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REVIEW

Nitroglycerin Use in the Emergency Department: Current Perspectives

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Abstract: Nitroglycerin, a fast-acting vasodilator, is commonly used as a first-line agent for angina in the emergency department and to manage chest pain due to acute coronary syndromes. It is also a treatment option for other disease states such as acute heart failure, pulmonary edema, and aortic dissection. Nitroglycerin is converted to nitric oxide, a potent vasodilator, in the body, leading to venodilation at lower dosages and arteriodilation at higher dosages that results in both preload and afterload reduction, respectively. Although nitroglycerin has historically been administered as a sublingual tablet and/or spray, it is often given intravenously in the emergency department as this enables titration to effect with predictable pharmacokinetics. In this review article, we outline the indications, mechanism of action, contraindications, and adverse effects of nitroglycerin as well as review relevant literature and make general recommendations regarding the use of nitroglycerin in the emergency department.

Keywords: acute coronary syndrome, chest pain, heart failure, hypertensive emergency, nitrates, nitroglycerin, pulmonary edema

Introduction

Nitroglycerin (NTG), also known as glycerol trinitrate, is a vasodilator primarily used for anginal relief in patients presenting with chest pain and suspected acute myocardial infarction (AMI). The vasodilatory effects of NTG come from release of nitric oxide (NO) with venodilation at lower dosages and arteriodilation at higher dosages resulting in preload and afterload reduction, respectively. NO mediates this process by activating the enzyme guanylyl cyclase driving an increase in the nucleotide cyclic guanosine monophosphate (cGMP) which leads to dephosphorylation of myosin in smooth muscle. This promotes smooth muscle relaxation, resulting in reduction of preload and afterload.[1] This effect is especially pronounced in the coronary vasculature, in turn increasing cardiac perfusion, making it ideal for the treatment of angina from an acute coronary syndrome (ACS),[2,3] and hypertensive emergencies like acute heart failure (AHF),[4–6] pulmonary edema,[6,7] and aortic dissection.[8] NTG is rapidly absorbed via the skin, mucous membranes, and gastrointestinal tract, making it highly bioavailable with a half-life of 1 to 3 minutes. Thus, NTG can be easily administered orally, lingually (as a spray), sublingually (spray or tablet), or topically (as an ointment or transdermal patch) as well as intravenously.[9]

Use of Nitroglycerin in the Emergency Department

Acute Coronary Syndromes

Broadly, ACS includes ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) which is further sub-categorized as non-ST elevation-ACS and unstable angina. Although recent chest pain guidelines suggest that the relief of chest pain by NTG should not be used as a diagnostic factor (as other etiologies of chest pain such as esophageal spasm may be relieved by NTG),[10] the current treatment guidelines for ACS include percutaneous coronary intervention (PCI), thrombolytics, oxygen, aspirin, P2Y12 inhibitors, anticoagulation, and NTG.[11] As per the recent guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC), NTG is a first-line treatment for ACS.[12,13] Similarly, the 2020 European Society of Cardiology recommends (Class I,

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Level C) the use of sublingual or IV nitrates in patients with ongoing ischemic symptoms and IV nitrates in patients with uncontrolled hypertension or signs of heart failure.[3] The early use of nitrates (IV nitroprusside or nitroglycerin) has been shown to reduce all-cause mortality, particularly mortality within the first 10 days from onset of symptoms.[14,15] It is believed that dual reduction in preload and afterload,[1] particularly towards the coronary arteries, confers this benefit during ischemic events.[16] Although the evidence for oral NTG appears to be adopted from IV nitrate studies, the recommended doses of NTG include sublingual or spray (0.3 to 0.6 mg) every 5 minutes up to a maximum of 3 doses.[17] If pain is not controlled and there are no contraindications (see below), IV infusions can be initiated at 5 to 10 µg/min titrated upwards to control symptoms[18] up to a maximum of 400 µg/min while carefully monitoring blood pressure.

Acute Hypertensive Heart Failure and Pulmonary Edema

Mainstay pharmaceutical therapy for AHF consists of vasodilators and diuretics. Because NTG provides both preload and afterload reduction, it is beneficial in AHF, especially for those who present with markedly elevated blood pressure (BP) and/or signs of heart failure.[3,19] In such patients, higher dose nitrates have been associated with lower rates of mechanical ventilation and endotracheal intubation (ETI), improved BP, and reduced myocardial injury.[4,20] This approach has also been shown to shorten hospital length of stay and decrease intensive care unit (ICU) admissions.[4]

Despite its inclusion in clinical treatment for patients with acute hypertensive heart failure, there are only a few trials directly comparing NTG to other vasodilators. One review noted six studies (only three of which were prospective) involving NTG treatment in patients with AHF, acute CHF, or acute cardiogenic pulmonary edema.[21] The review noted that nitrovasodilators used to treat AHF do resolve short-term symptoms and are safe to administer. In a nonrandomized open-label trial involving patients with severe AHF, similar conclusions were reached.[22] Another systematic review identified only four primary studies (two of which included NTG) comparing the efficacy of IV nitrates to alternative therapies in AHF patients.[23] The limitations of the studies led the authors to conclude that IV nitrates do not confer clinically important benefits in the ED, but that current guidelines[24] for using nitrates in patients with AHF and associated dyspnea should be upheld.

Recent studies have found that the use of high-dose intravenous (IV) NTG (>2 mg IV boluses every 3 to 5 min) in this setting may provide significant advantages over traditional treatment dosages.[4,25] A recent case report used ultrahigh dose boluses (with doses up to 16 mg), which is markedly higher than the 1–2 mg NTG traditionally given, and was shown to successfully stabilize a patient with acute cardiogenic pulmonary edema and markedly elevated BP.[25]

Although NTG's vasodilatory effect and relatively short half-life make it an ideal treatment option for patients with AHF, elevated BP, and acute cardiogenic pulmonary edema,[6] the aggressive dosing presented above needs further investigation to see if its effect will remain safe and effective for a broader group of patients presenting with acute hypertensive heart failure. Regardless, in unstable patients with hypertensive AHF, nitroglycerin should be provided as soon as feasible[26] as either an NTG IV infusions targeting a dose of 200–400 µg/min or by repeated intravenous boluses of up to 2 mg administered every 3 to 5 minutes.[22] Although several studies have shown this dosing to be safe and associated with improved outcomes,[26] randomized trials (and generalizability) are still needed.

Aortic Dissection and Aneurysm

Aortic dissections, classified into Type A (which involves the ascending aorta) and Type B (which involves the descending aorta), are clinically treated by surgery and/or medical management. Typically, Type A ascending dissections require surgical treatment while Type B descending dissections are initially medically managed[8,27] but endovascular repair has become more commonplace,[28] particularly if there is evidence of rupture or malperfusion.[29] Optimized medical management of Type B aortic dissections usually centers around antihypertensive agents,[30,31] which alleviate the hemodynamic stress on the damaged aortic wall, but randomized controlled studies to discern treatment options are lacking.[8] In a Type B aortic dissection, a false lumen (the newly created passage for blood) forms. Blood flow into this false lumen may enlarge and block blood flow into the true lumen, and this painful extension of the dissection typically requires emergent blood pressure management.[8,30]

The two-pronged goal of the medical management of Type B aortic dissections is to first limit the propagation of this false lumen followed by stabilization of any hemodynamic stress on the aortic wall. Beta-blockers such as labetalol or esmolol should be given first (to reduce cardiac output, decrease left ventricular velocity, and prevent reflexive

tachycardia) followed by an anti-hypertensive like NTG or nitroprusside[32,33] or calcium-channel blockers such as nicardipine or clevidipine or diltiazem.[27,32,34,35] Since NTG is a vasodilator and can cause reflex tachycardia and increase the force of left ventricular (LV) ejection, it is important that NTG is administered after a beta-blocker and not be used alone. Although nitrates such as nitroprusside and NTG are an important part of this regiment, current evidence shows that beta-blockers, not NTG, reduce dissection-related events and inhibit aortic dilatation.[8]

Pre-Eclampsia and Eclampsia

Pregnancy-induced hypertension is known as pre-eclampsia, and if left untreated, can lead to life-threatening eclampsia. The ultimate treatment of both of these disease states is delivery of the baby and placenta but there is often a risk-benefit trade-off for the baby and mother.[36] Treatment may include induction of labor and/or treatment with anti-hypertensives[37] with hydralazine, labetalol, or nifedipine. However, when pre-eclampsia is complicated by severe features such as cardiogenic pulmonary edema, intravenous NTG can be a possible treatment option;[38–40] albeit not typically first-line therapy. Transdermal NTG has also been used in women with pre-eclampsia and placental insufficiency at high risk for early delivery and was associated with reduced vascular resistance in the uterine and umbilical arteries.[41] A recent Cochrane review also explored the use of NTG as a tocolytic to reduce uterine contraction for pre-term labor and found it to be no better than other currently utilized tocolytics but NTG did appear to have less adverse serious side effects.[42] Overall, the use of NTG in pregnancy and pregnancy-related disease states is not well studied and it is not currently first-line therapy.

Hypertensive Strokes, Encephalopathy, and Sympathetic Crises

Despite classical teaching that NTG is contraindicated in patients with increased intracranial pressure[43] and several trials demonstrating no clear benefit of NTG for hypertensive strokes,[44–47] there is emerging evidence that NTG (and other nitric oxide donors) may provide benefit to functional outcomes when given acutely for hypertensive hemorrhagic strokes[48,49] or hypertensive stroke mimics.[50] There is currently no strong evidence to suggest NTG is the preferred anti-hypertensive agent to treat hypertensive encephalopathy such as posterior reversible encephalopathy syndrome (PRES) and in fact may be associated with harm.[51] Similarly, there is no known role in the use of NTG for adrenal sympathetic crises with the exception of cocaine-induced, hypertensive myocardial vasospasm[52] which should be treated as ACS.

Less Emergent Uses

Less emergent uses of NTG in the emergency department include treatment of anal fissures,[53] dysmenorrhea,[54] esophageal food boluses,[55] and Raynaud's phenomenon[56] but their use is generally limited due to lack of appropriate clinical trials.

Contraindications

Although allergic reactions to NTG are extremely rare, reports do exist. Therefore, NTG is contraindicated in patients that are hypersensitive to NTG or in patients who have reported allergic symptoms to the medication.[1] NTG and other vasodilatory nitrates should not be given to patients who have taken a phosphodiesterase-5 (PDE-5) inhibitor like sildenafil or tadalafil within 24–48 hours, due to risk of severe hypotension.[57] PDE-5 inhibitors have proven to accentuate the hypotensive effects of nitrates as they selectively block PDE-5; the enzyme necessary for the breakdown of cGMP. The additive effects of increased cGMP levels can result in excessive vasodilation and accentuates the hypotensive effects of nitrates and precipitates syncopal episodes. NTG should also be avoided in patients with hypertrophic cardiomyopathy with LV obstruction as NTG can exacerbate the obstruction by decreasing preload.[58]

NTG is contraindicated in patients with a known history of increased intracranial pressure or suspected head injuries as vasodilation and subsequent blood volume increase within the cranial cavity can increase or aggravate ICP and worsen clinical outcomes due to neurologic injury.[43] NTG is known to cause methemoglobinemia[59] and in patients with severe anemia, NTG should be avoided. In cases of inferior MI with right ventricular involvement, patients are heavily dependent on maintaining preload and NTG can cause significant hemodynamic instability.[17] As such, it is recommended in patients with a known inferior wall STEMI to caution NTG use and perform a right-sided ECG prior to administration of NTG. There is a paucity of pediatric studies using NTG but it has been used in infants and small children with heart

Table 1 Summary of Emergent Nitroglycerin Uses in the Emergency Department

Indication	Dosage Form	Route	Dose	Max Dose	Onset	Duration	Contraindications
Acute Coronary Syndromes	Sublingual tablets	Sublingual	0.3-0.4 mg at onset, repeat every 5 minutes if chest pain persists	3 tablets in 15 minutes	1-3 minutes	0.5-1 hour	• Hypersensitivity to nitroglycerin • Recent use of PDe-5 inhibitors within 24-48 hours • Angina caused by hypertrophic cardiomyopathy • Known history of increased ICP • Severe anemia • Known inferior wall STEMI • Severe hypotension (SBP <90 mmHg) and bradycardia (<50 bpm), or tachycardia in the absence of heart failure (>100 bmp)
	Translingual spray	Translingual	1-2 metered sprays (400 mcg/spray, repeat every 5 minutes if chest pain persists)	3 metered sprays in 15 minutes	2-4 minutes	0.5-1 hour	
	Intravenous infusion	IV	5-10 mcg/minute, titrate as needed by 5 mcg/minute every 5-10 minutes	400 mcg/ minute	Immediate	3-5 minutes	
Acute Hypertensive Decompensated Heart Failure and Pulmonary Edema	Intravenous boluses	IV	1-2 mg every 3-5 minutes		Immediate	3-5 minutes	
	Intravenous infusion		200-400 mcg/minute for arterial vasodilation				
	Sublingual tablets	Sublingual	0.8-1.2 mg if IV access not available		1-3 minutes	0.5-1 hour	
Aortic Dissection and Aneurysm	Intravenous infusion	IV	5 mcg/minute, titrate based on BP response in increments of 5 mcg/minute every 3-5 minutes up to 20 mcg/minute. If no response at 20 mcg/min, may increase by 10-20 mcg/minute every 3-5 minutes	200 mcg/ minute	Immediate	3-5 minutes	
Pre-Eclampsia and Eclampsia							

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failure secondary to congenital cardiac defects causing a left to right shunt[60] but should not be used in the emergency department without consulting a pediatric cardiologist. Finally, caution should be exercised when administering NTG to hypotensive and bradycardic patients as severe hypotensive shock may occur. Close hemodynamic monitoring is recommended and in patients with hypotension (SBP <90 mmHg or >30 mmHg below baseline), extreme bradycardia (<50 bpm), or tachycardia in the absence of heart failure (>100 bmp), NTG is not recommended.

Safety Profile and Side Effects

NTG's vasodilatory effect makes it a standard ED treatment for a range of cardiovascular conditions. However, this vasodilatory effect can have undesired side effects and contraindications (see above). The most common side effects include headaches (originally coined "NG head" or "bang head" by industrial workers), dizziness, weakness, palpitations, vertigo, nausea, vomiting, diaphoresis, and syncope.[61,62] There have also been reports of nitroglycerin-induced asystole.[63] Nonetheless, NTG has been a longstanding mainstay for treating angina and ACS and is generally well tolerated with a low risk for major adverse events even when used at exceptionally high doses (up to 121 mg sublingual and transdermal[64] or 56 mg IV bolus[25]). NTG use in pregnancy is also perceived to be of low risk; however, NTG does cross the placenta and is detectable in the umbilical cord/fetal serum.[65] NTG is currently listed by the US FDA as category C; however, there are no adequate or well-controlled studies during pregnancy, particularly during the first trimester. Predictably, transient drops in the mother's blood pressure can occur, but they are not believed to be sufficient enough to decrease placental perfusion. Caution should be exercised when administering NTG in pregnant females and use should only occur if clearly needed and if the potential benefits outweigh the risks.

Discussion/Conclusion

As reviewed in detail above, Table 1 summarizes the most commonly used indications for NTG, including routes of administration, dosing, time to onset, and duration of effect. NTG is a proven vasodilator for use across a wide range of cardiovascular diseases such as angina, AMI, ACS, hypertensive AHF, pulmonary edema, and aortic dissection.

Less is known about its utility for pre-eclampsia but when present with severe features including pulmonary edema, it could be considered as an option. NTG has broad clinical utility in the emergency department and is endorsed by long-standing guidelines for angina and ACS. There is also growing evidence supporting the use of IV NTG by continuous infusion or repeat bolus administration for acute hypertensive heart failure. Other uses of NTG exist; however, overall most indications suffer from a lack of robust, randomized trial data highlighting the need for further study of this time-honored medication.

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