Pathophysiology of Radiocontrast Nephropathy and Use of Fenoldopam for Its Prevention

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There are no proven therapeutic agents for the prevention or treatment of acute renal failure. Radiocontrast agents induce intense vasoconstriction in the renal medulla, which is hypoxic even in normal physiologic states, thereby aggravating the imbalance of medullary oxygen supply and demand. Fenoldopam specifically increases blood flow to the renal medulla through selective agonism of dopamine-1 receptors and has been found to prevent radiocontrast nephropathy in several investigations, including one randomized, double-blind, placebo-controlled trial.
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Acute renal failure is a common in-hospital clinical problem seen typically in perioperative or critically ill patients and in patients who have received substances known to cause renal vasoconstriction, including intravenous radiocontrast media, amphotericin B, or cyclosporine.[1] No proven therapeutic agents exist for the prevention or treatment of acute renal failure. Studies from several laboratories have demonstrated that prevention of renal ischemic injury depends on increasing mean renal blood flow generally and favorably impacting the supply and demand for energy, particularly to the nephron segments that are most susceptible to ischemic injury. Because of its low oxygen tension even under normal circumstances and its high oxygen demand, the medullary thick ascending limb is at greater risk from ischemic damage.[2] Similarly, because of high metabolic activity from ionic transport, the proximal convoluted tubule is likewise highly susceptible to reductions in oxygen supply.[3] It is known that radiocontrast agents specifically induce intense vasoconstriction in the renal medulla (see Figures 1 and 2).[4,5]

Pharmacology of Dopaminergic Agonists

Although "low-dose" dopamine (DA_1) has been extensively studied, there is no clear experimental or clinical evidence to support its use either to prevent or to treat acute renal failure.[6,7] Low-dose dopamine's lack of consistent effect may be attributable in part to its simultaneous interaction with renal DA_2[8] and α_1 receptors (Table 1).[9-13] Stimulation of these receptors decreases renal blood flow, glomerular filtration rate, and sodium excretion,[14] effects which are opposite to and which may offset those of DA_1 agonism (Table 2).[15] Dopamine's multiple receptor specificities and the lack of true separation of receptor activation by dose make it difficult to predictably activate only the DA_1 receptors.

DA_1 receptor agonism causes smooth muscle relaxation and has been found to reverse the vasoconstrictive effects of both endothelin and angiotensin II.[16] The observed vasodilation has been hypothesized to result both from a reduction in vascular smooth muscle cytosolic calcium and from an increase in cyclic adenosine monophosphate levels.[17]

Fenoldopam mesylate (*Corlopam*®) is the first commercially available selective DA_1 receptor agonist. Fenoldopam is a unique vasodilator that reduces systemic vascular resistance and lowers blood pressure in hypertensive subjects (doses of 0.1 µg/kg/min or higher), but one which can increase renal blood flow (at doses from 0.01 µg/kg/min) even during blood pressure lowering. In normotensive patients, renal blood flow increases within 30 minutes with little or no effects on systemic hemodynamics.[17-19] Unlike dopamine, which causes renal vasoconstriction at higher doses, higher doses of fenoldopam produce even greater renal vasodilatory effects (with a plateau effect occurring at doses of approximately 0.5 µg/kg/min).[19] These findings suggest that the dose-response curve for fenoldopam with respect to the renal vasculature is shifted to the left compared to that of the curve for the peripheral vasculature. The onset of renal vasodilation at lower doses than those required for systemic blood pressure reduction and the minimal effect of fenoldopam on the systemic blood pressure in normotensive subjects, even at higher doses, both suggest that the drug can be used in nonhypertensive patients without inducing substantive systemic hemodynamic alterations. Renal blood flow effects of fenoldopam appear to be independent of volume status.[17] Unlike other renal vasodilators ("low-dose" dopamine, atrial natriuretic peptide), which only increase perfusion to the renal cortex, fenoldopam increases both renal cortical and medullary blood flow.[20,21]

Fenoldopam is titratable (half-life of 5 minutes), requires no special monitoring, has no known metabolic drug-drug interactions, no contraindications, and requires no dose adjustment in end-stage hepatic or renal failure.[16] It is indicated for treatment of hypertension when rapidly reversible, titratable blood pressure control is desired in patients with and without acute end-organ damage. Like dopamine, it increases intraocular pressure and should be used with caution in patients with glaucoma. Side effects, which occur in a small minority of people, are associated with its vasodilatory phar-

Table 1
Adrenergic Agonist Activities of Fenoldopam and Dopamine[39]

Adrenergic receptor	Physiologic effect(s) of agonism	Dopamine	Fenoldopam
DA_1	Vasodilation	+ + +	+ + +
DA_2	Vasodilation, emesis, prolactin inhibition	+ + +	–
α_1	Vasoconstriction	+ +	–
β_1	Inotropy, choronotropy	+ + +	–
β_2	Vasodilation	+	–

+++, major action; ++, moderate action; +, mild action; –, no action

macology. The most common side effects are headache, nausea, cutaneous flushing, and hypotension. Notably, unlike dopamine, fenoldopam is not arrhythmogenic, presumably because of the lack of interaction with β_1-adrenergic receptors.[16]

Use of Fenoldopam for Renal Protection

Prior investigations suggest that fenoldopam increases blood flow to the medulla and cortex equally[21] and reduces ionic transport (i.e., sodium reabsorbtion) directly in the proximal tubule and the cortical collecting duct.[22] These findings suggest that fenoldopam may have utility as an agent to protect against ischemic acute renal failure. The renoprotective effects of fenoldopam have previously been described in settings of severe hypertension,[23,24] cyclosporine usage in renal transplant patients,[25] in cardiac surgery,[26] in sepsis,[27] and in vascular surgery.[28]

Fenoldopam fully attenuates the reduction in renal blood flow and glomerular filtration rate in dogs receiving radiocontrast.[29] Fenoldopam also appears to prevent the development of radiocontrast nephropathy in humans.[30-36] A recent multicenter, randomized, double-blind trial[30] compared the renal effects of "best of standard care"—one half normal saline and low ionic, low or iso-osmolar contrast—to the best of standard care plus fenoldopam 0.1 µg/kg/min starting at 60 to 90 minutes prior to radiocontrast injection and through

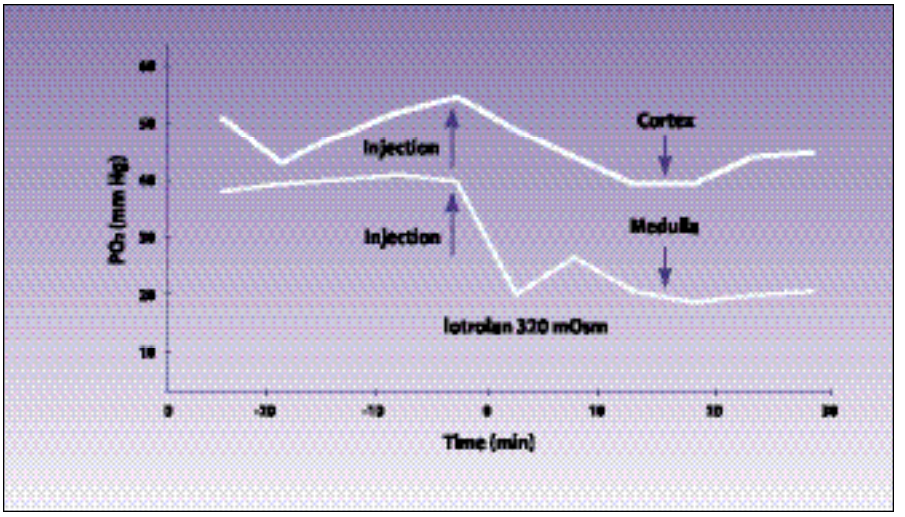

Figure 1. *Preferential reduction by radiocontrast dye of oxygen saturation in the outer medulla. Adapted from Liss et al,[3] with permission from Blackwell Science, Inc.*

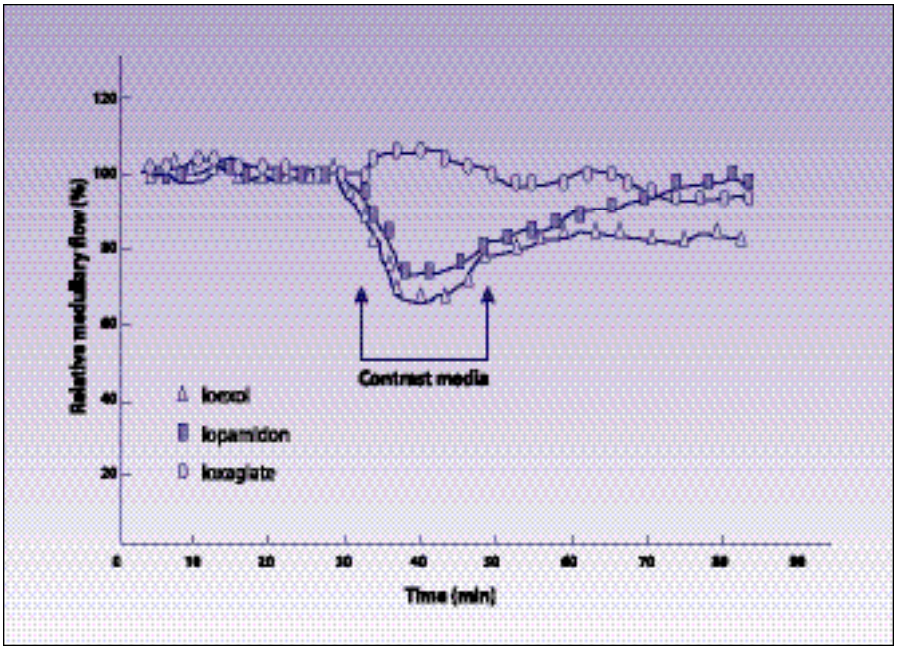

Figure 2. *Medullary blood flow in a rat model following infusion of contrast medium. Those receiving ioxaglate had a moderate increase; those receiving iohexol or iopamidol had a moderate decrease. Adapted from Nygren.[4]*

Main Points

- The incidence of radiocontrast nephropathy remains > 25% in patients with baseline renal insufficiency (serum creatinine > 1.6 mg/dL), despite the "best of standard care"--volume repletion and use of low ionic contrast media.
- Radiocontrast nephropathy is associated with 5.5-fold excess in mortality, even after adjustments for comorbid conditions.
- Fenoldopam is a highly specific agonist of dopamine -1 receptors that appears to prevent radiocontrast nephropathy in high-risk patients.

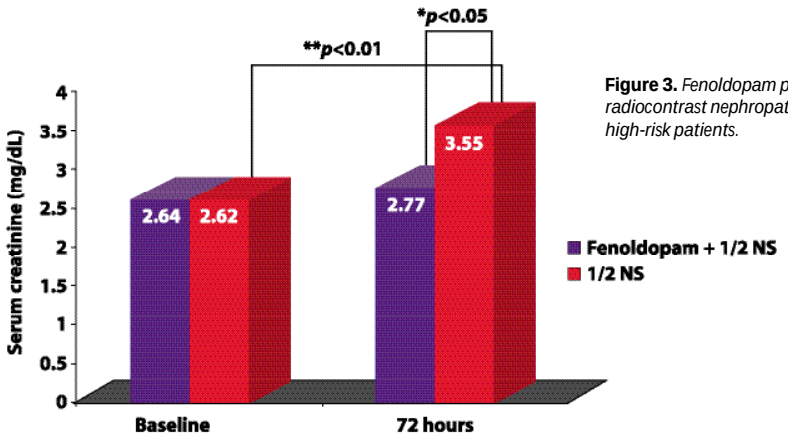

Figure 3. *Fenoldopam prevents radiocontrast nephropathy in high-risk patients.*

4 hours following injection. The patient population consisted of 45 randomized patients with baseline serum creatinine between 2 and 5 mg/dL who were undergoing angiography with or without angioplasty. Groups were balanced with respect to presence of diabetes, volume of contrast, demographics, and baseline serum creatinine. Renal vasoconstriction [para-amino-hippurate clearance (PAH)] at 1 hour post-contrast was predictive of the development of radiocontrast nephropathy. Fenoldopam fully attenuated this early vasoconstriction (PAH clearance at 1 hour relative to baseline +15.8% vs –33.2% in the fenoldopam and "best of standard care" arms). At 72 hours, serum creatinine had increased significantly in the best of standard care arm (2.6 to 3.6 mg/dL, $P < .01$) but not in the fenoldopam arm (Figure 3). The peak serum creatinine at this time was significantly higher in the best of standard care arm (3.6 ± 1.0 mg/dL) compared to the fenoldopam arm (2.8 ± 0.35; $P < .05$; see Figure 3). Incidence of radiocontrast nephropathy, prospectively defined as an increase in serum creatinine by 0.5 mg/dL at 48 hours following radiocontrast injection, was reduced by 50% in the fenoldopam arm (41% vs 21%, $P = .15$). Fenoldopam was well tolerated.

Table 2
Activation and Renal Physiology of Dopaminergic Recrptors

Agonist	DA_1	DA_2
	Fenoldopam	**Bromocriptine**
Renal effects	↑ Renal blood flow	↓ Renal blood flow
	↑ Glomerular filtration rate	↓ Glomerular filtration rate
	↑ Natriuresis	↓ Natriuresis
	↑ Diuresis	↓ Diuresis
	Inhibits sodium/ potassium exchange	Stimulates sodium/ potassium exchange

DA, dopamine agonist.
Adapted from Garwood S, Hines R. *Semin Anesthesia*.[15]

Conclusions

Ischemic acute renal failure has been a vexing problem for clinicians and the source of much morbidity and excess mortality among hospitalized patients.[37,38] Increasing evidence supports the use of fenoldopam for prevention of renal injury from substances that induce renal vasoconstriction, such as radiocontrast, and procedures that cause reduction or interruption of renal blood flow.

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