

Effect of Anesthetic Agents on Patients Receiving Reserpine Therapy

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ANESTHESIOLOGISTS have been aware that patients receiving Rauwolfia alkaloids frequently develop hypotension during anesthesia. Belladonna drugs, primarily atropine sulfate and oxyphenonium bromide, have been claimed to be more effective in the correction of this anesthesia-induced hypotension than were vasopressors.¹ It has been recommended that treatment with "reserpine compounds" should be discontinued 10 to 14 days before elective surgery. These concepts have served as guidance in the anesthetic management of reserpine-treated patients.²⁻⁵ In the meantime, much investigation has been directed toward an understanding of reserpine and its pharmacological effects. This work has explained many clinical impressions and serves as a foundation for a rational approach to the management of these patients.

Reserpine is used primarily in the treatment of psychiatric disorders and hypertension. Its value in the treatment of mental patients stems from its tranquilizing action, which, by an increase in dose, can be extended to the development of depression and melancholy.^{3, 6, 7} In slightly smaller doses than those used in psychiatry, the drug produces a mild, but definite, antihypertensive effect.^{6, 8-10}

Preparations

Rauwolfia serpentina is presently marketed in the powdered, whole root form (Raudixin) which contains all the active alkaloids in their naturally occurring quantities. Reserpine (Serpasil, Reserpoid) is the chief therapeutic alkaloid of Rauwolfia serpentina which

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can be isolated from the purified alseroxylylon (rauwiloid) fraction. Rescinnamine is another alkaloid of Rauwolfia serpentina, with somewhat less sedative effect than reserpine. Deserpine has similar properties; however, it is the alkaloid from Rauwolfia canesina. All of the above-named Rauwolfia alkaloids exert a tranquilizing effect as well as an antihypertensive effect.^{3, 6, 11}

Pharmacologic Action of Rauwolfia Alkaloids

The tissue depleting or releasing effect of these alkaloids on body stores of the amines, serotonin, adrenalin and noradrenalin, has been demonstrated conclusively.¹²⁻¹⁷ The central nervous system depressant effect of the Rauwolfia alkaloids is associated with a decrease in the brain serotonin level. This depression cannot be correlated with depletion of brain catechol amines.^{8, 12, 18} Conversely, the effect of reserpine on blood pressure has been traced to depletion of stores of catechol amines in the adrenals, heart and blood vessels, as well as other body tissues.^{8, 12}

Reserpine is unstable in the gut¹⁹ and varying amounts are absorbed. An adequate effect from oral therapy is slow in developing. Because of a cumulative action and a narrow margin between the desired hypotensive effect and central nervous system depression, it is not unusual for the latter depression to occur.¹² Parenterally, 1-5 mg. of reserpine lowers blood pressure in one to two hours. Maximum effects occur in two to five hours, with a duration of 4-8 hours.²⁰ The use of large parenteral doses of reserpine is not advised, since adrenergic reactions attributed to the sudden liberation of stored catechol amines may occur.²¹ After reserpine therapy is discontinued, there is a lag in the return to normal of body amine stores.^{7, 17}

Synthetic reserpine analogs, such as syro-

TABLE 1. Comparative Frequency of Neurocirculatory Imbalance Seen in Each Series of Patients Receiving Reserpine Therapy

	Total Cases	Demonstrated Changes
Original series on therapy— spinal or general anesthesia	16	9
Control series off therapy— general anesthesia	16	7
Present series on therapy— general anesthesia	26	13

singopine, are more selective in their catecholamine depleting action^{12, 19, 22} and, therefore, possess a wider margin of safety in the treatment of hypertension.¹² Compounds which selectively release brain serotonin, without affecting body catechol amine stores, are being studied^{8, 21} and may supplant reserpine in the treatment of psychiatric disorders.

Controversy existed as to whether reserpine causes a decrease in central sympathetic discharge or tone.^{9, 23} Now, most evidence suggests that sympathetic tone is not depressed centrally, and that the carotid sinus reflexes remain intact during administration of the usual antihypertensive dosages.^{8, 12, 23} Regardless of whether the "sympathetics" are blocked centrally or peripherally,^{12, 24} as a result of reserpine therapy, autonomic nervous system balance is disrupted, allowing the parasympathetic system to predominate. This can cause bradycardia, hypotension, hypothermia, ptosis, lacrimation, miosis, nasal stuffiness, hyperperistalsis and gastrointestinal hypersecretion.^{6, 10, 11}

Following sympathectomy, the cardiovascular effects of adrenalin are increased and those of tyramine and ephedrine decreased.²⁵ A similar response follows reserpine treatment.²⁶ Numerous studies have been carried out to determine which vasopressors can be used reliably for patients on reserpine therapy. It has been shown that the cardiovascular effect of adrenalin and noradrenalin administered parenterally to 'reserpinized' patients is potentiated or remains unchanged.^{28, 29, 30} Catechol-amine depleted tissues are hypersensitive to exogenous or endogenous catechol amines.^{21, 27-29} Maxwell³⁰ has divided vasopressors into three groups based on their effectiveness in this situation: (1) those producing an "augmented or unsuppressed" response: adrenalin, noradrenalin, metaraminol, phenyl-

ephrine, and methoxamine; (2) "reversibly blocked or inhibited": ephedrine and propadrine, although doses of five to twenty times normal will produce an effect; (3) "irreversibly blocked or inhibited": tyramine, parendrine and amphetamine. The latter two groups seem to be dependent for their action on stores of adrenalin and noradrenalin activated. This work has been substantiated by others.^{28, 31, 32}

Basis for the Present Study

In an early experience³³ 50 per cent of patients in whom Rauwolfia therapy had not been discontinued for 10-14 days before anesthesia, developed a marked lability of neurocirculatory balance (table 1). We found that although the responses to intermittent injection or continuous infusions of vasopressors were unpredictable, other supportive measures were effective in overcoming hypotension. We did not find it necessary to treat the bradycardia with vagal blocking agents. We concluded that a satisfactory combination of anesthetic agents had not been found to circumvent this problem and that Rauwolfia derivatives should be withdrawn 10-14 days before elective surgical procedures.

We followed this practice insofar as possible for two years at Brooke General Hospital. Sixteen patients who had Rauwolfia therapy discontinued before operation were anesthetized. Unintentionally, this group of patients became the "control" series. A survey of the anesthetic records of these 16 patients revealed that seven exhibited neurocirculatory instability (table 1). Fourteen patients received nitrous oxide-oxygen-ether anesthesia, of which six demonstrated hypotension during anesthesia. In four of these six, systolic blood pressure fell greater than 40 per cent prior to surgical intervention. In one patient the blood pressure fell from 175/105 to 115/75 (a 34 per cent decrease in systolic) during left lateral decubitus positioning. Another demonstrated circulatory responses more sensitive than usual to increasing anesthetic concentrations and blood loss, suggesting hypovolemia. All hypotensions were reversed without drug therapy by appropriately decreasing the ether concentration, administration

of intravenous fluids, and stimulation by tracheal intubation or the surgical procedure. One patient receiving halothane-nitrous oxide-oxygen anesthesia responded similarly to decreasing the halothane concentration. The remainder of the cases were uncomplicated. In all patients, thiopental, 2.5 per cent, was administered intravenously by intermittent doses of 25 to 100 mg. to assist induction of nitrous oxide-oxygen-ether anesthesia. A 4-6 liter/minute flow of nitrous oxide and a 2-3 liter/minute flow of oxygen were inhaled.

Present Study

During the past year therapy with Rauwolfia derivatives was not discontinued preoperatively in a series of 26 patients. During the pre-anesthetic visit, note was made of prescribed drug therapy. Meperidine 25-100 mg., morphine 2-10 mg., or pentobarbital 25-100 mg., was ordered as the usual premedicant. Unless contraindicated, scopolamine 0.3-0.5 mg. was the preferred belladonna drug. The choice of a general anesthetic agent was not related to the fact that the patient was receiving Rauwolfia. Nitrous oxide-oxygen-ether anesthesia was the preferred technique in most cases. Thiopental was given during inductions as described previously. Spinal anesthesia was usually contraindicated by the patient's cardiovascular status. An attempt was made to have the same person administer as many of these anesthetics as possible in order to standardize technique.

Results of Present Study

The 26 patients received general anesthetics lasting one hour or longer. This group of patients seemed to develop fewer and less severe problems during induction of anesthesia. Of 16 patients receiving nitrous oxide-oxygen-ether anesthesia, four had systolic blood pressure falls of greater than 40 per cent from pre-anesthetic levels and pulse rates below 60/minute during induction. Three of these responded to atropine (0.2-0.4 mg., total dose) given intravenously in conjunction with the supportive measures used in the control series. The fourth was corrected by surgical stimulation.

Six other patients receiving nitrous oxide-oxygen-ether had systolic blood pressure falls

of 30 to 35 per cent during induction, of which three were associated with a decrease in pulse rate. All were reversed spontaneously by the stimulus of tracheal intubation, surgical preparation, surgery, or by decreasing the concentration of ether administered.

One patient receiving cyclopropane had a systolic fall of greater than 30 per cent before the beginning of surgery. When the anesthetic concentration was decreased, the downward trend was reversed. This patient was not considered a good risk, and his blood pressure continued to be labile during the entire surgical procedure.

Two patients receiving halothane anesthesia deserve mention. The first, despite surgical stimulation, minimal blood loss and a light plane of anesthesia, sustained a steady, gradual fall in blood pressure from 200/85 to 110/80 during the first one and one-half hours of anesthesia. When halothane was discontinued and ether substituted, a very gradual rise in blood pressure to acceptable levels occurred. The second patient demonstrated a very labile blood pressure throughout surgery, although the halothane concentration (semiclosed technique) was not changed, and an active carotid sinus reflex (baroreceptor) was present.

The remainder of the cases (13) showed blood pressure falls of less than 30 per cent during induction and were considered to be uncomplicated.

In summary, in this present series, 13 of 26 patients showed varying degrees of neurocirculatory imbalance during induction of anesthesia (table 1), an incidence similar to the control series. Four patients in the present series (and four in the control series) had blood pressure drops of 40 per cent or more; the remainder in each series had lesser falls in pressure. All responded to the usual corrective measures. To us, this response indicated that careful anesthetic management would obviate the need to discontinue treatment with "reserpine compounds."

Discussion of Experience with Reserpine-Treated Patients

In the examination of a group of charts for a study such as this, it is difficult to determine, in many instances, whether a particular drug or agent, the patient, the surgeon, or the anes-

thetist was primarily responsible for a given change in vital signs. In an attempt to eliminate as many variables as possible, the patient response to the anesthetic induction was chosen as the standard of comparison.

In evaluating these records it was necessary to keep in mind that a depression of blood pressure and pulse-rate change may normally be expected to occur during the use of the various techniques employed. Upon first examination of the charts in this series, we believed that reserpine-treated patients showed an induction pattern that was characteristically depressed. Before concluding that this was directly related to drug therapy, it was necessary to review the factors not directly attributable to the anesthetist's technique, which may produce a pattern of depression, keeping in mind that the degree of depression can be increased directly by the effects of haste, relative overdose, or ineptness.

Hypertensive individuals may have unstable blood pressures during anesthesia. This is commonly owing to the loss of cardiovascular homeostatic mechanisms secondary to arteriosclerotic changes, whether they are receiving antihypertensive therapy or not. Hypertensive patients are frequently hypovolemic.³⁴ Anesthesia and hypovolemia together may produce exaggerated blood pressure changes. Myocardial depression with decreased cardiac output³⁵⁻³⁷ or vasodilatation with decreased peripheral resistance, or both,³⁸ may be caused by all general anesthetic agents. Obstruction of the venous return to the heart,⁴ traction reflexes causing increased vagal tone,^{5, 39} splanchnic pooling,⁴ anoxia,^{4, 40} minimal blood loss,⁴⁰ loss of the "pulmonary pump" with controlled respiration and muscular relaxation during anesthesia (reducing venous return),^{5, 41} all may produce blood pressure and/or pulse rate changes.

A discussion of the effect of anesthetic agents upon the 'reserpinized' patient will be published as a separate report. It does not change the conclusions of this study.

The use of atropine plus supportive measures was effective in reversing severe hypotension and bradycardia under the conditions described; however, supportive therapy produced a more normal physiological response.

Our experience indicates that the response

to vasopressors will be related to the pharmacological properties of the drug used, providing that supportive therapy is instituted concurrently with vasopressor administration.

It became apparent that the multiplicity of factors which cause a variation in patient response to anesthetic induction ruled out a "reserpine effect." A review of each record did not reveal such an effect in any other part of the anesthetic course.

Summary and Conclusions

Fifty-eight patients in three series were studied to determine the effect of reserpine therapy on their response to anesthesia. Forty-two of these patients remained on therapy up to five days or less of their surgical procedure. Sixteen patients (control series) were withdrawn from therapy eight days or more in advance of elective surgery. Nine of 16 patients (original series), 13 of 26 patients (present series) and 7 of 16 patients (control series) demonstrated neurocirculatory instability. No significant decrease in the incidence or severity of hypotension during induction of anesthesia was found in the control series.

Problems in the anesthetic management of the hypertensive patient do not occur exclusively in those treated with reserpine. Factors related to circulatory imbalance are proposed and corrective measures, including drug therapy, are discussed.

Administration of Rauwolfia derivatives need not be discontinued before anesthesia and surgery. It is apparent that withdrawing patients from reserpine therapy for the suggested period does not assure that circulatory instability will not occur. It is more important that the anesthetist be aware of the patient's drug intake and consider this in the overall anesthetic management.

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HYPOTHERMIA Excess lactate content of arterial blood rose during hypothermia in six patients undergoing cardiac surgery. This metabolic acidosis due to tissue hypoxia continued until the temperature of the peripheral muscle mass and the viscera were approximately the same. During warming the lactate fell but acidosis continued due to a rise in carbon dioxide tension. (*Ballinger, W. F., and others: Accumulation and Removal of Excess Lactate in Arterial Blood During Hypothermia and Biventricular Bypass, Surgery: 51: 738 (June) 1962.*)

HYPOTHERMIA Hypothermia was induced by means of a low flow partial cardiopulmonary bypass and a heat exchanger. Blood was taken from the right atrium and returned to the patient through a cannula placed in the external iliac artery. During the induction of deep hypothermia in fourteen patients by the technique described, normal sinus rhythm first slowed, then changed to atrial fibrillation. During a period of complete circulatory arrest at a pharyngeal temperature between 13° to 18° C., ventricular fibrillation was usually replaced by asystole and this was often interrupted by regular or irregular ventricular electrical complexes and occasionally by ventricular contractions. During the rewarming phase, ventricular fibrillation usually reappeared. Electrical defibrillation during warming was followed by bizarre ventricular complexes, atrial fibrillation, or nodal rhythm before the return of normal sinus rhythm. (*Tofer, O. B.: Electrocardiographic Changes During Profound Hypothermia, Brit. Heart J. 24: 265 (May) 1962.*)