Direct-Acting Vasodilators

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Key Points and Practical Recommendations

- Hydralazine and minoxidil act by dilating resistance arterioles, thus reducing peripheral resistance, with no dilating effect on the venous side of the circulation.
- There is a baroreflex-mediated venoconstriction, resulting in an increase in venous return to the heart, along with a direct catecholamine-mediated positive inotropic and chronotropic stimulation of the heart.
- Hydralazine therapy is usually combined with a sympathetic inhibitor to prevent expression of this reflex, as well as with a diuretic agent to prevent sodium retention caused by reduction in renal perfusion pressure.
- Hydralazine is indicated in the long-term therapy of essential hypertension, in the short-term therapy of pregnancy-induced hypertension and eclampsia, and in the therapy of hypertensive crisis.
- Adverse effects include the anticipated tachycardia, fluid retention, and headache, caused by the vasodilation, especially in the early days of therapy, but may frequently be prevented by the concomitant use of a β-blocker.
- As with other drugs that are *N*-acetylated, there is a low risk of lupus-like syndrome with high doses and long-term use.
- Because of the severity of adverse effects with minoxidil, its usage is limited to persons with severe hypertension unresponsive to other treatments.
- Hirsutism, a common side effect of minoxidil, is particularly bothersome in women and reverses in a few months after discontinuation.
- Sodium nitroprusside is used in the intensive care setting to lower pressure in hypertensive crisis or to treat severe left ventricular failure, particularly valuable when elevated pressure or severe left ventricular failure threatens the patient's survival.
- Although nitrates have not achieved widespread use as antihypertensive agents, they are effective in producing sustained blood pressure (BP) reductions when added to other antihypertensive regimens. *J Clin Hypertens (Greenwich).* 2011;13:690–692. ©2011 Wiley Periodicals, Inc.

Many drugs exert an arterial relaxing effect without interfering with known systemic or local constrictor mechanisms or interfering with calcium channels that mediate constriction. These drugs are usually clinically employed to augment the pressure-lowering effect of other agents rather than as initial first-line therapy. They vary in their vasodilator potency on large conduit arteries, small branch arteries, arterioles, and veins. Relaxation of conduit arteries increases their compliance and tends to lower systolic and pulse pressure. Relaxation of small arteries and arterioles reduces wave reflection and lowers systemic vascular resistance. Relaxation of veins increases systemic capacitance and lowers central venous pressure. The balance of these effects with individual drugs, combined with the reflex neurohormonal response, influences the overall hemodynamic effect of their administration.

Only a few of these drugs are commonly used in pharmacologic management of hypertension. We will confine our attention to those in frequent use.

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DOI: 10.1111/j.1751-7176.2011.00507.x

HYDRALAZINE

Mechanism of Action

Hydralazine acts by dilating resistance arterioles, thus reducing peripheral resistance. As there is no dilating effect on the venous side of the circulation, there is a baroreflex-mediated venoconstriction, resulting in an increase in venous return to the heart.[1] This effect, along with a direct catecholamine-mediated positive inotropic and chronotropic stimulation of the heart, results in an increase in cardiac output, which opposes the BP-lowering effect. Hydralazine therapy is usually combined with a sympathetic inhibitor to prevent expression of this reflex, as well as with a diuretic agent to prevent sodium retention caused by reduction in renal perfusion pressure.

Pharmacokinetics and Pharmacodynamics

Hydralazine is metabolized in the liver, primarily by *N*-acetylation, and also forms hydrazones (eg, the pyruvic acid hydrazone and the acetone hydrazone), which may have some activity in reducing BP. The rate of this *N*-acetylation step has a trimodal distribution and is determined genetically. This "acetylator status" determines the systemic bioavailability of the orally administered drug and, because response is determined

to a significant extent by drug levels in the blood, also determines response to the drug.[2] It has been estimated that oral availability is 10% to 30%, depending on acetylator status. The plasma half-life is short, approximately 90 minutes but, as with many antihypertensive drugs, the clinical effect far outlasts the presence of the drug in the blood and may be given effectively as a twice-a-day regimen.[3,4] There is a detectable long terminal phase half-life on maintenance dosing that could partially explain this discrepancy. The presently used dosage for clinical hypertension is from 25 mg twice a day to 50 mg three times a day.

Indications

Hydralazine is indicated for long-term therapy of essential hypertension and for short-term therapy of pregnancy-induced hypertension and eclampsia and in the therapy of hypertensive crisis. It has also been combined with isosorbide dinitrate to serve as an antioxidant to help sustain the effect of chronic nitrate therapy for heart failure (HF).[5]

Clinical Usage

As indicated above, it is usually combined with a sympathetic antagonist and a diuretic in the treatment of essential hypertension, when it is an inexpensive, effective, and relatively trouble-free means of reducing BP. Given in pregnancy, it is not toxic to the fetus and may be used parenterally in an emergent situation. In hypertensive crisis, it is not the best therapy in patients with coexisting ischemic heart disease, when it may worsen ischemia, or in aortic dissection, when it may increase stroke volume and extend the dissection.

Adverse effects include tachycardia and fluid retention. Headache caused by the vasodilation is seen, especially in the early days of therapy but may frequently be prevented by the concomitant use of a β-blocker. As with other drugs that are *N*-acetylated, there is a low risk for lupus-like syndrome with high doses and long-term use.[6] This is not the same disease as systemic lupus erythematosus and there is much lower risk of renal involvement. It is more likely to be seen in slow acetylators, as their systemic dose will be higher, and is less often seen in African American patients. If high doses are used (eg, 400 mg), an annual determination of antinuclear antibodies and inquiry at each clinic visit as to the onset of muscle aches and pains are appropriate safety precautions.

MINOXIDIL

Mechanism of Action

Minoxidil dilates resistance vessels[7] with little or no action on the venous bed. It acts by activation of adenosine triphosphate–sensitive potassium channels in arterial smooth muscle.[8,9] As a result, the smooth muscle membrane is hyperpolarized and calcium influx through voltage-gated calcium channels is inhibited. Cytosolic calcium concentration is reduced.

Oral absorption is 100%. Plasma half-life is 2.8 to 4.2 hours and plasma protein binding is negligible. Minoxidil is extensively metabolized in the liver along 4 pathways: glucuronidation (67%), hydroxylation (25%), sulphation, and conversion to an uncharacterized polar compound.[10] The sulphated metabolite is pharmacologically active and probably accounts for much of the activity of the parent drug.

Indications

Because of the severity of adverse effects, usage is limited to patients with severe hypertension unresponsive to other treatments.[11] Minoxidil is usually administered twice daily, with an initial dose of 2.5 mg to 5 mg. Once-daily dosing is occasionally employed. The maximum daily dose is usually 50 mg, although doses up to 100 mg have been used.

Clinical Usage

Pretreatment with a β-blocker limits sympathetic activation.[12] Sodium retention usually requires concomitant diuretic therapy, and a loop diuretic is often necessary. Minoxidil is excreted into breast milk and therefore is best avoided in breastfeeding mothers. Safety in pregnancy has not been established.

Tachycardia due to reflex sympathetic activation may account for electrocardiographic (ECG) changes, which are often observed during the first few days of therapy. ECG changes include ST depression and T-wave inversion[13] but are not associated with cardiac enzyme elevation. Angina may be aggravated in patients with ischemic heart disease. Pulmonary and dependent edema may be the result of fluid retention and also increased capillary pressure from arteriolar dilation without venous dilation. Flushing, palpitation, and headache may occur if a β-blocker is not taken concomitantly.

An uncommon cardiac adverse event is pericardial effusion, which is rarely associated with tamponade.[14]

A common side effect of minoxidil is hirsutism, which is particularly bothersome in women. Hypertrichosis affects mainly the forehead and face and is most apparent in dark-haired individuals. There is no pharmacologic treatment for excess hair growth, and the only remedy is removal of hair or discontinuation of the drug. After discontinuation, excessive hair growth reverses in a few months.

Other reported side effects with minoxidil include nasal stuffiness, nausea, breast tenderness, and skin reactions. Minoxidil and other agents with BP-lowering effects exhibit enhanced hypotensive effects in combination. Corticosteroids antagonize the antihypertensive effect of minoxidil. No other drug interactions are reported.

NITRATES AND NITROPRUSSIDE

Mechanism of Action

Nitrates and sodium nitroprusside may be viewed as nitric oxide donors, since their vascular effects appear

to be related to generation of nitric oxide gas as a consequence of their metabolic breakdown.[15] The pattern of vascular effect appears to differ, however, depending on the drug and its concentration at the vascular site of action. Oral nitrates exert a relaxing effect on veins, conduit arteries, and small arteries that influence reflected waves. They are not potent arteriolar dilators. Nitroprusside, on the other hand, is also active on arterioles and lowers systemic vascular resistance when given intravenously.

Indications

Sodium nitroprusside is used in the intensive care setting to lower pressure in patients with hypertensive crisis or to treat severe left ventricular failure by acutely reducing impedance to left ventricular emptying.[16] Its rapidity of action and reliability in stabilizing BP at desired levels make it particularly valuable when elevated pressure or severe left ventricular failure threatens the patient's survival.[17]

Long-term nitrate administration in the form of oral isosorbide dinitrate, isosorbide mononitrate, or transdermal nitroglycerin is more widely used to treat angina or HF than to lower BP in hypertension. Long-term outcome trials in hypertension have not been performed because the drugs are generic and of little commercial value. Nonetheless small, short-term studies have demonstrated effective BP lowering,[18] especially elevated systolic pressure in the elderly,[19] and the safety of the drugs has been assumed because of their generations of use in coronary disease and HF.

Clinical Usage

Nitroprusside is infused intravenously and up-titrated from low initial starting doses until the desired hemodynamic effect is achieved. The initial dose is usually 20 μg/min, which may be doubled at 5-minute intervals until BP is reduced or evidence of left ventricular failure is relieved. Headache and nausea are common side effects, but the primary concern during prolonged infusion is the development of cyanide toxicity, which requires termination of the infusion. Blood levels of thiocyanate may be monitored as a guide to potential cyanide toxicity, which is rare at infusion rates of $<$200 μg/min.

Although nitrates have not achieved widespread use as antihypertensive agents, they are effective in producing sustained BP reductions when added to other antihypertensive regimens.[18] Longer-acting preparations (isosorbide mononitrate 60–120 mg once daily or transdermal patches of nitroglycerin left on the skin for 16 hours daily) are effective in lowering systolic BP without tolerance. Headache is a major side effect but can be prevented by slow up-titration and resolves with continuous administration. Combination of nitrate with an antioxidant, such as hydralazine, inhibits nitrate tolerance[20] and is effective in slowing progression of HF[5] but has not been tested in hypertension.

Disclosure: The authors received no honoraria for their contribution to this issue.

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