

CLINICAL REPORT ON CONTROLLED HYPOTENSION WITH ARFONAD®*

SAM S. CLARK, M.D.,† WILLARD D. BENNETT, M.D.,† AND
JAMES R. FLAUTT, JR., M.D.†

Louisville, Kentucky

Arfonad® is a thiophanium compound with the formula *d*-3,4, (1',3'-dibenzyl-2'-keto-imidazolido)-1,2 trimethylene thiophanium *d*-camphor sulfonate. The effect of arfonad closely parallels the effect of hexamethonium, but offers the advantages of greater flexibility and rapid reversal on discontinuing its administration. Nicholson and others (1) reported a series of 25 cases receiving arfonad with presentation of selected case summaries. Nicholson observed no bad effects from the drug, but cautioned against indiscriminate use. Sadove and others (2) reported 50 cases in which arfonad was used.

In order to determine the safety and the scope of usefulness of arfonad, it was considered desirable to administer the drug to a larger number of patients undergoing a wide variety of surgical procedures.

CLINICAL INVESTIGATION

Arfonad was administered intravenously in a dilution of 0.05 per cent in 5 per cent glucose in water. The stock solution was saved and used repeatedly, providing it remained crystal clear. Arfonad was started immediately after induction of anesthesia in all but a few cases, and the patient's blood pressure was checked by palpation of the radial artery. A standard blood pressure cuff was used.

Table 1 shows the sex, the age, and the weight of 128 patients in this report. The youngest patient was 10 years of age. His response to arfonad administration was minimal lowering of the blood pressure. The oldest patient, who was 92 years old, was extremely susceptible to minute amounts of arfonad. No patient was absolutely refractory to arfonad. There was no apparent sex or weight correlation as to dose or effect of aronad in this study.

The anesthetic agents used in these patients are listed in table 2. It was generally felt that light levels of anesthesia could be maintained more smoothly when arfonad was being administered. No incompatibilities were apparent between arfonad and the anesthetic agents used.

* Accepted for publication July 19, 1954.

† Department of Anesthesiology, John N. Norton Memorial Infirmary, University of Louisville Medical School.

‡ The authors wish to express their gratitude to Dr. Thomas C. Fleming of the Clinical Research Department of Hoffmann-LaRoche Inc., for the drug used in this study.

TABLE 1
ARFONAD SERIES
(128 Cases)

Male—48 patients		Female—80 patients	
10-20 years 7 patients 14.4 ave.	21-40 years 44 patients 33.3 ave.	41-60 years 52 patients 50.9 ave.	61-92 years 25 patients 84 ave.
Weight in Pounds			
75-120 lbs. 28 patients	121-180 lbs. 84 patients	181-250 lbs. 16 patients	

It was interesting to note that those patients who were kept hypotensive during cyclopropane anesthesia showed the usual return to pre-anesthetic blood pressure level when the anesthetic was discontinued.

The operations in which arfonad was used are listed in table 3 according to region and type. There appears to be a definite correlation between the dose of arfonad and the time consumed by the operation. The percentage values of hypotension shown are based on the patient's preoperative blood pressure reading before any premedication was given.

Neurosurgical Operations. As reported by other investigators (1), this is a useful field for the application of controlled hypotension. Those patients who were operated upon in the sitting position, such as intracranial root sections and cervical disks, showed marked sensitivity to arfonad. This may be explained on the added effect of postural hypotension.

Thyroid and Neck Operations. Most of the thyroid operations were done with pentothal-nitrous oxide-oxygen anesthesia without an endotracheal tube. There is one patient in this group who had a radical neck dissection with thyroidectomy and laryngectomy which required 6 hours to perform. He received 4 pints of blood during the

TABLE 2
ANESTHETIC AGENTS USED *

Pentothal-nitrous-oxide with muscle relaxant	Cases 53
Pentothal-nitrous-oxide	41
Pentothal-ether with muscle relaxant	17
Pentothal-cyclopropane	7
Pentothal-oxygen (nasal catheter)	6
Local infiltration (xylocaine)	1
Spinal (pontocaine)	1
No anesthesia	2
	<hr/> 128 cases

* Endotracheal technique used in 55 patients.

operation. This patient also had proved cirrhosis of the liver which was not adversely affected by the anesthesia or operation. He was discharged on the eleventh postoperative day after an uneventful course.

TABLE 3

Type of Operation	Dose of Arfonad in Mg.	Time of Op. in Mins.	Fall in B. P. % Preop. Level	Time to Regain Pre-anes. B. P. Level in Mins.
1. NEUROSURGICAL OPERATIONS—14				
Brain tumor—4 (3 tumors, 1 neg. exploration)	190 (median) (100-250 range)	125 (ave.) (90-190 range)	48% (ave.) (33-69% range)	57 (ave.) (20-90 range)
Cerebral A. V. malformation—2 (1 ligation, 1 not operated on)	450,500	110 (90-130 range)	48% (39-57% range)	45 (30-60 range)
Intracranial root section—5 (Fifth cranial nerve)	50 (median) (15-160 range)	77 (60-130 range)	50% (30-65% range)	46 (35-65 range)
Herniated disk—3 (2 cervical, 1 lumbar)	200 (median) (15-385 range)	97 (65-130 range)	41% (38-47% range)	22 (15-30 range)
2. THYROID AND NECK OPERATIONS—19				
Thyroidectomy—14 (5 total, 9 partial)	125 (median) (35-300 range)	81 (45-135 range)	46% (45-59% range)	28 (15-80 range)
Parotid gland tumor—2	20,100	72 (40-105 range)	53% (50-56% range)	80 (40-120 range)
Radical neck dissection—2 (1 each with laryngectomy and thyroidectomy)	75,125	282 (205-360 range)	45% (39-56% range)	38 (15-60 range)
Recurrent branchial cleft cyst—1	250	110	30%	15
3. INTRA-ABDOMINAL OPERATIONS—16				
Stomach, colon, and gallbladder—5	125 (30-200 range)	119 (60-200 range)	41% (28-50% range)	34 (15-70 range)
Gynecological—6	370 (median) (75-600 range)	143 (90-120 range)	37% (17-47% range)	32 (10-60 range)
Spleen—3	150 (50-200 range)	93 (75-120 range)	47% (36-62% range)	17 (15-20 range)
Others—2	35,150	85 (50-120 range)	20% (19-21% range)	23 (15-30 range)

TABLE 3—Continued

Type of Operation	Dose of Arfonad in Mg.	Time of Op. in Mins.	Fall in B. P. % Preop. Level	Time to Regain Pre-ana. B. P. Level in Mins.
4. SPINE AND EXTREMITIES OPERATIONS—30				
Spine fusion with bone graft—8	180 (140-525 range)	107 (90-140 range)	51% (35-59% range)	25 (10-40 range)
Hip operation—9 (6 prostheses, 3 pins)	50 (20-150 range)	60 (40-100 range)	52% (44-61% range)	21 (10-35 range)
Amputation—3 (1 hip joint, 1 shoulder joint, 1 thigh)	210 (100-275 range)	122 (105-150 range)	44% (37-54% range)	22 (20-25 range)
Intramedullary nail, femur—2	45, 50	70 (35-115 range)	38% (34-42% range)	12 (10-15 range)
Others—8	95 (20-150 range)	55 (10-120 range)	38% (10-50% range)	12 (5-20 range)
5. MASTECTOMY—12 (11 radical, 1 bilat. simple)	115 (median) (25-310 range)	111 (75-255 range)	48% (33-65% range)	20 (10-30 range)
6. VAGINAL HYSTERECTOMY—18 (with A. P. colporrhaphy)	150 (30-450 range)	94 (60-135 range)	42% (25-63% range)	18 (4-15 range)
7. TRANSURETHRAL RESECTION OF PROSTATE—5	120 (25-175 range)	31 (20-40 range)	46% (33-57% range)	40 (15-60 range)
8. HICCUP—10	125 (15-500 range)	40 (5-175 range)	32% (10-50% range)	15 (5-35 range)
9. MISCELLANEOUS—4				
Plication aortic aneurysm—1	140	330	40%	10
Excision burn scar with graft (2 operations on same patient)				
Bistrium—1	50	145	100%	45
Arfonad—1	150	120	50%	15
Pharyngeal flap—1	100	70	36%	15

Intra-abdominal Operations. Because of the difficulty of diagnosing postoperative bleeding, we have been reluctant to use arfonad for hypotension in intra-abdominal procedures. One patient in this group was reopened for suspected bleeding after gastrectomy, but no definite

bleeding point was demonstrated. Boyan (3) reported good results with hypotension produced with hexamethonium in radical surgery of the pelvis.

Spine and Extremities Operations. Generally, the hip fixation procedures are on older individuals, and there is an unusual lability of blood pressure in this group so arfonad must be administered with extreme caution. Patients undergoing spine fusion present the added problem of anesthesia in the flexed prone position with danger of altered respiratory and circulatory physiology.

Mastectomy. Three of the 12 patients developed postoperative wound hematoma. The dissection was facilitated by the diminution in oozing so that the operative time was reduced. In each of the patients who bled postoperatively, the flaps were closed over a T-tube to which suction was applied for drainage. In only one instance was the bleeding severe enough to complicate the patient's postoperative course. Extreme care must be exercised in controlling all bleeding, and the blood pressure elevated either by discontinuing the arfonad drip or by administering vasopressors if necessary before closing the wound.

Vaginal Hysterectomy. When extensive anterior and posterior colporrhaphies are done in conjunction with vaginal hysterectomies, the blood loss is significant. This appears to be true particularly in younger patients where pelvic congestion is more likely to occur. While it has still been necessary to give most of these patients at least 1 pint of blood, they appear to profit by the conserving of a significant amount of blood when hypotension is induced.

Transurethral Resection of Prostate. This series is too small for any pertinent observations to be made. Here again are older patients who respond more dramatically to administration of arfonad.

Hiccup. When hiccup occurs at induction of pentothal anesthesia, administration of arfonad to the point of marked blood pressure depression has produced a cessation of hiccup in some instances. Two patients in this group had hiccup due to organic disease, and they were stopped only temporarily by administration of arfonad.

Miscellaneous. One patient in this group received hypotensive anesthesia on two occasions, one time with hexamethonium and the other with arfonad. Despite a residual rheumatic-heart disease, she tolerated the drugs equally well.

In most instances, there has been little change in the pulse rate due to arfonad. An occasional elevation or depression has been observed in the absence of other explanatory factors.

COMPLICATIONS

The most significant complication encountered was postoperative bleeding; this complication occurred 7 times in 128 cases. We feel that extreme caution should be exercised, and, if necessary, the blood pressure should be elevated to normal levels before closure is begun.

There was one death during the immediate postoperative period. This patient was in severe respiratory embarrassment as a result of an aneurysm of the right innominate artery, and at operation an attempt was made to plicate the aneurysm. Severe hemorrhage followed by cardiac arrest occurred during the operation. Heart action was restored by cardiac massage along with intra-arterial and intravenous administration of large amounts of blood. Although she recovered consciousness in the operating room, she died 6 hours postoperatively, and at postmortem examination it was established that her death was due to recurrent aortic bleeding.

A man, age 70, who received 120 mg. of arfonad during a thirty-five minute transurethral prostatic resection had an acute nonfatal myocardial infarction on the fifth postoperative day. He had been ambulatory since the third postoperative day.

A very obese 82 year old female with chronic myocardial insufficiency received 50 mg. of arfonad during a hip-pinning operation. She had a marked drop in blood pressure which returned to a normal level before the operation was completed. Although her postoperative course was without incident for the first three days, she developed cardiac failure on the fourth day and died on the fifth day after operation.

Another patient, age 71, who received 70 mg. of arfonad during an uneventful procedure for insertion of hip prosthesis, developed pulmonary and cerebral emboli on the eleventh postoperative day. She survived these episodes and was discharged to a nursing home on the twenty-first postoperative day.

There appeared to be a slightly higher incidence of postoperative nausea and vomiting in those who received arfonad; however, none of the patients developed paralytic ileus. There did not appear to be a significant increase in postoperative urinary retention.

Several patients complained of headache immediately on awakening from anesthesia where arfonad had been given. They were flushed and slightly hypertensive and gave the general appearance of histamine reaction. Histamine release has been noted by investigators (4, 5).

DISCUSSION

The contraindications to the use of arfonad for production of hypotension during surgery are relative, and they must be considered from the standpoint of the advantage outweighing the risk. A history of coronary, cerebral, or peripheral thromboses, impaired kidney or liver function, deficient blood volume, existing hypotension, or shock must be considered carefully before arfonad is administered. Patients with a known deficiency of blood volume should be treated preoperatively and blood loss during operations should be replaced as it is lost. In some procedures, where arfonad was being used and blood replacement

TABLE 4
ARFONAD SERIES
(128 Cases)

Median dose of arfonad	110 mg.
Average dose of arfonad	153 mg.
Average time of operation	92 mins.
Average rate of administration of arfonad	1.7 mg. per min.
Average fall in systolic blood pressure	44% (% preoperative level)
Average time to regain pre-anesthesia blood-pressure level	25 mins.

was not adequate during the operation, the time to regain the pre-operative blood pressure level was prolonged.

SUMMARY

Some observations on the administration of arfonad to 128 cases has been presented. Table 4 summarizes the findings.

CONCLUSIONS

Arfonad may be administered with caution to patients under anesthesia for a variety of surgical procedures.

REFERENCES

1. Nicholson, M. J., Sarnoff, S. J., and Crehan, J. P.: Intravenous Use of Thiophanium Derivative (Arfonad-RO2-2222) for Production of Flexible and Rapidly Reversible Hypotension During Surgery, *Anesthesiology* **14**: 215 (May) 1953.
2. Sadove, M. S., Wyant, G. M., and Gleave, G.: Controlled Hypotension: Study on Arfonad RO2-2222, *Anaesthesia* **8**: 175 (July) 1953.
3. Boyan, C. P., and Brunshwig, A.: Hypotensive Anesthesia in Radical Pelvic and Abdominal Surgery, *Surgery* **31**: 829 (June) 1952.
4. Mitchell, R., Newman, P. J., MacGillivray, D., and Clark, B. B.: Evaluation of Histamine Liberator Activity, Illustrated by Thiophanium Compound RO2-2222, *Fed. Proc.* **10**: 325 (March) 1951.
5. Holman, J., and Goth, A.: Histamine Release in Human Skin and Effect of Cortisone, *Fed. Proc.* **11**: 358 (March) 1952.