# The Role of the $DA_1$ Receptor Agonist Fenoldopam in the Management of Critically Ill, Transplant, and Hypertensive Patients

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*Fenoldopam, a selective agonist of dopamine-1 receptors, is a regional and systemic vasodilator. In randomized, controlled clinical trials, fenoldopam has been found to preserve renal function in situations of potential renal ischemia, such as during radiocontrast administration, cardiac and peripheral vascular surgery, liver transplantation, and treatment of severe hypertension. Fenoldopam lowers blood pressure in patients with hypertension, but has little or no effect on blood pressure in those who are normotensive. The role of fenoldopam in managing critically ill, transplant, and hypertensive patients is reviewed in this article.*

[Rev Cardiovasc Med. *2003;4(suppl 1):S35–S40*]



**Key words:** Fenoldopam • Acute renal failure • Positive end-expiratory pressure • Hypertension • Liver transplantation

## The Role of Fenoldopam in the Hypertensive Population

Numerous clinical trials have demonstrated the antihypertensive effects of intravenous fenoldopam in treating urgent and emergent hypertension.[1-3] The mechanism that induces fenoldopam's antihypertensive effect is systemic vasodilation, which is mediated by a selective agonist effect on dopamine-1 ($DA_1$) receptors in the arterial circulation. Fenoldopam has a short half-life (5 minutes) and is indicated for treatment of hypertension when rapid, titratable, but quickly reversible antihypertensive effects are desired.[4]

Table 1
Effects of Fenoldopam and Nitroprusside on Renal Function and Urinary Parameters in Hypertensive Patients

| Treatment group | Creatinine clearance (mL/min) | | Urine flow (mL/hour) | | Sodium excretion (μEq/min) | | Potassium excretion (μEq/min) | |
|---|---|---|---|---|---|---|---|---|
| | Before infusion (mean ± SEM) | During infusion (mean ± SEM) | Before infusion (mean ± SEM) | During infusion (mean ± SEM) | Before infusion (mean ± SEM) | During infusion (mean ± SEM) | Before infusion (mean ± SEM) | During infusion (mean ± SEM) |
| **Patients with hypertension and renal insufficiency** | | | | | | | | |
| Fenoldopam (n = 9) | 39 ± 7 | 75 ± 16 | 119 ± 37 | 275 ± 84 | 75 ± 22 | 227 ± 60 | 25 ± 5 | 68 ± 20 |
| | $P < .05$ | | $P < .01$ | | $P < .01$ | | $P < .05$ | |
| Nitroprusside (n = 10) | 38 ± 7 | 44 ± 9 | 110 ± 37 | 99 ± 36 | 86 ± 28 | 83 ± 47 | 24 ± 4 | 27 ± 8 |
| | $P$ = NS | | $P$ = NS | | $P$ = NS | | $P$ = NS | |
| **Patients with hypertension and normal renal function** | | | | | | | | |
| Fenoldopam (n = 11) | 97 ± 6 | 118 ± 8 | 126 ± 28 | 281 ± 72 | 246 ± 85 | 367 ± 102 | 42 ± 6 | 51 ± 7 |
| | $P < .05$ | | $P < .01$ | | $P < .01$ | | $P$ = NS | |
| Nitroprusside (n = 11) | 120 ± 11 | 97 ± 12 | 196 ± 42 | 167 ± 35 | 224 ± 57 | 212 ± 53 | 56 ± 12 | 49 ± 11 |
| | $P < .01$ | | $P$ = NS | | $P$ = NS | | $P$ = NS | |

SEM, standard error of the mean; NS, not significant.
Data adapted, with permission, from Shusterman et al.[2]

The onset of fenoldopam's antihypertensive effect takes place within 5 minutes, and the full effects occur within 20 to 25 minutes after the continuous infusion is initiated, or following a dose uptitration. The offset of the effect, following discontinuation of the infusion, begins within 5 minutes and is complete within 20 to 25 minutes.[5] The starting dose for the treatment of hypertension is 0.1 μg/kg/min, given as a continuous intravenous infusion, and titration can be performed every 15–20 minutes as needed, until the goal pressure is reached.[4] There is no rebound hypertension following cessation of the infusion.[5] No maximally tolerated dose of fenoldopam has been identified. In clinical trials, the maximum dose studied has been 1.6 μg/kg/min and there have been reports of uses of doses up to 2.5 μg/kg/min.[6]

In a randomized, controlled trial comparing nitroprusside with fenoldopam,[2] despite similar blood-pressure reductions, fenoldopam, but not nitroprusside, significantly increased creatinine clearance, urine flow rate, and sodium excretion rate in patients with and without baseline renal insufficiency (Table 1). Fenoldopam reduced blood pressure 214 ± 8/139 ± 6 mm Hg to 176 ± 8/107 ± 3 mm Hg ($P < .001$ for systolic and diastolic comparisons). Comparable values for nitroprusside were 226 ± 4/145 ± 5 mm Hg to 171 ± 6/108 ± 2 mm Hg ($P < .001$ for systolic and diastolic comparisons).

*The Role of Fenoldopam in Hypertensive Emergencies*

The safety and efficacy of

fenoldopam in patients with hypertensive emergency ("malignant hypertension")—defined as a diastolic blood pressure over 120 mm Hg and objective evidence of acute end-organ dysfunction resulting from hypertension (eg, acute renal failure, transient ischemic attack, myocardial ischemia, acute congestive heart failure, and acute retinal hemorrhages)—was evaluated in a dose-ranging, randomized trial of 94 patients.[1] In this trial, fenoldopam rapidly lowered blood pressure in a dose-dependent fashion, and clinical stabilization of deteriorating end-organ function was noted. For example, after 48 hours of follow-up, there were no deaths, no completed myocardial infarctions or strokes, and no patient required dialysis. Short half-life, rapid titratability, and the ability to improve or stabilize renal function render fenoldopam ideal for use in both the emergency department and intensive care unit.

*An agent that has a short half-life, an ability to be rapidly up-titrated during the hypertensive emergency and down-titrated as the clinical status stabilizes, and enhances renal function is ideal for use in both the emergency department and intensive care unit.*

### *The Role of Fenoldopam in Postoperative Hypertension*

The use of fenoldopam for the management of postoperative hypertension following cardiac surgery and general surgery has been evaluated in several randomized, controlled trials.[7,8] Fenoldopam effectively lowered blood pressure, in a manner similar to nitroprusside, increased cardiac index, and lowered pulmonary pressures in cardiac surgical patients.[7,8] Unlike nitroprusside, however, no significant intrapulmonary shunting was observed.[8] Preload reductions were less remarkable in these patients presumably because of fenoldopam's lack of venodilatory effects. Compared to nitroprusside, fenoldopam has the practical advantages of being light-stable, not producing toxic metabolites, and not requiring continuous blood-pressure monitoring with an arterial line.[4,9] Published case reports have described successful use of fenoldopam to treat hypertension caused by pheochromocytoma[10] and hypertension in children.[11]

Significant reflex tachycardia can be observed in hypertensive patients treated with fenoldopam at doses ≥ 0.3 μg/kg/min. However, slow up-titration can minimize the tachycardic effects. Despite fenoldopam's potential for tachycardia, no increase was seen in double-product (systolic blood pressure times heart rate), a measure of myocardial oxygen demand.[9] A partial loss of effect (tachyphylaxis) occurs by 48 hours continuous administration of fenoldopam at antihypertensive doses, and this effect can presumably be overcome by dose up-titration.

*Fenoldopam effectively lowered blood pressure, in a manner similar to nitroprusside, increased cardiac index, and lowered pulmonary pressures in cardiac surgical patients.*

## The Role of Fenoldopam in the Critically Ill Population

The intensive care unit population may be hypertensive, normotensive, or hypotensive, and the risk of renal dysfunction resulting from the use of nephrotoxic and vasoconstrictive drugs and radiocontrast media, shock states, prerenal conditions, and recent surgery is significant. Because fenoldopam increases renal blood flow without significantly altering systemic blood pressure in those without hypertension,[12] it can be considered for use in normotensive patients. Doses that increase renal blood flow begin as low as 0.01 μg/kg/min[13]; therefore, dose-titration in patients with unstable hemodynamics can begin at doses ten-fold lower than doses that result in significant systemic vasodilation (0.1 μg/kg/min and higher) in hypertensives. *In vitro* studies have demonstrated the ability of fenoldopam to fully reverse norepinephrine-induced renal vasoconstriction.[14] A human study confirmed the ability of fenoldopam to reverse systemic vasoconstriction from angiotensin II and norepinephrine.[15]

### *Effect of Fenoldopam in Patients Receiving Positive End-Expiratory Pressure*

In a study of 33 intubated patients with respiratory failure having renal dysfunction from positive end-expiratory pressure (PEEP), with or without vasopressors,[16,17] fenoldopam was titrated to a mean dose of 0.2 μg/kg/min. In this population, fenoldopam did not reduce mean arterial pressure by > 8%, but did increase creatinine clearance, renal plasma flow, sodium excretion rate, and urine volume from baseline (Figure 1). Fenoldopam also attenuated renal dysfunction in amphotericin-treated dogs[18] and reversed

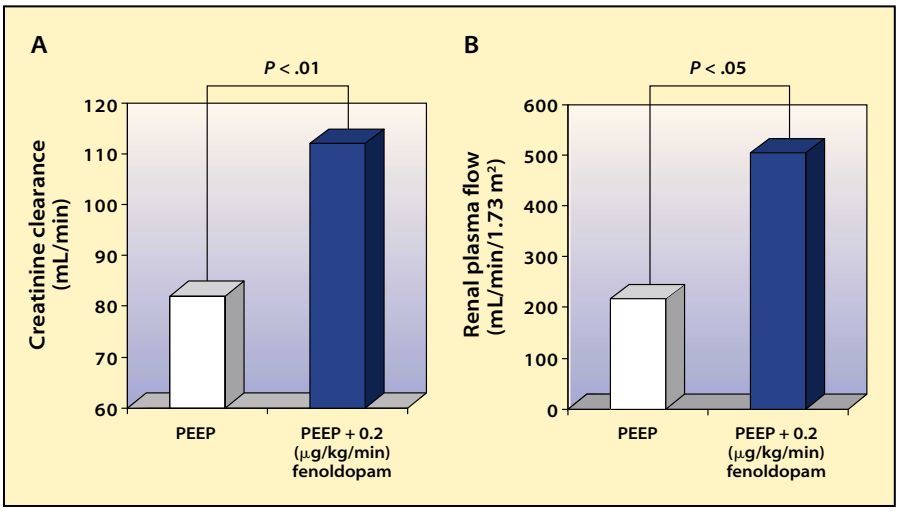


**Figure 1.** *The renal hemodynamic and functional effects of fenoldopam in patients treated with positive end-expiratory pressure (PEEP). Fenoldopam titrated up to 0.2 μg/kg/min in a population of patients with respiratory failure and renal dysfunction on PEEP significantly increased (A) creatinine clearance and (B) renal plasma flow. Adapted from Schuster et al[16] and Poinsot et al.[17]*

cyclosporine-mediated renal vasoconstriction in renal transplant patients.[19] The renal effects of fenoldopam are currently being evaluated in a study of patients with systemic inflammatory response syndrome (SIRS).

*Effect of Fenoldopam in Patients with Acute Tubular Necrosis*

Fenoldopam was studied in a retrospective series of 100 patients with established acute tubular necrosis (ATN) in the medical and surgical intensive care unit for 48 hours to 7 days. A dose-dependent reversal of serum creatinine was observed, and only 16 out of 100 patients required dialysis.[20,21] A randomized, double-blind, placebo-controlled trial of 300 patients with established ATN of any etiology in the intensive care unit is currently ongoing.

*Effect of Fenoldopam on Gut Perfusion*

Fenoldopam also increases perfusion to the intestinal mucosal lining in a dose-dependent manner in animal models. In a dog hemorrhage model in which splanchnic hemorrhage was induced, fenoldopam restored portal vein blood flow to near baseline, maintained the splanchnic fraction of cardiac output, attenuated the rise in gut mucosal $PCO_2$, and redistributed blood flow away from the serosal layer in favor of the mucosa during basal conditions and after hemorrhage.[22] This physiologic effect may have clinical implications in the shock patient if it results in preserving the integrity of gut mucosa, such that translocation of intestinal flora into the circulation does not occur. Pilot studies in patients with SIRS and those undergoing coronary artery bypass graft (CABG) surgery are currently underway to evaluate the effects of fenoldopam on gut perfusion in these populations.

*Fenoldopam has a number of physiologic and clinical effects relevant to the transplant population.*

## The Role of Fenoldopam in the Transplant Population

Fenoldopam has a number of physiologic and clinical effects relevant to the transplant population: 1) antihypertensive effects associated with improved renal function[2]; 2) lack of significant blood-pressure effects in normotensives[12]; 3) attenuation of radiocontrast-mediated nephrotoxicity[23]; 4) increased urine volume and sodium excretion[2,19]; 5) reversal of cyclosporine-mediated renal vasoconstriction, without affecting cyclosporine blood levels[19]; and 6) afterload reduction and secondary increases in cardiac output.[7] In addition, animal data suggesting improved splanchnic perfusion, particularly to gut mucosa,[22] and the ability of fenoldopam to attenuate amphotericin-mediated nephrotoxicity[18] may prove to be of clinical relevance in this population as well.

Two randomized, controlled trials of patients undergoing orthotopic liver transplantation compared fenoldopam (0.03–0.15 μg/kg/min titrated to blood pressure for 24 hours) to placebo (n = 19),[24] and fenoldopam (0.1 μg/kg/min for 48 hours, following induction of anesthesia) to low-dose dopamine (2.0 μg/kg/min) (n = 42). Fenoldopam significantly increased urine volumes and required a lesser need for furosemide and mannitol than low-dose dopamine did. From a similar baseline creatinine, postoperative serum creatinine in the fenoldopam group was 1.2 mg/dL compared to 1.6 mg/dL in the dopamine group.[25] Further, the use of fenoldopam was associated with significant increases in creatinine clearance compared to placebo, postoperatively (Figure 2).[24]

## Conclusion

Fenoldopam is a novel, short-acting,

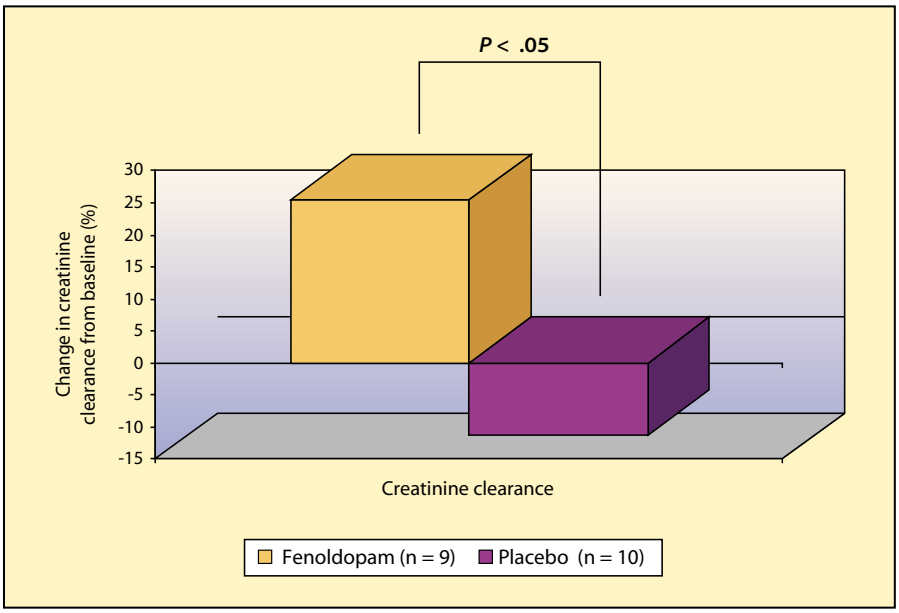


**Figure 2.** *Effects of fenoldopam on renal function following orthotopic liver transplantation, postoperative day 1. Treatment with 0.03–0.15μg/kg/min of fenoldopam titrated to blood pressure for 24 hours was associated with significantly greater improvement in creatinine clearance on postoperative day 1 compared to placebo. Adapted from Ramsay et al.*[24]

systemic and renal vasodilator that can improve renal function in a variety of situations including during treatment of hypertension and during positive end-expiratory pressure treatment, and following liver transplantation. ■

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## Main Points

- Fenoldopam is a titratable, antihypertensive agent with rapid onset and offset of hemodynamic effect, and it improves renal function, renal perfusion, and diuresis during blood-pressure lowering.
- In patients without hypertension, blood-pressure lowering with fenoldopam is minimal.
- Fenoldopam significantly increases creatinine clearance and renal blood flow in critically ill patients on positive end-expiratory pressure.
- Fenoldopam reverses some of the renal vasoconstriction from cyclosporine and is associated with improvements in creatinine clearance and increased urine output during and following orthotopic liver transplantation.

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