Bergen, F. H., Weatherhead, D. S., Treloar, A. E., Dobkin, A. B., and Buckley, J. J.: Comparison of indirect and direct methods of measuring arterial blood pressure, Circulation **10**: 481, 1954.
21. Walcott, W. W.: Blood volume in experimental hemorrhagic shock, Am. J. Physiol. **143**: 247, 1945.
22. Wiggers, H. C., Goldberg, H., Roemhild, F., and Ingraham, R. C.: Impending hemorrhagic shock and course of events following administration of dibenamine, Circulation **2**: 179, 1950.
23. Wiklund, P. E.: Controlled hypotension at intracranial operations, J. Neurosurg. **10**: 617, 1953.