MEDICATION WHICH MAY INHIBIT CARDIOVASCULAR REACTIVITY TO STRESS*

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THERE HAS BEEN such a tremendous proliferation of new drugs, pharmaceutical compounds, brand names, and trade names that it is impossible for the well-informed physician to be fully cognizant of all their constituents and properties. Some of the compounds may produce their desired effect by relatively innocuous means. However, some achieve their desired effect by influencing very profoundly a basic body mechanism. This effect often becomes apparent only when the patient is under severe stress, as during a surgical operation.

The drugs which concern the anaesthetist may cause electrolyte imbalance, interfere with an enzyme system, or reduce the body's production of basic substances. One of the distressing side-effects is a reduced vascular reactivity to catecholamines. If effective, some of these drugs cause a suppression of the adrenal response and a relative increase in parasympathetic activity. Under these circumstances anaesthetic agents may produce a greater than expected cardiovascular depression. This may be manifested as severe hypotension with bradycardia. The sympathoadrenal system serves as a compensatory mechanism to ensure adequate venous return and cardiac output particularly during intermittent positive pressure ventilation and to offset the cardiovascular depression of anaesthetic drugs.

The Ephedrine Response Test is a means of evaluating the status of a patient's sympathoadrenal system because it demonstrates the ability of the cardiovascular system to react to stress. Ephedrine is given intravenously and causes a release of catecholamines or vasopressor substances from their storage sites in the body. This enables us to determine the vascular reactivity to and availability of catecholamines in the body.

The Ephedrine Response Test consists of two parts. An intravenous injection of 10 mg of ephedrine in 1 c.c. of solution is first made. If there is not an adequate response by the patient a second dose of 5 mg of ephedrine is given intravenously. If after 15 mg of ephedrine an adequate response does not occur, then spinal, epidural, and general anaesthetics are contraindicated. By an adequate response we mean an increase in systolic blood pressure of over 20 mm Hg and an increase in the heart rate of at least 10 beats per minute. If this response does not occur, it will indicate that there is a depletion of catecholamines in the body and that the patient's cardiovascular system has a very limited ability to compensate for stress.

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In any case, if the treatment for hypertension has not been successful, there will have been no effect on the patient's catecholamine stores and there will be no necessity to perform the Ephedrine Response Test.

The Rauwolfia alkaloids are very popular in the treatment of hypertension. The cardiovascular effects of Rauwolfia alkaloids consist of a reduction of arterial blood pressure and a slowing of the heart rate. This may result from a central depression of the vasomotor system because centrally mediated cardiovascular reflexes such as the carotid sinus baroreflex are inhibited. This decreases the body's ability to compensate for blood loss and position change. The Rauwolfia alkaloids are believed to deplete the catecholamine (vasopressor) stores centrally from the hypothalamic centres and peripherally from the postganglionic nerve endings. With Rauwolfia the phosphorylase activity of the myocardium, which is important in the production of energy for the maintenance of myocardial contractility, is decreased.

In man the cardiovascular actions of Rauwolfia become apparent after 3–4 days of continuous therapy and do not become maximal for several weeks. Goodman and Gillman state that the hypotensive action of Rauwolfia is more prominent when it is combined with one or more of the other antihypertensive agents. The Rauwolfia alkaloids themselves disappear rapidly from the body, but the catecholamine stores such as epinephrine and norepinephrine are replenished gradually over a 10–14 day period. It is for this reason that a patient should not be anaesthetized for fourteen days after his last dose of Rauwolfia alkaloid. Theoretically a Rauwolfia-induced hypotension can be corrected by supplying the necessary amines, i.e., norepinephrine, methoxamine, or phenylephrine.

The following is a list of current preparations containing Rauwolfia alkaloids.

RAUWOLFIA ALKALOIDS

<i>Ingredient</i>	<i>Trade name</i>	<i>Company</i>
Rauwolfia	Raudixin	Squibb
	Rautracyl	Squibb
	Rautrax	Squibb
	Raufia	P. Nancy
	Rauloid	Riker
	Rauloid & Veriloid	Riker
	Veriloid	Riker
Reserpine	Serpasil	Ciba
	Serpasil-Esidix	Ciba
Active principle in Rauwolfia	Serpasil-Apresoline	Ciba
	Ser-ap-es	Ciba
	Serpatilin	Ciba
	Diupres	Merck
	Hydiopres	Merck
	Alserin	Frosst
	Serfin	P. D. Co.
	Bitab #33	Canada Pharmacal
	Bitab #44	Canada Pharmacal
	Bitab #66	Canada Pharmacal
	Bitab #506 (Tened)	Canada Pharmacal
	Butiserpine	McNeill

<i>Ingredient</i>	<i>Trade name</i>	<i>Company</i>
Reserpidine or Deserpidine	Decaserpyl Harmony N	Roussel Abbott

Guanethidine

The drug Guanethidine seems to have the same pharmacologic actions as Bretylium Tosylate. These two drugs are enjoying limited popularity as antihypertensives and sedatives. Their action appears to be an inhibition of the peripheral release of catecholamines from the postganglionic sympathetic nerve endings. They do not appear to affect the catecholamine concentration of the adrenal medulla or the brain. However, they are believed to decrease the norepinephrine content of heart muscle. The action of Guanethidine and possibly Bretylium Tosylate persists for seven days after the last dose of medication. Therefore, it would be unwise to give a patient an anaesthetic until he has had at least a week to recover from the effects of the drug. However, theoretically a hypotensive episode due to this medication could be corrected by the giving of peripherally acting vasopressors such as methoxamine, norepinephrine, or phenylephrine.

<i>Ingredient</i>	<i>Trade name</i>	<i>Company</i>
Guanethidine	Ismelin	Ciba
	Ismelin-Esdrin	Ciba
Bretylium Tosylate	Darenthin	B W

Monoamine Oxidase Inhibitors

Monoamine oxidase is an enzyme connected with the breakdown of serotonin, norepinephrine, and epinephrine. This enzyme causes an increase in the ganglionic norepinephrine content. This paradoxically causes hypotension. Apparently an increased concentration of these amines decreases ganglionic transmission and decreases the body's ability to compensate for hypovolaemia and hypotension.

Monoamine oxidase inhibitors are used to treat depressed patients. These drugs are termed psychic energizers because they increase the concentration of the amines serotonin and norepinephrine in the brain. The effect of these antidepressants lasts for days to weeks after their withdrawal. The monoamine oxidase inhibitors potentiate the effect of many drugs, for example (1) morphine, (2) barbiturates, (3) anaesthetic agents, (4) atropine, (5) ganglionic blocking agents.

As yet there are few, if any, reports of adverse effects by monoamine oxidase inhibitors in anaesthetic journals. However, patients on these drugs should be treated with even greater caution. Monoamine oxidase inhibitors include the amphetamines and their analogues.

<i>Ingredient</i>	<i>Trade name</i>	<i>Company</i>
Amphetamine and derivative	Ambar Bitab #33 Bitab #77	Robins Canada Pharmacal Canada Pharmacal
	} Mild effect	

<i>Ingredient</i>	<i>Trade name</i>	<i>Company</i>
	Desoxyn	Abbott
	Dexamyl	S K F.
	Dexadrine	S K F
	Methedrine	B & W.
Methylphenidate	Ritalin	Ciba
Amitriptyline	Elavil	Merck
Isocarboxazid	Marplan	Roche
Nialamide	Niamid	Pfizer
Phenelzine	Nardil	Warner Chilcott
Tranlycypromine	Parnate	S K F
Tranlycypromine with stelazine	Parstelin	S K F
Imipramine	Tofranil	Geigy
Imipramine with sparine	Tofranazine	Geigy

A more recent product is

Pargline	Eutonyl	Abbott
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This is an antihypertensive agent, with the antidepressant properties of monoamine oxidase inhibitors

Diuretics Especially Thiazide Derivatives

These cause a decreased vascular reactivity to catecholamines and other vaso-pressors, an effect which is related to sodium depletion in the peripheral vascular wall. They can also cause a low serum potassium level which enhances digitalis toxicity. Because of this, an anaesthetic should not be given to patients until four days after they have received their last dose of Thiazide medication.

These agents will potentiate the hypotensive effects of preganglionic blockades of spinal and epidural anaesthesia and the ganglionic blockade of *d*-tubocurarine. Hypotension caused by these drugs is best treated by a plasma volume expander.

<i>Ingredient</i>	<i>Trade name</i>	<i>Company</i>
Acetazolamide	Diamox	Lederle
Chlorothiazide	Diuril	Merck
Chlorothiazide with reserpine	Diupres	Merck
Hydrochlorothiazide	Hydrodiuril, Esidrix Oretic	Merck, Ciba and Abbott
Hydrochlorothiazide with reserpine	Hydropres	Merck
Hydrochlorothiazide with reserpine	Serpasil-Esidrix	Ciba
Hydrochlorothiazide	Ser-ap-es	Ciba
Hydroflumethiazide	Saluron	Bristol
Bendroflumethiazide	Naturetin	Squibb
Trichloromethiazide	Naqua	Schering
Polythiazide	Renese	Roerig
Methylclothiazide	Duretic	Abbott
Benzthiazide	Exna	Robins

Non Thiazide products with similar actions are

Chlorthalidone
Spironolactone

Hygroton
Aldactone

Geigy
Searle

Decarboxylase Inhibitors

The drug Aldomet TN inhibits the metabolic decarboxylation of dopamine, a precursor of norepinephrine and serotonin. This drug is largely excreted by the kidneys. Therefore, patients with impaired renal function will respond to smaller doses. Aldomet (TN) has a short duration of action, a withdrawal is followed by a prompt return to previous blood pressure levels within 48 hours.

As this drug is relatively new, its impact upon the anaesthetized patient has not been published. However, patients on this medication should be treated with much caution.

<i>Drug</i>	<i>Trade name</i>	<i>Company</i>
Methyldopa	Aldomet	Meick

RÉSUMÉ

Il y a eu une telle avalanche de nouveaux médicaments, de produits pharmaceutiques, de marques de commerce qu'il est impossible que le médecin—même bien renseigné—soit au courant de la composition et des propriétés de tous ces produits. Quelques-uns de ces composés peuvent produire l'effet désiré sans inconvénient. D'autres cependant produisent leur effet en affectant certains mécanismes importants du corps humain. Souvent cet effet ne se fait sentir qu'à l'occasion d'un stress sérieux, p ex une opération chirurgicale.

Les produits qui intéressent l'anesthésie peuvent produire des troubles de l'équilibre électrolytique, gêner un système d'enzymes, ou diminuer la production de substances de base. Un des effets secondaires assez alarmant est une diminution de la réaction vasculaire aux catécholamines. S'ils sont efficaces, quelques-uns de ces produits abolissent la réponse surrénalienne et augmentent l'activité parasympathique. Dans ces conditions, les agents anesthésiques peuvent produire une dépression cardio-vasculaire plus importante que celle qu'on avait prévue. Ceci se manifeste par une hypotension grave avec bradycardie. Le système sympathico-surrénalien agit comme mécanisme compensateur pour assurer un retour veineux et un débit cardiaque suffisants durant les manoeuvres de ventilation par pression positive intermittente, il remédie aussi à la dépression cardio-vasculaire produite par les agents anesthésiques.

Les auteurs ont décrit brièvement l'action pharmacologique des alcaloïdes de la Rauwolfia, de la Guanéthidine, des inhibiteurs de la Mono-amine oxydase et de la décarboxylase, des dérivés de la Thiazine, et ils ont fourni une liste des médicaments composés à base de ces substances, du nom sous lesquels ils sont mis sur le marché et du nom du manufacturier.