Pediatric Focused Safety Review: Sodium Nitroprusside (Nitropress®)

Pediatric Advisory Committee Meeting
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Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information: Sodium Nitroprusside (Nitropress®)

- **Original Market approval:** 1981
- **Therapeutic Category:** Direct acting vasodilator
- **Sponsor:** Hospira
- **Indications :**
  1. Immediate reduction of Blood Pressure (BP) in hypertensive crises (**adult and pediatric**)
  2. For producing controlled hypotension to reduce bleeding during surgery
  3. Treatment of acute congestive heart failure
- **Mechanism of action:** Relaxation of vascular smooth muscle
- **Dosage and Administration:** Intravenous infusion starting at 0.3mcg/kg/min and titrated up to 10mcg/kg/min (NOT to exceed 10mcg/kg/min for 10min)

Pediatric Labeling
Sodium Nitroprusside (Nitropress®)

- **November 22, 2013**
- **Pediatric Use**

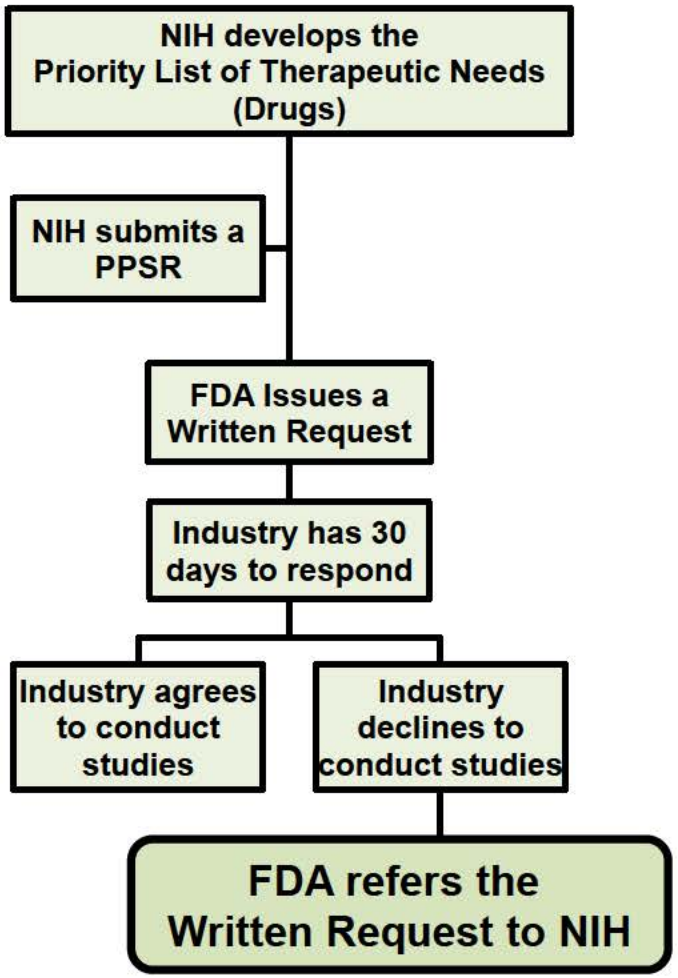
  Efficacy in the pediatric population was established based on adult trials and 2 clinical trials in children birth to less than 17 years of age. No novel safety issues were seen in these studies in pediatric patients.

- **Dosing:**

  Same as in adults; 0.3mcg/kg/min and titrated up to 10mcg/kg/min (NOT to exceed 10mcg/kg/min for 10min)

Pediatric Studies: Sodium Nitroprusside (Nitropress®)

- Pediatric studies were conducted under the Best Pharmaceuticals Children's Act (BPCA)
- BPCA provides a mechanism for study of off-patent drugs by NIH
- Nitroprusside pediatric studies were conducted by NIH in response to An off-patent Written Request issued by the FDA



Known Adverse Effects: Sodium Nitroprusside (Nitropress®)

Cyanide toxicity (WARNINGS section) :

- Occurs typically at doses ≥ 10 mcg/kg/min
- Toxic effects are rapid and fatal
- Manifestation of cyanide toxicity include lactic acidosis, shortness of breath, confusion and death.

Thiocyanate:

- Mildly neurotoxic at serum levels of 1 mmol/L (60 mg/L) and life-threatening when levels are 3 or 4 times higher (200 mg/L)
- Toxicity typically associated with high dose and prolonged infusions (doses>3mcg/kg/min or 1mcg/kg/min in anuric patients for >3 days)

Methemoglobinemia:

- Clinically significant methemoglobinemia (>10%) rarely seen

Drug Utilization:
Sodium Nitroprusside (Nitropress®)

Nationally estimated number of patients with an inpatient or outpatient hospital discharge billing for Nitropress® (sodium nitroprusside) from U.S. non-federal hospitals†, stratified by patient age groups*, November 2013 to July 2016, aggregated

	November 2013 - July 2016	
	Patient Count‡ N	Share %
Nitropress Total Patients	**262,243**	***100.0%***
0-16 years	**14,808**	***5.6%***
0-1 year	**8,621**	***58.2%***
2-11 years	**4,119**	***27.8%***
12-16 years	**2,106**	***14.2%***
17 years and older	**247,435**	***94.4%***

Source: IMS Health, Inpatient HealthCare Utilization System. November 2013 - July 2016. Data extracted October 2016. File: IHCarUS 2016-1586 Nitroprusside by age, 10-21-2016

†**Data from standalone pediatric and other specialty hospitals are not available.**

***Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months).**

‡**Unique patient counts may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in the individual categories.**

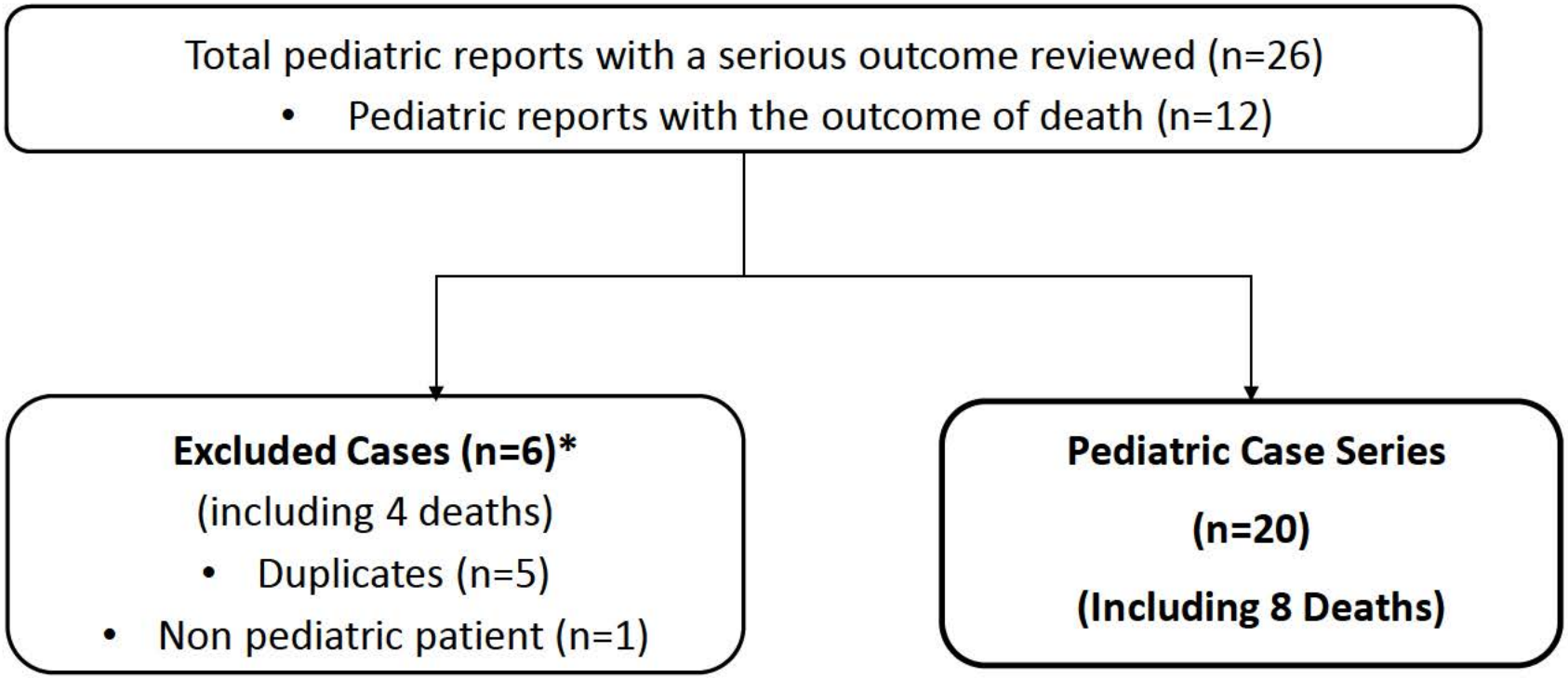
Total Number* of Nitroprusside Adverse Event Reports (August 1, 1988 - October 24, 2016)

	All reports (US)	Serious (US)†	Death (US)
Adults (≥ 17 yrs.)	116 (96)	80(60)	16(14)
Pediatrics (0-<17 yrs.)	26 (17)	**26 (17)**	**12 (10)**

*May include duplicates and transplacental exposures, and have not been assessed for causality

†For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

Selection of Serious Pediatric FAERS Cases: Sodium Nitroprusside (Nitropress®)



*Reviewed and excluded for stated reasons.

Summary of Serious Adverse Event Cases (n=20)

- **Fatal Adverse Events (n=8)**
  - Cyanide toxicity (n=3)
  - Cardiovascular events (n=2)
  - Lack of effect (n=2)*
  - Carboxyhemoglobinemia (n=1) (COHb at 6.4% but death due to underlying disease)

- **Nonfatal Serious Adverse Events (n=12)**
  - Carboxyhemoglobinemia (n=4) (COHb at 1.2-7.7% with no associated symptoms)
  - Cyanide toxicity and poisoning (n=3)
  - Cardiovascular events (n=2): High BP, cardiac arrest, vasodilatation, and ventricular tachycardia
  - Lack of effect (n=2)*
  - Transient blindness (n=1)

Unlabeled events are underlined.

* For regulatory purposes, the FDA does not consider lack of effect to be an adverse event.

Fatal Adverse Events Cases
Cyanide Toxicity/Poisoning (n=3)

- 3 patients with complex congenital heart defects and complicated intraoperative and/or post-operative course had cyanide levels reported as "toxic" following nitroprusside infusion. All 3 patients died within few days of their surgical repair.

  The cause of death in all cases was likely associated with complex underlying disease although it is unclear if cyanide toxicity contributed to the fatal outcome. Cyanide toxicity is a known adverse event and is included in the Warning section of the product labeling.

Fatal Adverse Event Cases
Cardiovascular Events (n=2)

- A 10-month old patient with CHD died during surgical repair. The pt received intra-operative nitroprusside and dobutamine infusions.
- A 2-year old patient with fetal alcohol syndrome experienced hypotension after a bolus of nitroprusside was inadvertently administered. BP normalized after the infusion was stopped. The patient died the following day following a series of three cardiac arrests.

The cause of death in both cases was likely associated with underlying disease. Hypotension is a known adverse reaction of nitroprusside and is due to an extension of its active pharmacologic properties.

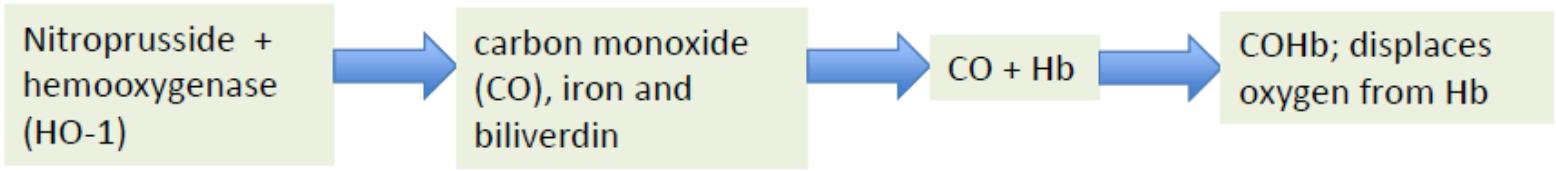
Cases of Elevation in Carboxyhemoglobin Levels

- Five patients had elevated carboxyhemoglobin (COHb) levels, ranging from 5.3% to 16%:
  - One fatality in a 4 y/o with complicated underlying medical history who received a high dose of nitroprusside (16mcg/kg/min x 12 hrs) as a result of a medication error.
  - The remaining patients had no signs of systemic toxicity or hemolysis and recovered without sequelae.

Patient Age	Relevant underlying condition	Nitroprusside Infusion	Carboxyhemoglobin level	Outcome
4 y/o	Pre-existing cardiogenic shock; cardiomyopathy; cardiac transplant; ECMO	2 mcg/kg/min x 8 days; then **16 mcg/kg/min x 12 hrs** (medication error)	**6.4%** after high dose infusion	Pt required cardiopulmonary support (ECMO) and was unresponsive prior to administration of high dose nitroprusside; **Patient ultimately died.**
6 months old	Cardiac transplant; cardiomyopathy; hypertension	8 mcg/kg/min	**5.5%**; normal after nitroprusside discontinuation	No signs of systemic toxicity or hemolysis; recovered with no sequelae.
2 y/o	Cardiac transplant; hypertension	7 mcg/kg/min x 5 days	**7.7%** initially; normal after nitroprusside discontinuation	No signs of systemic toxicity or hemolysis; recovered with no sequelae.
2 y/o	Cardiac transplant	6.5 mcg/kg/min	1.2% at baseline; 3.7% at 24hrs; **5.3%** at 48 hrs after start of nitroprusside infusion; normal after discontinuation	No signs of systemic toxicity or hemolysis; recovered with no sequelae.
14 y/o	Renal failure	"relatively high" doses x 4 days	**16%** an unknown time after starting nitroprusside; level returned to NL after discontinuation	No signs of systemic toxicity or hemolysis; recovered with no sequelae.

Mechanism of Nitroprusside Induced Elevation in Carboxyhemoglobin Levels

- A plausible mechanism for nitroprusside induced elevation in COHb levels has been reported:



(Lopez-Herce J et al. *Intensive Care Med* 2005)

- COHb level is typically < 2% in nonsmokers and < 9% in smokers.

(Hampson N et al. *The American Journal of Emergency Medicine* 2008)

- For minimum to moderate elevation in COHb levels, symptoms and severity are variable:
  - Mild/moderate elevation: Headache, nausea, etc.
  - Severe elevation: Seizure, syncope, acidosis, etc.

Elevation in Carboxyhemoglobin Levels Summary of Findings

OSE Assessment

- Documented temporal rise in COHb levels in 5 patients.
- Patients with complicated underlying disease (four post-operative cardiac transplant)
- Decrease in COHb levels with nitroprusside discontinuation in four cases. No reported COHb-related symptoms.
- No additional cases in adults or children in literature or FAERS.
- OSE recommends adding "increase in COHb levels" as a laboratory finding in pediatric patients to labeling.

DCRP/PharmTox Assessment

- There is a plausible relationship between nitroprusside exposure and elevated COHb production.
- Documented levels in patients were not associated with any COHb-related symptoms raising uncertainty about the clinical relevance of the finding.
- A label change may result in an unwarranted clinical decision to stop nitroprusside administration.
- DCRP conclusion: The lack of correlation between COHb levels and any signs of COHb-related toxicity does not support a labeling change

Summary Pediatric Focused Safety Review: Sodium Nitroprusside (Nitropress®)

- This concludes the pediatric safety review.
- Most cases included known adverse events in patients with complex underlying medical conditions.
- Nitroprusside exposure is associated with elevated carboxyhemoglobin levels of uncertain clinical relevance.
- **Question to the Committee:**
  - **Are available data sufficient to support labeling for elevation of carboxyhemoglobin level at this time?**

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