

Anesthesia, Surgery and Rauwolfia

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One hundred patients on Rauwolfia therapy were studied during anesthesia and operation. A fall in blood pressure of more than 30 per cent was observed in 18 patients. The fall in blood pressure was usually associated with blood loss, speed of anesthetic induction, surgical manipulation, position changes, and excessive amounts of anesthetic agents. Ephedrine was effective in temporarily raising the blood pressure. The 100 patients on Rauwolfia therapy were compared with a randomly selected group of 100 hypertensive patients not treated with Rauwolfia drugs. A fall in blood pressure of more than 30 per cent was observed in 30 of the hypertensive patients. The results suggest that patients on Rauwolfia therapy tolerate anesthesia and operation satisfactorily, and at least as well as hypertensive patients not treated with Rauwolfia. Elective surgery may be safely undertaken without discontinuing Rauwolfia therapy.

SINCE 1955 it has been suggested that patients receiving Rauwolfia alkaloids tolerate anesthesia and surgical operation poorly and should not be operated upon except in emergencies. The main problem is said to be hypotension during anesthesia which responds poorly or not at all to the intravenous injection of vasopressors.^{1, 2, 3} Although we were aware of these reported difficulties, from 1955-1961 we did not observe unusual problems in the management of patients on Rauwolfia alkaloids. We gradually came to believe that treatment of patients with these agents was not a contraindication to elective anesthesia and operation.

In 1961 Smessaert and Hicks,⁴ on the basis of experience with 48 patients, reported that: (1) Small amounts of anesthetic agent were sufficient to maintain anesthesia throughout the

entire procedure. (2) In 70 per cent of the patients it was necessary to use a vasopressor at least during part of the operation. (3) It was necessary to omit opiates as premedicant drugs. (4) The use of spinal anesthesia is not recommended except for specific indications. (5) Ether and halothane are not recommended. (6) Succinylcholine chloride is adequate for relaxation, however, the use of long acting curarizing agents is not advised. (7) Anesthesia and operation should not be performed on patients taking Rauwolfia medication except in emergencies.

The paper quoted prompted a retrospective analysis of our experience with patients on Rauwolfia therapy with special attention to these seven points. Our experience differed and did not appear to support the conclusions listed above. Because of the difficulties of retrospective analysis and the importance of the clinical problem, a prospective study was started in September 1961 and continued through December 1962.

Clinical Data

One hundred patients maintained on Rauwolfia therapy up to at least 48 hours before operation were studied. The doses used in these patients who were under treatment for hypertension (rather than psychiatric disease) were usually 0.25-0.5 mg./day of reserpine (range = 0.1-0.75 mg./day). The adequacy of therapy was determined by a significant reduction in blood pressure and heart rate. The duration of therapy varied from 6 months to 6 years. Preanesthetic medication usually consisted of a barbiturate (secobarbital or pentobarbital, 50 to 100 mg.) and/or a narcotic (meperidine 25 to 100 mg. or morphine 5 to 10 mg.) and a belladonna drug (atropine, 0.4 to 0.8 mg. or scopolamine, 0.3 to 0.6 mg.). Induction was accomplished with thiopental sodium or thiamylal sodium. Intubation was carried out with the aid of succinylcholine in 57 patients. The anesthetic

* Accepted for publication November 1, 1963. The authors are in the Department of Anesthesiology, College of Physicians and Surgeons, Columbia University and the Anesthesiology Service, The Presbyterian Hospital, New York, New York. This work was supported by U.S.P.H.S. Grant GM-09089-02.

TABLE 1. Patients on *Rauwolfia*

Age Years		Duration of Anesthesia Minutes		Physical Status		Operation	
0-9	1	0-59	15	1	14	Urologic	22
10-19	0	60-119	30	2	74	Gynecologic	16
20-29	0	120-179	29	3	3	Upper Abdominal	16
30-39	5	180-239	10	4	0	Head, Neck	10
40-49	13	240-299	9	5	3	Extremities	9
50-59	23	300-359	4	6	4	Lower Abdominal	4
60-69	41	375	1	7	2	Radical Mastectomy	3
70-79	14	480	1			Pulmonary	3
80-89	3	540	1			Aneurysm:	
						Cranial	3
						Aortic	3
						Miscellaneous	11
Mean = 59 years		Mean = 138 minutes					

agents were selected on the basis of appropriate clinical indications and included halothane, cyclopropane, nitrous oxide supplemented by thiobarbiturates or meperidine, methoxyflurane, ether, trichlorethylene, halopropane and ethylene. Relaxation was obtained with *d*-tubocurare in 23 patients, succinylcholine in 8 (not including intubation) and gallamine in 1. Regional anesthesia was used 9 times (subarachnoid block 4, lumbar epidural block 3, caudal block 2). Ninety-one patients were anesthetized by residents in training, and 9 by attending anesthesiologists.

The age distribution, duration of anesthesia, physical status, and nature of operation are listed in table 1. The initial systolic blood pressure after preanesthetic medication and prior to induction was greater than 200 mm.

of mercury in 6 patients, 150 to 199 mm. of mercury in 45 patients, and less than 150 mm. of mercury in 49 patients. Changes in systolic pressure during operation were compared with the initial blood pressure for each patient.

Eighteen patients experienced falls in systolic pressure greater than 30 per cent; 16 during operation, 1 after preanesthetic medication, and 1 in the early postoperative period. An additional 14 patients experienced 20-29 per cent falls in systolic blood pressure. In these 32 patients the fall in pressure was associated with blood loss in 13, induction of anesthesia in 8, position changes in 4, surgical manipulation in 3, excessive depth of anesthesia in 2, excessive preanesthetic medication in 1 and postoperative emergence in 1.

The anesthetic agents used in these 32 cases

TABLE 2. Patients on *Rauwolfia*: Frequency of Blood Pressure Fall with Various Agents

Number of Patients Receiving Agent	Number of Patients with Systolic Blood Pressure Fall of:			
	20-29%	30-34%	35-39%	40% or Greater
Halothane 47	7	8	0	2
Cyclopropane 22	2	0	1	1
Thiopental, N ₂ O, meperidine 11	4	1	0	0
Regional block				
Subarachnoid 4)	0	0	0	0
Lumbar epidural 3}				
Caudal 2)				
Methoxyflurane 4	1	1	1	0
Ether 3	0	1	1	0
Miscellaneous 4	0	0	0	1*
	—	—	—	—
	14	11	3	4

* After preanesthetic medication.

TABLE 3. Hypertensive Patients Not Receiving *Rauwolfia*

Age Years		Duration of Anesthesia Minutes		Physical Status		Operation	
0-9	0	0-59	9	1	34	Urologic	27
10-19	0	60-119	34	2	54	Gynecologic	15
20-29	0	120-179	42	3	3	Upper Abdominal	9
30-39	1	180-239	9	4	0	Head, Neck	11
40-49	8	240-299	6	5	3	Extremities	10
50-59	19			6	4	Lower Abdominal	10
60-69	43			7	2	Radical Mastectomy	2
70-79	24					Pulmonary	1
80-89	5					Aneurysm; Aortic	5
						Miscellaneous	10
Mean = 64 years		Mean = 119 minutes					

were: halothane in 17; nitrous oxide, thio-barbiturate and/or meperidine in 5; cyclopropane in 4; methoxyflurane in 3; ether in 2; and secobarbital 100 mg. meperidine 100 mg., and atropine 0.5 mg. in 1 (table 2).

Before undertaking specific therapy (transfusion, cessation of manipulation, or decrease in concentration of anesthetic agent) the response to an intravenously administered vasopressor (usually ephedrine) was assessed in 23 patients. In all 23 patients the vasopressor (15-50 mg. of ephedrine in 22 cases and 10 mg. of methoxamine in 1 case) increased systolic pressure by at least 20 per cent.

The 100 patients on reserpine therapy were compared to a randomly selected group of 100 known hypertensive patients operated on between September 1961 and December 1962. This group was selected by using the patient's unit number and a table of random numbers. The charts obtained were examined and included in the study if the systolic pressure was greater than 150, the diastolic greater than 100, and a diagnosis of hypertension made by the physician in charge. These patients were either not treated with drugs or were on drug therapy other than *Rauwolfia* alkaloids (barbiturates in 7 patients, chlorothiazide in 4). Unlike the *Rauwolfia* group this was a retrospective analysis. The anesthetic management of these patients was similar to that of the *Rauwolfia* group. The age distribution, duration of anesthesia, physical status and nature of operation are listed in table 3. The initial systolic blood pressure after preanesthetic medication and prior to

induction was greater than 200 mm. of mercury in 12 patients, 150 to 199 mm. of mercury in 59 patients and less than 150 mm. of mercury in 29 patients. Thirty patients experienced falls in systolic pressure greater than 30 per cent and 16 patients falls of 20-29 per cent. The anesthetic agents used in these patients are listed in table 4.

Discussion

These observations differ from those obtained by previous investigators with respect to frequency of hypotension, time of occurrence of hypotension and responsiveness to sympathomimetic amines. In this study of 100 patients on *Rauwolfia* therapy 18 per cent developed systolic blood pressure falls greater than 30 per cent during the operative period (from time of premedication to discharge from recovery room). This finding contrasts with the study of Smessaert and Hicks,⁴ and Munson and Jenicek⁵ in which 56 per cent (27 of 48) and 50 per cent (13 of 26) developed similar falls in pressure. It also differs from the data of Coakley *et al.*³ who reported a greater than 40 mm. of mercury fall in systolic pressure in 40 per cent (16 of 40) of the patients studied. We observed a fall of this magnitude in only 19 per cent (19 of 100) of our patients. In the three studies cited an unexplained fall in blood pressure usually occurred during induction of anesthesia and was attributed to *Rauwolfia* in two of these studies.^{3, 4} In the present study, although hypotension during induction was seen, in the majority of cases the fall in blood

pressure occurred in response to well-documented stimuli (blood loss, intra-abdominal manipulation, position changes, excess of anesthetic agents) which are capable of producing hypotension in any patient.

In contrast to the unpredictable responses to sympathomimetic amines reported by others, we found that ephedrine was uniformly effective in raising the blood pressure. Burn and Rand,⁶ Maxwell and associates,⁷ and Eger and Hamilton⁸ studied the pressor effects of sympathomimetic amines in animals depleted of catechol amines by *Rauwolfia* alkaloids. Epinephrine, norepinephrine and phenylephrine raised the blood pressure and were believed to exert this effect by a direct action on the blood vessel wall or myocardium. Ephedrine, amphetamine, mephentermine and tyramine which were ineffective were believed to work indirectly by the release of catecholamines. On the other hand, Moore and Moran⁹ showed in the dog that the cardio-stimulant and vasopressor actions of ephedrine were not suppressed by acute or chronic treatment with reserpine. Trendelenburg¹⁰ in a recent review pointed out that the classification of sympathomimetic amines as direct or indirect on the basis of a single test dose of amine is erroneous. By studying dose-response curves he demonstrated that although some sympathomimetic amines work indirectly (tyramine) and others directly (norepinephrine) most of the amines have varying degrees of direct and indirect actions. The effective-

ness of ephedrine in our patients may be due to either incomplete depletion of catecholamines by the clinically used doses of *Rauwolfia* or to a direct action of ephedrine on the effector organs.

The Ephedrine Response Test (E.R.T.) was proposed by Crandell as a simple clinical screening test for evaluating a patient's ability to react favorably to operation and anesthesia.¹¹ The test depends upon the ability of 15 mg. of ephedrine given intravenously to increase the pulse rate 10 beats/minute and raise the systolic pressure 20 mm. of mercury. No clinical evidence for its value was reported. Because ephedrine acts not only indirectly by the release of catecholamines but also directly on the effector organs¹⁰ the test does not appear to be pharmacologically sound. Hamelberg and Bosomworth who attempted to utilize the test under clinical conditions found it to be unreliable in predicting hypotension in anesthetized patients previously treated with reserpine.¹² Tyramine which acts indirectly by the release of catecholamines¹⁰ would seem to be a better test of the degree of catecholamine depletion. However, Mashford *et al.*¹³ demonstrated that the use of the blood pressure response to a small dose of tyramine as a test of the adequacy of tissue catecholamines is complicated by considerable variability among patients, especially if a single dose rather than a dose-response curve is used.

The frequency of a fall in systolic blood

TABLE 4. Hypertensive Patients Not Receiving *Rauwolfia*: Frequency of Blood Pressure Fall with Various Agents

Number of Patients Receiving Agent		Number of Patients with Systolic Blood Pressure Fall of:			
		20-29%	30-34%	35-39%	40% or Greater
Halothane	47	8	3	9	4
Cyclopropane	10	2	2	1	0
Thiopental, N ₂ O, meperidine	22	3	2	3	1
Regional block					
Subarachnoid	5	1	2	0	0
Lumbar epidural	2	0	0	0	0
Caudal	2	1	0	0	0
Trichlorethylene	5	0	0	0	0
Ether	4	1	0	1	2
Miscellaneous	3	0	0	0	0
		—	—	—	—
		16	9	14	7

pressure greater than 30 per cent during the operative period in 100 randomly selected hypertensive patients was 30 per cent as compared with 18 per cent in patients on *Rauwolfia* therapy. The "hypertensive patients" should not be considered a control group for the "*Rauwolfia* patients." The former were chosen retrospectively and the latter prospectively. These two groups differ in at least two other major respects. The "*Rauwolfia* patients" were all on therapy, while the majority of "hypertensive patients" were not, and the blood pressure of the patients in the *Rauwolfia* group was lower. It is possible that therapy which has lowered the blood pressure toward normal may account for the lower incidence of further hypotension during anesthesia in the *Rauwolfia* group. The ideal study of the problem should be a prospective one including at least four comparable groups of patients undergoing anesthesia and operation: (1) normotensive patients, (2) hypertensive patients not on therapy, (3) hypertensive patients on *Rauwolfia*, (4) normotensive patients on *Rauwolfia* for psychiatric reasons.

The incidence of blood pressure falls greater than 30 per cent in both the "*Rauwolfia*" and "hypertensive" patients (18 per cent and 30 per cent) appears high. It is our belief that hypertensive patients do not tolerate intra-abdominal manipulation, position changes, excess of anesthetic agents, and blood loss as well as normal patients with respect to the maintenance of a steady blood pressure. Furthermore, many of these patients were elderly, had major surgery of prolonged duration, and experienced significant blood loss. In addition to their cardiovascular disease, manifested by hypertension, some patients suffered from other diseases (cancer, diabetes, renal disease). All of these factors influenced the patients' course during operation. To ignore these other factors and attribute their vulnerability during anesthesia to *Rauwolfia*, rather than to the underlying cardiovascular disease does not appear to be justified.

The results of this study suggest that patients on *Rauwolfia* therapy tolerate anesthesia and operation satisfactorily, and at least as well as hypertensive patients not treated with

Rauwolfia. Elective surgery may be safely undertaken without discontinuing *Rauwolfia* therapy.

It was not possible, with the modest number of patients studied, to state categorically that any agent or technique was indicated or contraindicated. It is our view that the choice of premedicant drugs, techniques, anesthetic agents and muscle relaxants was less important than individualized management of each patient based on a careful evaluation of the total situation.

Since the completion of this study an excellent review article by Alper and co-workers on the pharmacology of reserpine and its implications for anesthesia has been published.¹⁴ The authors point out that circulatory homeostatic reflexes (cold pressor test, responses to tilt table, hypoxia, and exercise) function adequately in patients receiving reserpine. In addition, despite lower absolute values after reserpine, the slopes of regression lines relating hemodynamic effects to inspired concentration of anesthetic agents were not significantly different in normal and reserpine pretreated animals. Finally the authors conclude that discontinuation of reserpine therapy before anesthesia and operation is not mandatory since the danger of circulatory depression does not appear to be excessive and can be controlled by careful anesthetic management.

Summary

One hundred patients on *Rauwolfia* therapy undergoing anesthesia and operation were studied. A fall in blood pressure greater than 30 per cent was observed in 18 patients. The fall in pressure was usually associated with blood loss, speed of anesthetic induction, surgical manipulation, position changes and excessive amounts of anesthetic agents. Ephedrine, when used, was effective in temporarily raising the blood pressure. Patients on *Rauwolfia* therapy tolerated anesthesia and operation satisfactorily and at least as well as hypertensive patients not treated with *Rauwolfia*. It was concluded that there is no contraindication to elective anesthesia and operation in patients receiving *Rauwolfia* therapy.

References

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HEMODYNAMICS OF PREGNANCY Review of the cardiovascular physiologic changes occurring during pregnancy reveals that the heart is displaced superiorly, laterally, and anteriorly, and that extrasystoles and palpitations may appear. The heart rate usually increases. The blood pressure usually does not change. Blood volume increases, with much of the increased volume located in the placenta and uterine vessels. Both plasma and red cell volume are increased. The most important change in the circulation during pregnancy appears to be an increase in cardiac output. Blood flow to the pregnant uterus appears to be about 500 ml. per minute. During effective contractions in labor, the cardiac output may increase one third above that in the resting state. The cardiac output returns to normal, nonpregnant levels by the fourth postpartum day. (*Vorys, N., Hamusek, G., and Ullery, J. C.: Hemodynamic Changes in Pregnancy, Surg. Gynec. Obstet.* **116**: 511 (June) 1963.)