DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Cardiovascular and Renal Products

Date:	February 1, 2017
From:	Rama Dwivedi, PhD Pharmacologist Fortunato Senatore, MD Medical Officer Thomas Papoian, PhD, DABT Supervisory Pharmacologist
Through:	Thomas Papoian, PhD, DABT Supervisory Pharmacologist
To:	ANDA #71961 (Nitropress®; sodium nitroprusside) (b) (4) TSI #001753 (sodium nitroprusside for intravenous infusion, regarding a potential risk of carboxyhemoglobinemia)
Product Name:	Nitropress® (sodium nitroprusside) injection
Subject:	Safety-001753 BPCA Safety Review ANDA 071961
Sponsor:	Hospira, Inc.

Background Information

Nitropress® injection (sodium nitroprusside; SNP) was approved by the FDA on August 1, 1988, and is manufactured by Hospira under ANDA 071961. Nitropress® is indicated for the 1) immediate reduction of blood pressure (BP) of adult and pediatric patients in hypertensive crises, 2) producing controlled hypotension in order to reduce bleeding during surgery, and 3) treatment of acute congestive heart failure.

Other than the risk of acute hypotension, SNP infusions at rates above 2 mcg/kg/min can generate cyanide ion from the breadkdown of SNP which can reach toxic, potentially lethal levels with symptoms similar to that of cyanide poisoning. This requires periodic monitoring for

blood thiocyanate levels, and the rate and duration of treatment may be limited if levels are increased faster than ability of the body to metabolize cyanide.

A search of the Adverse Event Reporting System (FAERS) database for Nitropress® by the FDA staff in CDER, created a new DARRTS Tracked Safety Issue (TSI) on November 29, 2016 for a potential risk of "carboxyhemoglobinemia" resulting from intravenous infusion of SNP. This uncommon finding, similar to that seen with carbon monoxide poisoning, is unrelated to the well known issue of increased thiocyanate levels, but the two may share similar clinical signs and symptoms.

Results of the data search identified 20 serious pediatric cases associated with SNP therapy, which included 8 deaths and 12 non-fatal post-marketing cases. Of these, one case with an outcome of death and 4 non-fatal cases were reported to be associated with increased levels of carboxyhemoglobin (Lopez-Herce et al. 2005). In the fatal case, the cause of death may have been secondary to a medication error where the patient received 16 μg/kg/min SNP for 12 hours instead of the intended 8 μg/kg/min for 12 hours. All cases documented a positive dechallenge upon SNP withdrawal. No cases of carboxyhemoglobinemia were identified in the adult population.

In view of these adverse events reported by FAERS, OSE recommends adding "carboxyhemoglobinemia" to the Adverse Reactions section of the label for Nitroprusside.

The Division of Cardiovascular and Renal Products (DCRP) Safety Team, therefore, requested an opinion of Pharmacology/Toxicology to address the following concerns:

1. Is elevation of carboxyhemoglobin plausibly related to sodium nitroprusside therapy?
2. What level of carboxyhemoglobin is clinically relevant with regards to toxicity?

Reviewers' comments

Is elevation of carboxyhemoglobin plausibly related to sodium nitroprusside?

Sodium nitroprusside (SNP) was first discovered in 1850, but its hypotensive effects were not noticed until 1929. Since then, SNP has been widely used to control blood pressure in adults, children, and infants in the perioperative period. SNP is a direct-acting vasodilator commonly used for blood pressure control. SNP breaks down in circulation to release nitric oxide (NO), which in turn activates guanylate cyclase in vascular smooth muscle to produce cGMP which induces vascular smooth muscle relaxation, vasodilation, and increased blood flow.
Results from several *in vitro* studies have shown that NO and NO donors, such as SNP, induce heme oxygenase (HO-1) expression in many cell types (Durante et al. 1997; Rusca et al. 2004; Ryter et al. 2006; Chen and Maines 2000; Morse and Choi 2002). HO-1 in turn breaks down heme molecules to yield equimolar quantities of biliverdin, free iron, and carbon monoxide (CO) (Vesely et al., 1988; Hara et al. 1999; Morse and Choi 2002; Chung et al. 2008; Otterbein et al. 2016) (Figure 1; Otterbein et al. 2016).

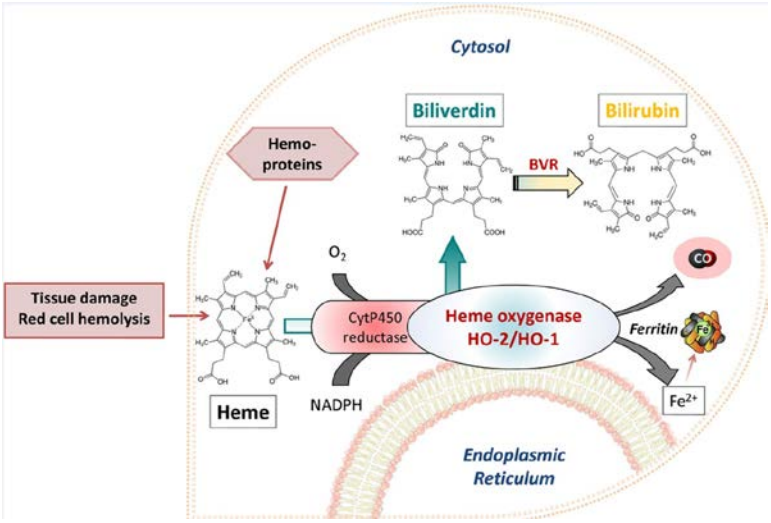

Fig 1. Schematic representation of the heme oxygenase pathway (Otterbein et al. 2016)

CO binds rapidly to hemoglobin (Hb), leading to the formation of carboxyhemoglobin (COHb). This decreases the oxygen carrying capacity of the Hb in red blood cells, causing tissue hypoxia. The affinity of Hb for CO is 210 times that of O_2 and easily displaces oxygen from the Hb molecule. The amount of COHb produced depends on the duration and level of exposure to CO, and most of the adverse effects of CO poisoning have long been attributed to hypoxemia.

However, the relationship between levels of COHb and symptom severity do not always correlate, such as the cardiac arrhythmias that appear to be unrelated to the hypoxia, or the cognitive dysfunction seen weeks to months following initial CO exposure (reviewed in Roderique et al. 2015; Sykes and Walker 2016). There are several reports of near zero levels in patients showing neurologic deficits ranging from partial paralysis to coma (Norkool 1985; Myers 1989; Myers et al. 1995). Some of this disconnect between COHb levels and clinical signs may be attributable to the short half-life of COHb in the blood (50-74 min) and the time at which blood is sampled for analysis, oftentimes hours following acute CO poisoning (reviewed in Sykes and Walker 2016). There have also been other reports of a poor correlation between severity of CO exposure to severity of outcome and symptoms, regardless of the timing of blood sampling (reviewed in Sykes and Walker 2016). Further, multiple studies have questioned whether COHb levels accurately reflect the adverse effects seen, and whether mechanisms or pathways other than the binding of CO to hemoglobin may contribute to the various toxicities and symptoms seen.

For example, the discovery of nitric oxide (NO) as an endogenously produced gas with cellular signaling activity led to the finding that CO produced from breakdown of hemoglobin by HO-1 was involved in multiple cellular processes as well, including effects on soluble guanylate cyclase, ion channels, mitochondria , cytochromes, NADPH oxidase, and xanthine oxidase

(reviewed in Roderique et al. 2015). This led to the suggestion that elevated COHb and ischemia were not the sole cause of toxicity, but rather the blocking by CO of vital cellular processes, such as oxidative phosphorylation, may also be a major contributor. Also, victims of CO poisoning did not appear to have worse outcomes if oxygen treatment was delayed, indicating that reversal of COHb levels with oxygen did not provide additional protection against the adverse effects seen when compared to room air alone, suggesting that toxic mechanisms other than COHb may be involved.

Although increased COHb levels during SNP therapy may reflect actual CO production and possible risk of hypoxia-induced injury, more recent evidence for involvement of CO in multiple cellular pathways and its adverse cellular effects when levels are increased may question whether measurement of COHb alone is an accurate overall indicator of potential CO-mediated toxicity or its severity, and whether monitoring COHb levels will provide clinically meaningful information to assess risk of adverse effects with continued SNP exposure. Some have suggested that monitoring for metabolic acidosis, such as blood pH, bicarbonate, and base deficit, may be more useful markers of CO-mediated intracellular damage (Sykes and Walker 2016).

What level of carboxyhemoglobin is clinically relevant with regards to toxicity?

The potential risk of "carboxyhemoglobinemia" during the intravenous infusion of sodium nitroprusside is essentially based on published results from a 2005 clinical study that demonstrated a moderate increase in carboxyhemoglobin levels after SNP administration in three pediatric patients with heart transplantation and the normalization of carboxyhemoglobin levels following withdrawal of the drug (Table 1; Lopez-Herce et al. 2005).

Table 1
(Lopez-Herce et al. 2005)

Table 1 Initial and maximum dose of nitroprusside, ventilator parameters, blood gas parameters, co-oximetry, and other treatments administered in the four patients (*NR* not recorded)

	Patient 1		Patient 2		Patient 3		Patient 4	
	Initial	Max.	Initial	Max.	Initial	Max.	Initial	Max.
Day	0	6	0	5	0	0.5	0	2
Nitroprusside ose (μg kg^{-1} min^{-1})	0	8	0	7	2	16	0	6.5
Ventilator parameters								
Tidal volume (ml)	50	50	95	95	100	100	95	95
PEEP (cmH_2O)	2	2	4	4	6	6	3	3
Respiratory rate (rpm)	30	28	25	25	10	10	25	15
FIO_2 (%)	0.5	0.5	0.4	0.4	0.3	0.3	0.45	0.4
Blood gas parameters								
pH	7.45	7.47	7.42	7.47	7.32	7.41	7.44	7.44
PaO_2 (torr)	166	151	165	172	255	120	169	143
$PaCO_2$ (torr)	51	50	42	43	46.2	41	41.6	46.2
Hemoglobin saturation (%)	99.5	99.4	99.4	99.6	99.8	98.7	99.5	99.3
Co-oximetry								
Oxyhemoglobin (%)	97.6	93	NR	88.9	98	88	97.3	92.2
Carboxyhemoglobin (%)	1.2	5.5	NR	7.7	1.9	6.4	1.7	5.3
Methemoglobin (%)	0.7	1	NR	2	3.1	2.7	1	1.7
Lactate (mmol/l)	1	0.8	NR	1.5	2.5	3.8	0.9	2
Other treatments	–	–	–	–	ECMO	ECMO	–	–
Nitric oxide (ppm)	10	8	7	6	0	0	10	10
Dopamine (μg kg^{-1} min^{-1})	10	10	8	5	5	5	5	5
Milrinone (μg kg^{-1} min^{-1})	0.5	0.5	0.7	0.7	0.7	0.7	0.7	0.7
Isoproterenol (μg kg^{-1} min^{-1})	0.04	004	0.03	0.01	–	–	0.04	0.01

As shown in Table 1, COHb levels were significantly increased (5.3 to 7.7% range) in SNP treated patients when compared with baseline levels (1.2 to 1.9% range). However, the percentage increase in COHb did not appear to be well correlated with the dose of SNP administered (6.5 to 16 µg/kg/min). For example, in patient # 3 where SNP dose was high (16 µg/kg/min) resulting in a COHb level of 6.4%, COHb was not much different (7.7%) in patient #2 that received less than half that dose (7 µg/kg/min). Although increased COHb levels were associated with SNP treatment in these patients, and all four cases documented a positive dechallenge upon SNP withdrawal, there did not appear to be a clear linear correlation between SNP dose and COHb levels from this study.

In the case of CO poisoning, the severity of observed symptoms correlates roughly with the observed levels of COHb usually taken at some variable time after exposure (O'Malley and O'Malley, 2015; Crocker, 1984; Groman et al. 1992), but COHb levels measured may be low if blood sampling was delayed. In the case of SNP therapy, the non-specific nature of these presenting symptoms makes distinguishing between CO-mediated effects from cyanide-related effects difficult.

In many cases when COHb levels are less than 10% the patient is usually asymptomatic (Table 2; Veron and Marik 1997). As COHb increases above 20%, the patient may develop headache, dizziness, confusion and nausea. Coma and seizures due to cerebral edema are common with levels greater than 40%, and death is likely above 60%.

Table 2. Percentage COHb Levels and Symptomatology
(Veron and Marik 1997)

10%	Asymptomatic or may have headaches
20%	Dizzyness, nausea, and syncope
30%	Visual disturbances
40%	Confusion and syncope
50%	Seizures and coma
60%	Cardiopulmonary dysfunction and death

The levels of COHb achieved in the pediatric study cited (maximum of 7.7%) (Lopez-Herce et al. 2005) did not rise above levels known to be associated with symptoms (10-20%), and the authors did not attribute any symptoms to these rises in COHb.

From a clinical perspective, addition of "carboxyhemoglobinemia" to the Adverse Reactions section of Nitropress® product labelling may raise clinical questions about what a clinician should do if carboxyhemoglobinemia is detected at some undefined level in the setting of a still uncertain safety concern. This may possibly result in an unwarranted clinical decision to stop

SNP administration, thus adversely impacting patient management if the therapy was proving effective in reducing hypertension.

Summary and Conclusion

Results from several in vitro studies have shown that breakdown of SNP to nitric oxide (NO) can induce heme oxygenase (HO-1) expression in many cell types, and that HO-1 in turn produces carbon monoxide (CO) by breakdown of heme molecules. Further, CO has been shown to be an endogenous signaling molecule involved in multiple cellular processes, suggesting that elevated COHb and resulting ischemia may not be the sole cause of toxicity, but rather the blocking by CO of vital intracellular processes may also be a major contributor. Although increased COHb levels during SNP therapy may reflect actual CO production and possible risk of hypoxia-induced injury, more recent evidence for involvement of CO in multiple cellular pathways and its adverse cellular effects when CO levels are increased may question whether measurement of COHb alone is an accurate overall indicator of potential CO-mediated toxicity or its severity.

Results from a pediatric clinical study (Lopez-Herce et al. 2005) reported a moderate increase in carboxyhemoglobin levels (up to 7.7%) after SNP administration in four pediatric patients with heart transplantation. Normalization of carboxyhemoglobin level following the withdrawal of the drug indicated a good correlation between SNP exposure and COHb production. However, the percentage increase in COHb did not appear to correlate well with the dose of SNP administered. Further, the authors did not attribute any adverse consequence to these elevations, nor did it prompt them to withdraw presumably effective SNP therapy based on these increases.

Based on the absence of such reports previously given the near 30 years of clinical experience with SNP, it appears that SNP treatment does not result in obvious clinically-meaningful elevations of COHb. Rather, it appears that a COHb level of 10% or more is needed for a clinically relevant measure of possible CO-mediated toxicity when blood sampling is well timed relative to SNP treatment (Veron and Marik 1997).

Further, a label change regarding the addition of carboxyhemoglobinemia to the Adverse Reactions section without clearer documentation regarding any observed adverse findings may negatively impact patient management.

In conclusion, it is our view that a better correlation between actual reported COHb levels in the clinical setting of SNP treatment and subsequent documented safety signals due to CO-mediated toxicity is needed before such a labeling change as an Adverse Reaction is enacted.

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