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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KEY WORDS • minoxidil • plasma norepinephrine • antihypertensive drugs • vasodilators

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 vasodilatating 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.1 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 administration2 3 than other equiactive 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.4 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 dra-
matic lowering of blood pressure when administered in
this manner. The explanation for this lowering is rela-
tively simple. The vasodilating activity is directly pro-
portional 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 substi-
tute for β-blocking agents as antagonists of the
vasodilator drug-induced sympathetic nervous system
overactivity,8 we find that β-blockers are preferable
except in patients with congestive heart failure or other
contraindications to β-blockers.

The side effect of cardiac stimulation from vasodila-
tor drug-induced norepinephrine release into the card-
iac 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 dura-
tion of minoxidil’s action, we have used this side effect
to advantage in several patients. This potentially ben-
ficial side effect should be systematically studied, par-
cularly in older patients in whom the problems of
conduction abnormalities and hypertension coexist.
Obviously, those patients whose Stokes-Adams symp-
toms or conduction defects (or both) are precipitated
by β-blockers or calcium channel blockers would be
most likely to benefit from this novel therapeutic ap-
proach.

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 head-
ache that peaks at ½ 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 vaso-
dilator, the physician can usually guarantee relief of
the hydralazine headache within 5 days after substi-
tution of minoxidil. The positive ANA titer occurs in
15 to 20% of patients on chronic hydralazine therapy.

The lupus syndrome from hydralazine is rare, particu-
larly when dosages less than 300 mg/day are used.
Apparently, this lupus syndrome does not involve the
kidneys.6

Minoxidil and Diazoxide

Minoxidil is an extraordinarily powerful and long-
lasing vasodilating agent that has altered the course of
patients with severe hypertension.7 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,8 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 sodi-
um and water resulting in impressive weight gain, car-
diac 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 fre-
quently to 160 mg/day.

Pulmonary hypertension has been reported in sever-
al minoxidil-treated hypertensive patients.9 However,
this finding appears to be due simply to patient selec-
tion. Candidates for minoxidil therapy generally have
been selected because of the severity of their hyperten-
sion. There is a direct and proportional relationship
between severity of hypertension, increased peripheral
resistance, and increased pulmonary vascular resis-
tance.10 Thus, an association between minoxidil ther-
apy and pulmonary hypertension appears to be due to
selection bias.

Pericardial effusion occurs occasionally in minoxi-
dil-treated patients having advanced renal disease and
has been reported rarely to require surgical interven-
tion for tamponade. This complication is usually asso-
ciated with marked salt and water retention and con-
ceivably 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 pa-
tients. However, these same patients may have de-
creased glomerular filtration with CEI, and renal func-
tion 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 in-
terstitial 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
deema loss after discontinuing minoxidil, the mecha-
nism 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.

References
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