

The Dangers of Immediate-Release Nifedipine for Hypertensive Crises

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Educational Objectives

- Recognize the difference between hypertensive emergency and urgency
- Understand the pharmacology of IR nifedipine
- Explain the etiology of adverse events related to IR nifedipine

Abstract

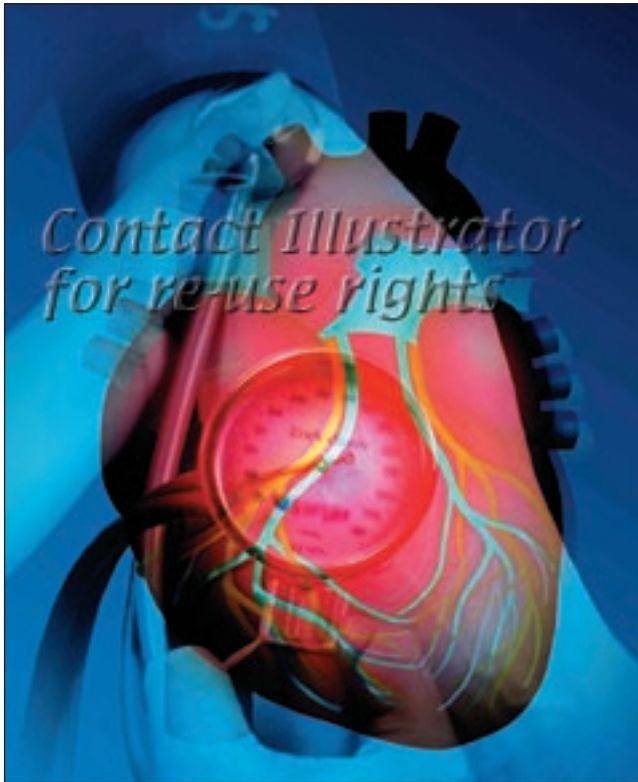
Hypertensive crises, without prompt treatment, are associated with high morbidity and mortality. Although effective management of chronic hypertension has reduced the incidence of hypertensive crises to less than 1%, the problem is still significant enough to warrant concern. In the past, immediate-release (IR) nifedipine was the treatment of choice for hypertensive crises because it produced an antihypertensive effect within 15 minutes and was easy to administer. However, the medical literature contains numerous reports and editorials emphasizing various problems associated with IR nifedipine. These problems include: hypotension, myocardial ischemia or infarction, prolonged QT interval, ventricular fibrillation, and cerebral ischemia. Despite the reported adverse events, the use of IR nifedipine remains widespread. Because of these potential problems, nifedipine should be avoided in patients presenting with hypertensive crises.



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Hypertensive crises, without prompt treatment, are often associated with morbidity and mortality. Although effective management of chronic hypertension has reduced the incidence of hypertensive crises to less than 1% in all Americans with hypertension, the problem still warrants concern.¹ The acute treatment of hypertensive crises with immediate-release (IR) nifedipine remains a controversial subject. In the past, nifedipine (sublingual or oral) was the treatment of choice for hypertensive crises because it produced an antihypertensive effect within 15 minutes, and it was easy to administer. However, The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC-VI], states that the use of immediate-release sublingual nifedipine is “unacceptable.”² Many reports and editorials have emphasized the various problems associated with IR nifedipine use, including: hypotension, myocardial ischemia or infarction, prolonged QT interval, ventricular fibrillation, and cerebral ischemia.³⁻⁵ Furthermore, in 1985, the Food and Drug Administration (FDA) concluded that the use of IR nifedipine for hypertensive emergencies is neither safe nor effective and therefore it should not be used.⁶ Despite these recommendations, the use of IR nifedipine for hypertensive emergencies remains prevalent in the U.S. and abroad.⁷⁻⁹

Traditionally, hypertensive crises have been classified as emergencies or urgencies. Whereas emergencies require blood pressure (BP) reduction within hours, urgencies can be treated with oral medications to reduce BP within a day. The BP value itself is not used to distinguish between an emergency and an urgency. The presence or absence of target organ damage, such as hypertensive encephalopathy, acute left ventricular failure, pheochromocytoma crisis, eclampsia, acute aortic dissection, intracerebral bleeding, acute brain infarcts, myocardial infarction (MI), unstable angina, and acute renal failure determines the agent, route, and duration of therapy.^{2,10} The optimal drug used to treat hypertensive emergency would have a rapid onset, a short half-life, an intravenous (IV) formulation, and the ability to be easily titrated. Parenteral drugs recommended for hypertensive emergency include nitroprusside, nitroglycerin, labetalol, and nicardipine (Table 1).^{2,10,11} The oral drugs



most commonly used for hypertensive urgency include clonidine, captopril, and labetalol (Table 2).^{2,10}

Why Nifedipine is Used for Hypertensive Emergencies

The goal of therapy with hypertensive emergency is to reduce BP by a maximum of 25% within minutes to two hours, then to bring it below 160/100 mmHg within two to six hours.² Excessive, abrupt decreases in BP should be avoided because they might precipitate cerebral, renal, or coronary ischemia.² Ischemia manifests itself via three mechanisms: 1) sudden decreased perfusion pressure; 2) peripheral vasodilation, which produces a redistribution of blood away from certain vascular beds ("steal phenomenon"); and 3) reflex sympathetic nervous system activation and catecholamine release secondary to a negative inotropic effect.⁶

In the past, nifedipine was among the most widely used of the oral agents, because it decreases blood pressure within 15 minutes. Nifedipine is a dihydropyridine calcium channel antagonist that dilates the vascular bed and reduces peripheral vascular resistance, thus reducing the arterial blood pressure. It is available as immediate-release liquid-filled capsules and in various slow-release formulations. The usual dose of nifedipine for hypertensive crises was 10 mg orally (PO) or sublingually (SL), repeated after 30 minutes.¹¹ The peak effect when given SL is generally observed at 20 to 30 minutes, with a duration of action of four to five hours.¹² It is worth mentioning that IR nifedipine is only FDA-approved for variant angina.⁷ The main adverse effects reported with nifedipine capsules are flushing, headache, and tachycardia. Although prospective controlled studies have not

been performed, numerous case reports have documented more severe adverse events, including cardiac and cerebral ischemia.⁶

Medline Case Reports

A Medline search revealed numerous case reports of problems associated with immediate-release nifedipine. Watcher et al.³ reported three cases of symptomatic hypotension in which patients developed tachycardia, dizziness, nausea, and substernal discomfort after multiple doses of IR nifedipine. In addition, all three patients developed new T-wave inversions within 15 to 90 minutes of nifedipine administration. None of the patients had any significant past medical history of cardiac disease, nor did they have predisposing factors for developing hypotension (e.g. hypovolemia, beta-blocker use, alpha-blocker use, etc.). The authors concluded that IR nifedipine increases the risk of symptomatic hypotension. They also noted that multiple doses administered less than one hour apart should be used with extreme caution in malignant hypertension, and in fact should be avoided in hypertensive urgency.³

Immediate-release nifedipine, when used for hypertensive urgencies, has also been associated with myocardial ischemia or infarction.⁴ O'Mailia et al.⁴ reported three cases of patients with a history of hypertension, but no other cardiac disease, who developed severe, sudden hypotension following the administration of 10-mg IR nifedipine. Two of these patients had evidence of acute anterior myocardial infarcts based on elevations of cardiac enzymes and echocardiographic (EKG) changes. The other patient developed ST segment elevation, which normalized after the restoration of BP. The authors advised that patients with a history of coronary artery disease or left ventricular hypertrophy (LVH) should be monitored carefully or given another agent.⁴ The study by Ishibashi et al.¹³ confirms the observations seen by O'Mailia et al.⁴; it showed that 5 mg of IR nifedipine given SL to 93 hypertensive patients without coronary artery disease, ages 65 years and older, lowered blood pressure significantly while increasing heart rate. In six of 55 patients with LVH, EKG changes consistent with myocardial ischemia were observed. Based on these results, low-dose nifedipine might be sufficient to cause myocardial ischemia in some patients with LVH who are 65 years of age and older.¹³

Shettigar et al.¹⁴ outlined reports of two patients who died after IR nifedipine was administered for unstable angina. An MI was diagnosed at autopsy for both patients. The authors postulated that the fatal MIs might have been caused by decreased coronary blood flow secondary to decreased BP.¹⁴ Messerli et al.⁷ also described a case of a patient receiving chronic beta blockers who was treated with IR nifedipine in the physician's office for hypertensive urgency. This patient went into cardiac arrest and later died. The addition of nifedipine to chronic beta-blocker therapy might have contributed to his death.⁷ Nifedipine produces a negative inotropic effect that is normally counteracted by a reflexive increase in catecholamine release. Catecholamines are inhibited in patients taking beta blockers, thus making the patients more susceptible to precipitous drops in BP.⁷

Table 1 Parenteral Agents Used to Treat Hypertensive Emergency^{2,10,11}

Drug	Dose/ Route	Onset of Action	Duration of Action	Side Effects	Caution	Monitoring	Note
Nitroprusside	0.25– 8 mcg/ kg/min IV	Seconds	3–5 min	Cyanide and thiocyanate toxicity, hypotension	Pregnancy, increased intracranial pressure, renal failure	<ul style="list-style-type: none"> ■ Continuous intra-arterial BP ■ Cyanide toxicity (mental status change, coma metabolic status, lactic acidosis, seizures, smell of almonds) 	<ul style="list-style-type: none"> ■ Considered first-line ■ ↑ dose slowly by 0.25 mcg/kg/min; Max 10 mcg/kg/min; If BP control not achieved within 10 min of max rate, D/C drip ■ Cyanide toxicity usually seen at infusion >3 mcg/kg/min
Fenoldopam	0.1– 0.3 mcg/ kg/min ↑ dosage by 0.05–0.1 mcg/kg/min q15 min	< 5 min	30 min	Headache, flushing, dizziness, tachycardia	Glaucoma, intraocular hypertension	BP, serum electrolytes, (low K ⁺)	<ul style="list-style-type: none"> ■ Expensive
Labetolol	2 mg/min IV or 20– 80 mg q10 min up to max dose of 300 mg	≤ 5 min	3–6 hours pain,	Orthostatic hypotension, abdominal decompen- dizziness, nausea, vomiting, diarrhea	Asthma, bradycardia, heart block, sated CHF	Orthostasis, BP or following vascular	<ul style="list-style-type: none"> ■ Use in patients with underlying CAD, acute MI, angina, surgical procedures ■ Might be useful in patients with cerebrovascular disease ■ May use in patients with eclampsia
Hydralazine	10–20 mg IV 10–50 mg IM	10–30 min (IV) 20–40 min (IM)	2–6 hours	Angina, tachycardia, headache	Coronary ischemia, angina, MI, aortic dissection		<ul style="list-style-type: none"> ■ Use in patients with eclampsia ■ Rarely used to treat crises because of unpredictable response. Avoid use.
Nitroglycerin	5–100 mcg/min IV infusion	2–5 min	5–10 min after D/C infusion	Methemoglo- binemia, headache, tachycardia, nausea, vomiting, flushing, tolerance with prolonged use	Pericardial tamponade, pericarditis, increased intracranial pressure		<ul style="list-style-type: none"> ■ Preferred in patients with coronary ischemia, unstable angina, acute MI
Esmolol	250–500 mg/kg/min for 1 min then 50– 100 mg/ kg/min for 4 min; may repeat sequence	1–2 min	10–20 min	Thrombo- phlebitis, hypotension, nausea	Asthma, bradycardia, heart block, decompensated CHF	BP, heart rate	<ul style="list-style-type: none"> ■ May be used for perioperative HTN and aortic dissection ■ Expensive

BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure
D/C = discontinue; HTN = hypertension; ↑ = increase

Table 2 Oral agents used to treat hypertensive urgency^{2,10}

	Clonidine	Captopril	Labetalol
Dose	0.2 mg PO initial, 0.1 mg q1 hour Max = 0.8 mg	6.25–50 mg PO or SL	100–300 mg PO q2–3 hours or 200–400 mg PO q2–3 hours
Onset	0.5–2 hours	15 minutes	30 minutes–2 hours
Duration	6–8 hours	4–6 hours	4 hours
Side Effects	Sedation, dry mouth, dizziness	Rash, pruritus, proteinuria, loss of taste, hypotension	Orthostatic hypotension, nausea, vomiting
Caution	Altered mental status, severe carotid artery stenosis	RAS, hyperkalemia, dehydration, renal failure, pregnancy	CHF, asthma, bradycardia, heart block

CHF = congestive heart failure; PO = orally; q = every; RAS = renal artery stenosis; SL = sublingually.

Peters et al.⁵ reported one case of hypotension and prolonged QT interval following sublingual nifedipine treatment. One hour after nifedipine administration, the patient was found unconscious and in ventricular fibrillation. The authors felt that the patient experienced subendocardial ischemia, resulting in torsade de pointes and ventricular fibrillation.⁵ Based on this case, the authors stated that “there is no place for nifedipine in the treatment of hypertension emergencies.”⁵

Oral nifedipine has also been associated with cerebrovascular accidents, most likely secondary to a sudden lowering of blood pressure. Schwartz et al.¹⁵ reported a case of a 44-year-old man who presented with a BP of 270/140 and an unremarkable neurological exam. After 10 mg nifedipine SL, his BP decreased to 160/100; 15 minutes later, the patient developed left-sided hemiparesis. In another instance, the same patient presented with a BP of 200/120 and was given nifedipine SL. His BP dropped to 150/90 and two hours later, he was found to have right-sided hemiparesis. A head CT was consistent with an old, right-sided parietotemporal and a recent, left-sided parietal infarction. The authors felt that the cerebrovascular accidents were related to nifedipine-induced decreases in BP and the subsequent steal phenomenon.¹⁵

Conclusion

It is clear that the adverse events associated with IR nifedipine SL for hypertensive crises can be life-threatening. For patients with myocardial ischemia, infarction or cerebral artery disease, any drug that decreases arterial blood pressure and increases cardiac acceleration is contraindicated. The medical literature contains numerous references warning against its use.^{6,7} Although the oral route might be convenient, intravenous infusions of nitroprusside and similar drugs, which are easily titrated, are deemed preferable for patients presenting with hypertensive emergencies. IR nifedipine should be avoided in patients presenting with hypertensive crises, even though it might have accepted therapeutic value in other indications. ■

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Disclosure

Dr. Mansoor and Dr. von Hagel Keefer declared that they have no financial arrangements or affiliations with any corporate organization offering financial support or grant monies for this CME program or with any corporate organization whose product(s) will be discussed in their presentation. They have indicated that they will/may include discussion of investigation of off-label uses of products.



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