Side Effects of Vasodilator Therapy

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SUMMARY Vasodilating antihypertensive drugs have in common the capacity to activate the peripheral sympathetic nervous system through the carotid sinus baroreceptor reflex mechanism, thereby increasing heart rate, renin release, and sodium and water retention. They differ in their tendencies to augment cardiac output and to relieve or precipitate cardiac failure and arrhythmias. Vasodilating antihypertensive drugs can produce an array of side effects and toxicity including headache, facial changes, hair growth, varying degrees of sodium and water retention, and rarely systemic lupus erythematosus and allergic reactions. Detailed knowledge of these effects is a prerequisite to skillful individualization of antihypertensive regimens.

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MOST antihypertensive drugs, including β-adrenergic receptor, calcium channel, and α₁-adrenergic receptor blockers (i.e., prazosin), and agents that activate α₂-adrenergic receptors in the central nervous system decrease peripheral resistance. However, their primary pharmacological site of action is not at the vascular smooth muscle and are thus not considered as vasodilating antihypertensive drugs in this discussion.

Direct acting vasodilating agents include hydralazine, minoxidil, diazoxide, nitroprusside, and nitroglycerin, and side effects of these drugs will constitute the focus of this discussion.

Side Effects Resulting from Sympathetic Nervous System Activation

Antihypertensive drugs either decrease or increase peripheral sympathetic nervous system activity. Agents that increase this activity do so through the carotid sinus baroreceptor reflex mechanism. This activation or inhibition can be monitored by measurement of circulating plasma norepinephrine levels. With acute activation of this reflex mechanism, plasma norepinephrine levels increase dramatically. During chronic therapy, the magnitude of the increases in plasma norepinephrine is less, but the elevations persist as long as the antihypertensive drugs are administered, and the magnitude is proportional to the antihypertensive activity of the combined peripherally acting antihypertensive drugs. Alternatively, those antihypertensive drugs, such as methyldopa, clonidine, and guanabenz, whose primary site of action is in the central nervous system and those agents, such as guanethidine, debrisoquin, and monoamine oxidase inhibitors, that block norepinephrine release by an action on the sympathetic nerve terminal suppress sympathetic nerve activity and plasma norepinephrine levels. Nearly all of the other antihypertensive drugs, including diuretics and calcium channel blockers, elevate plasma norepinephrine. Interestingly, the angiotensin converting enzyme inhibitor captopril has less effect on plasma norepinephrine during chronic administration than other equieffective antihypertensive drugs.

Hemodynamic Characteristics of Vasodilators

Acute Effects

Cardiac output and heart rate changes occur with acute administration of vasodilating agents with the potential for developing congestive heart failure, acute pulmonary edema, tachyarrhythmias, and myocardial infarction in occasional patients. These effects are functions of the lack of venodilatory component of the drug's action, the rapidity of onset of the drugs, the volume status of the patient, and the character of the cardiac disease.

The venodilatory capacity of nitroprusside and nitroglycerin is considerable, whereas diazoxide is intermediate, and hydralazine has very little venodilatory capacity. Hydralazine fails to counteract the venoconstriction resulting from reflex-mediated norepinephrine-induced venous tone. Thus, hydralazine administered intravenously or intramuscularly markedly increases venous return and cardiac output and rate. In patients with congestive heart failure or noncompliant ventricular tachyarrhythmias (or both), acute pulmonary edema may occur with parenterally administered hydralazine.

Nitroglycerin and nitroprusside, on the other hand, are potent venodilators and tend to reduce venous return and thereby reduce heart failure symptoms. Diazoxide is intermediate in its venodilatory action, and bolus injection can produce tachyarrhythmias and
myocardial infarction. However, because of its partial venodilatory action and because of its long duration of action, diazoxide is far preferable to hydralazine for parenteral administration. Diazoxide is provided in a 300-mg ampule, and in order to permit slow equilibration with albumin binding sites, it should be given intravenously over a 3- to 5-minute period.

Rapid bolus administration of diazoxide was initially recommended because of its capacity for more dramatic lowering of blood pressure when administered in this manner. The explanation for this lowering is relatively simple. The vasodilating activity is directly proportional to the free drug concentration in plasma. At the moment of injection, 100% of the drug is free. A few minutes after administration when the protein reaches an equilibrium state, only 3% is free, and 97% is bound to albumin. Thus, in a few minutes, there is a 30-fold reduction of vasodilatory activity after a rapid bolus injection. To minimize the possibility of drastic blood pressure reduction, the 300-mg ampule should be given over a 3- to 5-minute period.

**Chronic Hemodynamic Effects**

While clonidine, and probably methyldopa, can substitute for \( \beta \)-blocking agents as antagonists of the vasodilator drug–induced sympathetic nervous system overactivity, we find that \( \beta \)-blockers are preferable except in patients with congestive heart failure or other contraindications to \( \beta \)-blockers.

The side effect of cardiac stimulation from vasodilator drug–induced norepinephrine release into the cardiac conduction system can be beneficial in patients with conduction abnormalities such as sick sinus syndrome and heart block (W.A. Pettinger and H.C. Mitchell, unpublished observations). Because of the long duration of minoxidil’s action, we have used this side effect to advantage in several patients. This potentially beneficial side effect should be systematically studied, particularly in older patients in whom the problems of conduction abnormalities and hypertension coexist. Obviously, those patients whose Stokes-Adams symptoms or conduction defects (or both) are precipitated by \( \beta \)-blockers or calcium channel blockers would be most likely to benefit from this novel therapeutic approach.

**Specific Drug Side Effects**

**Hydralazine**

Hydralazine-induced headaches are one of the most common side effects that limits use of this drug. In the lower dose of 50 mg, there may be a constant dull suboccipital pain. The characteristic throbbing headache that peaks at 1/2 to 1 hour after drug administration is usually associated with doses higher than 50 mg. Hydralazine-induced headaches may continue for as long as 5 days after discontinuing the drug. Interestingly, even though minoxidil is a much more potent vasodilator, the physician can usually guarantee relief of the hydralazine headache within 5 days after substitution of minoxidil. The positive ANA titer occurs in 15 to 20% of patients on chronic hydralazine therapy. The lupus syndrome from hydralazine is rare, particularly when dosages less than 300 mg/day are used. Apparently, this lupus syndrome does not involve the kidneys.

**Minoxidil and Diazoxide**

Minoxidil is an extraordinarily powerful and long-lasting vasodilating agent that has altered the course of patients with severe hypertension. Long-term use of this drug as the primary antihypertensive agent over an 18-month period can reduce the antihypertensive drug requirements and increase the glomerular filtration rate of patients with hypertensive nephrosclerosis, even in the absence of signs of malignant hypertension. Whether other antihypertensive drugs can achieve similar beneficial effects in these patients is unknown.

Minoxidil can cause marked renal retention of sodium and water resulting in impressive weight gain, cardiac enlargement, increased diuretic requirement, and peripheral edema. While these effects are related to direct renal effects of minoxidil, cardiac dilation prior to use of the drug is an important predisposing factor and is predictive of the magnitude of the problem. High-dose (1 g/day) furosemide may be required to control salt and water retention. However, the addition of thiazide diuretics markedly potentiates furosemide’s action, permitting reduction of the high doses frequently to 160 mg/day.

Pulmonary hypertension has been reported in several minoxidil-treated hypertensive patients. However, this finding appears to be due simply to patient selection. Candidates for minoxidil therapy generally have been selected because of the severity of their hypertension. There is a direct and proportional relationship between severity of hypertension, increased peripheral resistance, and increased pulmonary vascular resistance. Thus, an association between minoxidil therapy and pulmonary hypertension appears to be due to selection bias.

Pericardial effusion occurs occasionally in minoxidil-treated patients having advanced renal disease and has been reported rarely to require surgical intervention for tamponade. This complication is usually associated with marked salt and water retention and conceivably may be controlled by prevention of the severely edematous state. Substitution of angiotensin converting enzyme inhibitors (CEI) for minoxidil has been of value in management of some of these patients. However, these same patients may have decreased glomerular filtration with CEI, and renal function should be monitored (W.A. Pettinger and H.C. Mitchell, unpublished observations).

Coarsening of facial features can be impressive. The degree to which this coarsening is exaggerated by interstitial and intracellular edema is unclear. However, since up to 4 months are required for reversal of the altered features and only a few days are required for edema loss after discontinuing minoxidil, the mechanism for the hypertrichosis and facial changes may be related.

Increased hair growth occurs with the long-acting
vasodilators minoxidil and diazoxide. In contrast to hirsutism, this increased hair growth is independent of gonadal hormones. Vasodilator-induced hair growth texture is soft, and the hairs are relatively short. The degree of hair growth is highly variable. It is most noticeable around the eyes, in the external ear canal, and over the trunk. In women, the forearm hair growth may be quite noticeable.

Eyelashes become thicker and longer, and trimming may be required to prevent contact with eyeglasses. Two of our patients have complained of hair growth in the external ear canal and some hearing loss that was reversed by discontinuing minoxidil. While there is considerable interest in topical application of minoxidil for scalp hair growth, particularly in males, we expect that it may be most useful in alopecia areata and for its effect on eyelashes in women. Most of the excess hair growth subsides within 4 months of discontinuing minoxidil.

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