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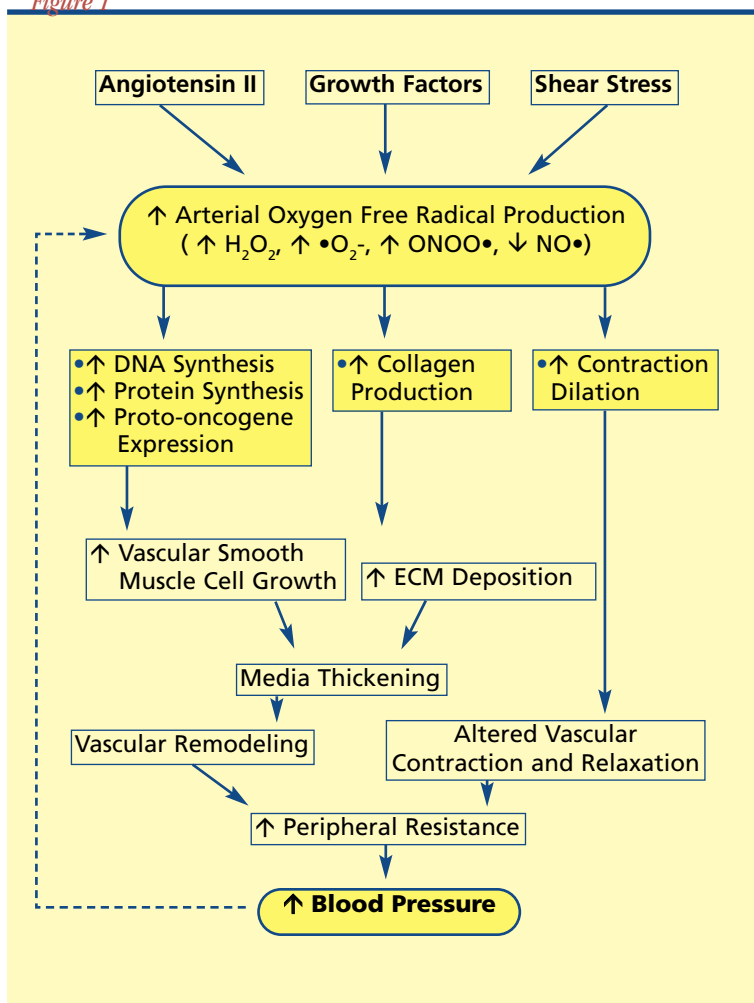
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Dopamine (DA) is an endogenous catecholamine precursor of norepinephrine with important roles in behavior and central nervous system function. Thirty-four years ago, following his pioneering work on vascular DA receptors, Dr. Leon Goldberg and his colleagues administered DA to severely hypertensive humans. They observed that this catecholamine vasopressor could be paradoxically antihypertensive in man, with markedly enhanced activity when its effects at α_1 -adrenergic receptors were blocked. Its effects appeared unique in that renal perfusion and diuresis were enhanced and tachycardia limited, in spite of profound vasodilation. More recently, an explosion of basic research has elucidated the roles of multiple DA receptors in the kidney, brain, and vasculature that have major roles in blood pressure (BP) regulation and, perhaps, in the pathogenesis of hypertension.

In this issue, Drs. Pedro Jose, Martin Bek, Gilbert Eisner, and Robin Felder discuss the physiology of DA receptors and their possible involvement in hypertension. In addition, Drs. Amos Bodner and Patrick Murray provide a succinct review of fenoldopam, a selective D_1 -receptor agonist which appears, as Goldberg predicted, to have special utility in managing hypertensive emergencies and urgencies where oral antihypertensives appear impractical.

In addition to these excellent articles on the role of dopamine receptors and the dopamine receptor antagonist fenoldopam, we have a very informative exposition on the role of oxidative stress in vascular injury by Dr. Touyz. This is a topic of great current interest and Dr. Touyz's informative discussion enhances our understanding of this important and emerging area of vascular disease.

Figure 1



Legend

Flow chart shows mechanisms whereby oxidative stress mediates vascular, structural, and functional changes in hypertension. Angiotensin II, growth factors, shear stress, as well as elevated blood pressure itself, stimulate generation of arterial reactive oxygen species, which lead to increased cell growth, media thickening, enhanced contraction, and reduced dilation. These vascular changes result in increased peripheral resistance and ultimately elevated blood pressure.

DNA – deoxyribonucleic acid
ECM – extracellular matrix

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There is increasing evidence that oxidative stress mediates vascular injury in various cardiovascular pathologies, including hypertension, atherosclerosis, and ischemia-reperfusion. This development has evoked considerable interest because of the possibilities that therapies targeted against oxygen radicals may be useful in minimizing vascular injury. Metabolism of oxygen by cells generates potentially deleterious reactive oxygen species including the superoxide anion ($\bullet\text{O}_2^-$), hydrogen peroxide (H_2O_2), hydroxyl radical ($\bullet\text{OH}$), and nitric oxide ($\text{NO}\bullet$) which act as intercellular and intracellular mediators of signal transduction processes. Under normal physiological conditions the rate and magnitude of oxidant formation is balanced by the rate of oxidant elimination. However, an imbalance between pro-oxidants and antioxidants results in oxidative stress which is the pathogenic outcome of overproduction of oxidants that overwhelms the cellular antioxidant capacity.

In the vasculature, reactive oxygen species modulate vascular tone and structure. $\bullet\text{O}_2^-$ and H_2O_2 have been shown to induce vascular contraction¹ and vascular smooth muscle cell growth,^{2,3} whereas $\text{NO}\bullet$ plays a pivotal role in endothelium-dependent relaxation.⁴ Furthermore, oxygen free radicals are proinflammatory and stimulate monocyte migration and formation of oxidized low-density lipoproteins, which are toxic to vascular cells and impair vascular endothelial function.⁵ Consequently excessive reactive oxygen species may underlie pathologic processes associated with endothelial dysfunction and vascular remodeling, which are characteristic features of small vessels in hypertension.

Vascular Effects of Reactive Oxygen Species in Hypertension

Vascular remodeling. Vascular damage in hypertension is associated with increased production of reactive oxygen species, particularly in angiotensin II-dependent hypertension.⁶⁻⁸ Oxidative stress promotes vascular smooth muscle cell proliferation and hypertrophy, collagen deposition, and alterations in activity of matrix metalloproteinases, which lead to thickening of the vascular media and arterial remodeling. The role of oxidative stress in remodeling was also suggested in studies demonstrating that antioxidant vitamins increase lumen diameter and regress arterial remodeling in damaged pig coronary arteries.⁹ Furthermore, superoxide dismutase (SOD) mimetics improve endothelial function and reduce blood pressure (BP) in experimental models of hypertension.^{6,10}

In addition to oxidative stress influencing arterial structure, media thickening itself affects vessel redox state. Vascular wall thickening increases the distance required for diffusion of oxygen from the lumen. Reduced oxygen partial pressure, in turn, results in incomplete oxidation and increased concentrations of free radicals and abnormalities of the oxidant state. This $\bullet\text{O}_2^-$ formation further contributes to vascular smooth muscle cell growth, endothelial dysfunction, and vascular damage in hypertension.

Endothelial Dysfunction. Increased $\bullet\text{O}_2^-$ in hypertension impairs endothelium-dependent vascular relaxation and increases vascular contractile reactivity.¹¹ These effects may be mediated directly by increasing cytosolic Ca^{2+} concentration or indirectly by reducing con-

centrations of the vasodilator $\text{NO}\bullet$. Oxygen radicals also induce endothelial permeability, with extravasation of plasma proteins and other macromolecules, and recruitment of inflammatory proteins and cells, which could further impair endothelial function and aggravate vascular damage. Many of the redox-sensitive vascular changes that occur in hypertension also exist in atherosclerotic vessels.¹² In fact, oxidative stress-mediated vascular damage may be a link between hypertension and atherosclerosis.¹³

Antioxidants and Vascular Damage in Hypertension

The prospect that vascular injury can be avoided or minimized by reducing oxidative stress through increased intake of antioxidants is appealing. A few studies reported that antioxidant vitamins, SOD mimetics, and liposome-entrapped SOD normalize endothelial dysfunction and improve vascular remodeling in experimental hypertension.^{6,10,14} A recent meta-analysis demonstrated that chronic intake of antioxidants improve endothelial function in conduit arteries but not in resistance arteries.¹⁵ Furthermore, it has been suggested that some of the beneficial effects of antihypertensive agents such as angiotensin-converting enzyme inhibitors, angiotensin type 1 receptor antagonists, and calcium channel blockers may be mediated by modulating oxidative stress. Although the experimental data and preliminary clinical results are encouraging, it is premature at this time to advocate antioxidants as therapeutic modalities in the management of hypertension.

Conclusions

Oxidative stress in hypertension contributes to vascular damage by promoting vascular smooth muscle cell proliferation, endothelial dysfunction, vascular tone alteration, and matrix metalloproteinases activation. These processes induce vascular remodeling and contraction-relaxation abnormalities, which characterize vascular injury in hypertension. With a greater understanding of mechanisms that regulate vascular reactive oxygen species metabolism and identification of processes that tip the balance to states of oxidative stress which cause vascular damage, it should be possible to target therapies more effectively so that detrimental actions of vascular oxygen free radicals can be reduced and beneficial effects of $\text{NO}\bullet$ can be enhanced. Such therapies would be useful in the prevention and treatment of many disease processes associated with vascular damage, including hypertension, atherosclerosis, and diabetes.

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Dopamine (DA) has recently been recognized as an important regulator of systemic blood pressure (BP). It affects fluid and electrolyte balance by actions on renal hemodynamics and epithelial transport and by regulation of hormones and humoral agents such as aldosterone, catecholamines, endothelin, prolactin, pro-opiomelanocortin, renin, and vasopressin. It can also modulate fluid and sodium intake via “appetite” centers in the brain and gastrointestinal transport. Additionally, DA controls BP by actions on neuronal cardiovascular centers, the heart, arteries, and veins.

DA exerts its actions via 2 families (D_1 -like and D_2 -like) of cell surface G protein-coupled receptors. The D_1 -like receptors (D_1 and D_5) stimulate adenylate cyclase via stimulatory $G_s\alpha$ while the D_2 -like receptors (D_2 , D_3 , and D_4) inhibit adenylate cyclase via G_i/Go . The affinity of DA to its receptors ranges from low nanomolar to low micromolar range. At higher concentrations, α - and β -adrenergic and serotonin receptors are occupied. Circulating (picomolar) concentrations of DA are insufficient to activate its own receptors. This is in contrast to DA-producing tissues, where high nanomolar to micromolar concentrations can be attained. DA can be synthesized not only in noradrenergic and dopaminergic nerves but also in non-neural tissues (e.g. kidney, gastrointestinal tract).

Regulation of Fluid and Electrolyte Balance by DA

DA regulates water and electrolyte excretion indirectly by actions on renal hemodynamics and on the secretion, release, and action of vasoactive hormones and peptides, and directly by its actions on renal tubules. D_1 -like receptors act at several nephron segments to inhibit multiple mechanisms of sodium reabsorption. While most of these effects are mediated by cyclic adenosine monophosphate (cAMP) and protein kinase A and by eicosanoid pathways, other signal transduction pathways also contribute. By contrast, activation of D_2 -like receptors decreases cAMP and stimulates sodium transport. In collecting duct cells, D_2 -like receptors antagonize the actions of aldosterone and vasopressin.

Some actions of DA appear to be counter regulatory (e.g. D_1 -like inhibition and D_2 -like stimulation of sodium transport, D_1 -like stimulation of renin and vasopressin secretion and D_2 -like inhibition of renin and aldosterone secretion). The state of sodium balance determines which of these DA receptor subtype functions predominate. The natriuretic effect of DA is noted under “normal” sodium intake and magnified under conditions of “moderate” sodium excess. Under sodium replete states, endogenous renal DA is responsible for regulating more than 50% of sodium excretion. D_1 -like receptors are sufficient to inhibit Na^+/H^+ exchanger isoform 3 (NHE3) and sodium bicarbonate cotransporter activities. However, in sodium-replete states, D_1 - and D_2 -like receptors (rather than acting in opposing directions) synergistically inhibit Na^+/K^+ -ATPase activity to further increase sodium excretion. This effect is associated with increased renal DA production and an augmented effect on sodium transporters but not with increased expression of DA receptors or effector proteins. However, sodium-induced decreases in hormonal or humoral factors that oppose D_1 -like receptor action (e.g. angiotensin II, adenosine, serotonin) may further enhance DA-induced natriuresis. The stimulatory effect of D_1 -like

receptors on renin release is attenuated while the D_2 -like inhibitory effects on renin release and aldosterone secretion are enhanced in volume-loaded states. During volume expansion, D_4 receptors may also facilitate diuresis and natriuresis by antagonizing vasopressin and aldosterone effects in the cortical collecting duct.

When sodium loading is excessive, the natriuretic effect of DA is no longer evident, presumably because other natriuretic factors predominate. When renal tubular endogenous DA subserves a paracrine and/or autocrine function, its natriuretic effect (via D_1 -like receptors) is due mainly to tubular rather than glomerular or renal hemodynamic action. However, DA produced by renal nerves may participate, via D_3 receptors, in the regulation of the glomerular filtration rate.

Regulation of Vascular Tone by DA

In addition to dopaminergic regulation of fluid and electrolyte balance, DA regulates the central cardiovascular centers and catecholamine release by sympathetic nerves and adrenal medulla. Direct and indirect actions of DA receptors can cause vasorelaxation (D_1 and D_5) or vasoconstriction (D_3). At higher concentrations (high micromolar range), DA produces vasoconstriction by occupation of α_1 -adrenergic receptors. These apparently counter-regulatory actions are influenced by the basal arterial tone. When tone is high, D_2 -like receptors promote relaxation and the opposite action occurs when basal tone is low.

DA and Hypertension

Abnormalities in DA production and receptor function have been described in genetic models of hypertension. Inhibition of DA synthesis outside the central nervous system accelerates the development of hypertension in the spontaneously hypertensive rat (SHR). DA receptor blockade is associated with the development of hypertension in saline loaded Wistar rats and potentiates the renal effects of nitric oxide inhibition.

D₁-Like Receptors. The renal autocrine and paracrine natriuretic function of DA, via D_1 -like receptors, is impaired in both the SHR and Dahl salt sensitive rat via receptor uncoupling from its G protein and effector protein complex in both an organ and nephron segment-specific manner. Preservation of the vasodilatory and “distal” renal tubular responses to D_1 -like agonists in these models of hypertension explains the ability of fenoldopam, a D_1 -like agonist to decrease BP and produce natriuresis, even in hypertensive subjects.

Disruption of the D_5 receptor gene in mice results in the development of hypertension. The D_5 mutant mice have no impairment in ability

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to excrete an acute saline load. However, the high BP in the D_5 receptor knockout mouse is normalized by blockade of α -adrenergic and V_1 vasopressin receptors. Because the major receptor involved in DA-mediated natriuresis is the D_1 receptor, we have suggested that the renal dopaminergic defect in genetic hypertension probably involves the D_1 rather than the D_3 receptor. The D_1 receptor locus is linked to variations in systolic BP levels in caucasian humans and cardiac hypertrophy in rats. Disruption of the D_1 receptor in mice likewise leads to hypertension.

D₂-Like Receptors. Several abnormalities of D_2 -like receptor function have also been reported in hypertension. Disruption of the D_2 receptor gene in mice produces hypertension without a decreased ability to excrete a sodium load. Rather, the hypertension in D_2 receptor knockout mice is caused by increased activity of the adrenergic nervous system. An unexpected finding in D_2 knockout mice was the normalization of BP by an endothelin B (ET_B) antagonist.

D_1 receptors stimulate while D_2 -like receptors inhibit renin secretion in rats. DA also regulates angiotensin II type 1 (AT_1) receptor expression in the kidney. Moreover, D_2 -like receptors downregulate AT_1 receptor expression and function. Disruption of the D_3 receptor gene in mice is associated with renin-dependent hypertension and a decreased ability to excrete an acute saline load. Aberrant dopaminergic regulation of aldosterone secretion (via D_3 receptors) may be involved in some forms of hyperaldosteronism and hypertension.

Conclusions

DA regulates fluid and electrolyte balance by direct and indirect actions in the kidney, blood vessels, gastrointestinal tract, adrenal glands, sympathetic nervous system, hypothalamus, and other "brain centers". Dopaminergic regulation of the secretion of angiotensin and aldosterone, catecholamines, and vasopressin contributes to this process. Furthermore, DA can also regulate the expression of receptors other than its own (e.g. ET_B , AT_1). DA receptor knockout models lead to hypertension by mechanisms that vary with the specific receptor deleted. Abnormalities of DA receptors (or their regulation) may be important in the pathogenesis of essential hypertension.

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Parenteral antihypertensives are preferred for pharmacotherapy in hypertensive emergencies and many urgencies where oral agents are impractical, including perioperative hypertension. The therapeutic goal in hypertensive crises

is prompt and controlled blood pressure (BP) reduction while maintaining vital organ perfusion. The ideal therapeutic agent would possess the following characteristics: parenteral administration, rapid onset and offset in minutes, easy titratability, reliable efficacy, safety across patient populations, ease of use, and cost effectiveness. Titratability is crucial to permit controlled BP reduction without precipitating hypoperfusion and end-organ ischemia in circulatory beds (cerebral, renal) autoregulated to hypertensive perfusion pressures. The Sixth Joint National Committee on the Detection, Treatment, and Evaluation of High Blood Pressure recommendations of parenteral agents with potential utility in hypertensive crises for the first time included fenoldopam, a novel parenteral dopaminergic vasodilator with efficacy and titratability comparable to sodium nitroprusside (SNP), and some interesting, potentially advantageous renal effects.

Fenoldopam is a benzazepine derivative of dopamine (DA) which binds selectively to D_1 -like (D_1) receptors without effect at D_2 -like (D_2) receptors, or either α_1 - or β -adrenoceptors (although it has activity at α_2 -adrenoceptors). Peripheral D_1 receptors are located postsynaptically in the systemic and renal vasculature, at various sites in renal tubules, in the gastrointestinal tract, and elsewhere. They mediate systemic, renal, and mesenteric vasodilation, along with a direct renal tubular natriuretic effect. Fenoldopam does not cross the blood-brain barrier and, therefore, does not activate central nervous system D_1 receptors. Effects on coronary blood flow, determined only in animal studies, are inconsistent. Systemic effects in hypertensive subjects have been well-characterized, including a consistent pharmacokinetic (PK) and pharmacodynamic (PD) profile. In a PK and PD study of fenoldopam infusion in hypertensive patients, the PK profile was linear, with a short $T_{1/2}$ of 5 min, achieving full effect within 30 to 60 minutes. The PD profile was similarly predictable, with dose-dependent systolic and diastolic BP reductions and development of associated reflex tachycardia. During prolonged infusion there was some evidence of tolerance but no rebound hypertension following abrupt discontinuation after 48 h. In this study, infusion rates as high as 0.8 $\mu\text{g}/\text{kg}/\text{min}$ were tolerated with no serious adverse effects. In a previous small study, adverse events occurred at doses $>0.8 \mu\text{g}/\text{kg}/\text{min}$, including 2 subjects (receiving 0.9 and 1.9 $\mu\text{g}/\text{kg}/\text{min}$) who developed severe bradycardia (presumed Bezold-Jarisch reflex). Clinically recommended doses are 0.1 to 1.6 $\mu\text{g}/\text{kg}/\text{min}$, with adverse effects including reflex tachycardia, hypotension, hypokalemia (by diuresis), and

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increased intraocular pressure. Fenoldopam is metabolized by conjugation to a variety of inactive renally excreted methoxy-, sulfate, and glucuronide metabolites. It is not a substrate for cytochrome P-450 and has few known major drug interactions, although formal studies are lacking. Fenoldopam clearance is not impaired in patients with hepatic or renal impairment.

Fenoldopam is approved by the Food and Drug Administration for inpatient, short-term management of severe hypertension, including malignant hypertension. In 94 patients with hypertensive emergencies (DBP \geq 120 mm Hg with target organ damage [TOD]), fenoldopam led to rapid, dose-related (0.01 to 0.3 $\mu\text{g}/\text{kg}/\text{min}$) decreases in SBP and DBP, and increases in HR. In 183 severely hypertensive subjects, some with TOD, fenoldopam and SNP were equally effective in lowering BP. In 28 severely hypertensive patients who received fenoldopam or SNP, fenoldopam decreased BP from 214/136 mm Hg to 175/100 mm Hg at a mean dose of 0.3 $\mu\text{g}/\text{kg}/\text{min}$, similar to the effect seen with SNP. Another comparison with SNP in 41 severely hypertensive patients similarly found equivalent BP control and increased creatinine clearance (39 to 75 mL/min), urinary volume, sodium, and potassium excretion in fenoldopam-treated subjects. These parameters were unchanged in the SNP group.

Several studies suggest fenoldopam's utility for control of perioperative hypertension. It was superior to SNP in the preservation of renal blood flow in anesthetized dogs during induced hypotension, which is used in several surgical procedures. Studies in cardiac surgery found antihypertensive efficacy superior to nifedipine and equivalent to SNP. Fenoldopam was more often successful (76%) than intravenous nifedipine (30%) in controlling early hypertension after coronary artery bypass graft (CABG) surgery. In both groups, systemic and pulmonary vascular resistances decreased and cardiac index increased, along with mild increases in intrapulmonary shunt. In another CABG trial, fenoldopam and SNP lowered BP similarly but only fenoldopam significantly increased cardiac index, whereas only SNP significantly decreased pulmonary artery pressures and increased intrapulmonary shunt. On balance, these cardiac surgery studies suggest that fenoldopam has some pulmonary vasodilator effect but seems less likely than SNP to aggravate shunt in patients with hypoxemia due to pulmonary edema or other intrapulmonary processes. More importantly, these data suggest that fenoldopam should be useful for afterload reduction in patients with left ventricular (LV) systolic dysfunction, even absent severe systemic hypertension, and especially in the setting of renal insufficiency. Indeed, in a crossover trial comparing the hemodynamic effects of fenoldopam to those of SNP in patients with congestive heart failure (CHF) and severe LV dysfunction, there was a greater reduction in mean arterial pressure with SNP but the cardiac index increased similarly with each agent, principally through afterload reduction and increased stroke volume. As in the cardiac surgery studies discussed above, both agents decreased pulmonary vascular resistance but only SNP decreased right and left atrial pressures (presumably by increased capacitance due to venodilation). Several other noncomparative studies of fenoldopam in CHF reveal systemic and pulmonary vasodilation with increased cardiac index, without evaluation of intra-

pulmonary shunt. Taken together, these data suggest fenoldopam's utility in cardiac surgery, other severely hypertensive perioperative patients, and possibly for acute CHF therapy.

In 2 studies of normotensive human subjects, fenoldopam (0.025 to 0.5 $\mu\text{g}/\text{kg}/\text{min}$) dose-dependently increased renal blood flow (RBF). The greatest effect occurred from 0.025 to 0.1 $\mu\text{g}/\text{kg}/\text{min}$; increased RBF was associated with increased urine flow without changes in BP or heart rate. Unlike DA, which causes renal vasoconstriction at higher doses due to α_1 -adrenergic effects, higher doses of fenoldopam produced even greater renal vasodilation, increasing RBF by 75% at 0.3 $\mu\text{g}/\text{kg}/\text{min}$. Glomerular filtration rate (GFR) was unchanged and filtration fraction, therefore, reduced. Higher fenoldopam doses (0.1 to 0.5 $\mu\text{g}/\text{kg}/\text{min}$), which significantly reduce BP in hypertensive patients, caused mild sinus tachycardia, minimally decreased diastolic BP, and did not affect systolic BP in these normotensive subjects. Fenoldopam's minimal hypotensive effect in normal subjects might, in part, be explained by a limited role of small vessel vasoconstriction in BP control compared to that in hypertensive patients and also by the absence of the DA receptor coupling defect which has been described in several models of hypertension and patient populations. Fenoldopam was additionally shown to reverse PEEP-induced decrements in GFR in mechanically-ventilated ICU patients, cyclosporine-induced renal vasoconstriction in renal transplant recipients, and radiocontrast-induced vasoconstriction in rats. Although the rationale of reversing renal vasoconstriction to prevent or treat ischemic acute renal failure appears compelling, the available data are insufficient to currently support use of fenoldopam for this indication, except perhaps in the setting of severe hypertension or CHF.

In summary, fenoldopam causes peripheral vasodilation via stimulation of D_1 receptors, effectively lowering BP in hypertensive crises and perioperative hypertension. Fenoldopam has PK and PD profiles compatible with easy titratability, benign adverse effect and drug-drug interaction profiles, and no active or toxic metabolites. Compared to other vasodilators, the systemic vasodilation mediated by fenoldopam disproportionately involves the renal circulation. In addition, fenoldopam has a direct renal tubular natriuretic effect, unique among parenteral antihypertensive agents. Fenoldopam is the first parenteral antihypertensive vasodilator to offer a truly titratable alternative to SNP for hypertensive crisis management. Afterload reduction in patients with acute CHF due to LV systolic dysfunction and use as a selective renal vasodilator in patients with renal insufficiency and increased renovascular resistance are among the other potential uses of this drug.

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