

Weekly Pharmacy Pearl: High Dose Nitroglycerin for Pulmonary Edema

Background

In **acute decompensated hypertensive heart failure (ADHF)**, increased afterload and decreased venous capacitance lead to fluid shifts from the splanchnic vasculature to the pulmonary vasculature.¹

Sympathetic crashing acute pulmonary edema (SCAPE) is an extreme form of ADHF characterized by rapid onset of respiratory decompensation, sympathetic surge, and agitation/anxiety in the setting of acute onset hypoxia. It is important to note that despite marked pulmonary edema, many present with euolemic or even volume depleted status. Thus, a treatment plan focused on reducing both preload and afterload may be more beneficial than IV diuretics.²

Pharmacology of High Dose Nitroglycerin (NTG) in the Setting of Hypertensive Heart Failure

- Mechanism of action: nitric oxide mediated dilation of both veins and arteries³
 - NTG is a prodrug that requires enzymatic metabolism to become the active vasodilator nitric oxide⁴
- IV bolus: 500-2000 mcg every 2-5 minutes PRN (Max cumulative dose 20 mg)⁵⁻¹⁰
- IV infusion: initiate at 200-400 mcg/min and titrate by 50 mcg/min Q 3-5 min PRN to resolution of symptoms⁵⁻¹⁰
- Adverse effects:
 - High dose NTG is well tolerated in the literature with a very few instances of SBP < 90 mmHg.
 - Volume depleted patients are at the highest risk of hypotension from nitrate therapy.
 - Some studies have used POCUS-guided assessment of IVC to assess fluid status in patients presenting with SCAPE.²
 - Headache
- Contraindications to high dose NTG infusion:
 - Use of sildenafil or vardenafil within 24 hours or tadalafil within 48 hours
 - Hypertrophic cardiomyopathy
 - Severe aortic stenosis
 - Anaphylaxis to nitrates

Evidence Summary for High Dose Nitroglycerin in ADHF and SCAPE

| Study | Population | Intervention | Results |
|----------------------------------|--|--|---|
| Mathew et al. 2021 ⁵ | Prospective observational study 25 patients presenting to the ED with SCAPE | Combination of IV bolus + infusion + NIV Bolus: 600-1000 mcg (mean 872 mcg) Infusion: 100 mcg/min and titrated by 20 mcg/min Q 10 min | <ul style="list-style-type: none"> • 24/25 discharged home • 11/24 had symptom resolution within 3 hrs and the remaining within 6 hrs • Average ED LOS 15 hrs • No hypotension after bolus • 2 transient hypotension during infusion that responded to small fluid bolus |
| Stemple et al. 2021 ⁶ | Case series N = 4 Presented in SCAPE in obvious respiratory distress | Infusion without IV bolus N =1: 400 mcg/min x 30 min, increased to 800 mcg/min x 4 min and then weaned off. N =2: 400 mcg/min x 8 min, increased to 800 mcg/min x 28 min and then weaned off. N=3: 400 mcg/min x 8 min, increased to 800 mcg/min x 26 min and then weaned off. N=4: 200 mcg/min and remained at > 150 mcg/min for ~ 2 hrs and then weaned off. | <ul style="list-style-type: none"> • None required intubation nor experienced hypotension • 3 of 4 admitted to general cards floor • 1 discharged after adjustment of chronic hypertensive meds |
| Paone et al. 2018 ⁷ | Case report N=1 Presented with SCAPE in obvious respiratory distress | Infusion started at 400 mcg/min and titrated down by 50 mcg/min Q 5 min as tolerated until resolution of hypertension and respiratory distress | <ul style="list-style-type: none"> • Symptom resolution 6 min after initiation of infusion • Not intubated and admitted to a general medical ward • No rebound HTN or respiratory distress recurred |

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| Hseih et al. 2018 ⁸ | Case series N = 3 Present with SCAPE in obvious respiratory distress | Initial treatment: 3 consecutive SL NITROSTAT 0.6 mg tablets Refractory to SL Nitrostat: 1 mg IV bolus every 2 min PRN (maximum 10 mg) | <ul style="list-style-type: none"> All responded to intermittent bolus therapy after failing SL None intubated 1 admitted to general cards floor for HF 2 discharged after hemodialysis No incidence of hypotension |
| Wilson et al. 2017 ⁹ | Retrospective observational cohort study N = 395 | IV bolus: 0.5 mg to 2 mg Q 3 to 5 min (median total dose 2 mg) VS Infusion only: median initial rate 20 mcg/min titrated to median maximum rate of 35 mcg/min VS Combination IV bolus + infusion median rate 20 mcg/min titrated to median max rate of 60 mcg/min) | <ul style="list-style-type: none"> No difference in intubation rates, bipap use, ED LOS, ICU LOS, or hospital LOS among the different dosing strategies Low incidence of hypotension, with highest in the combination bolus + infusion group (5/82 patients) 79% treated with IV bolus only required one dose No serious adverse effects noted with the use of high-dose NTG bolus, infusion or combination bolus and infusion therapy |
| Levy et al. 2007 ¹⁰ | Nonrandomized, open-label, single-arm study 29 with severe HTN ADHF, not responsive to 4 doses of 0.4 mg SL tabs, IVP furosemide, and 100% FiO2 NRB | Combination IV bolus + infusion Bolus: 2 mg once with an option for additional 2 mg IV Q 3-5 min per physician discretion (Max cumulative dose 20 mg) Infusion: 0.3-0.5 mcg/kg/min titrated by 20 mcg/min Q 1-3 min PRN (max 400 mcg/min) | <ul style="list-style-type: none"> 4/29 patients required intubation 25/29 received more than one bolus 1 patient had documented hypotension Mean initial infusion rate: 23.6 mcg/min Mean final infusion rate: 50 mcg/min Mean furosemide dose: 85.5 mg IVP |

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