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Stability of Sodium Nitroprusside and Sodium Thiosulfate 1:10 Intravenous Admixture

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Introduction

Sodium nitroprusside (NPS) is a potent vasodilator used in critical care and peri-operative patients. Due to its chemical composition and metabolic pathways, it has the potential to cause cyanide and thiocyanate toxicity.[1-2] Patients with compromised renal function are also at risk for toxicity since both cyanide and thiocyanate are cleared by the kidneys. As a consequence of a potentially dangerous toxicity profile, nitroprusside has fallen out of favor with prescribers at our institution. Alternative agents, such as nicardipine and clevidipine, are substantially more expensive than nitroprusside, and nicardipine does not lower blood pressure as quickly as nitroprusside.[3] Reducing the risk of toxicity with nitroprusside may provide prescribers with a safe, effective, and economical choice to control blood pressure in critically ill patients.

To combat cyanide toxicity, thiosulfate (TS) can be administered with nitroprusside, which has been demonstrated to have equal efficacy in the treatment of hypertensive crises[4] and cerebral vasospasm,[5] with no adverse events reported.

This study was designed to determine chemical stability, via a high performance liquid chromatography (HPLC) assay, and physical stability via visual inspection of a 1:10 nitroprusside and thiosulfate intravenous (IV) admixture. The economic consequence of a shift in utilization from higher cost alternative therapies was also considered.

Materials & Methods

Chemical Stability

Materials

Stability samples were prepared by adding the contents of a 50 mg vial of nitroprusside sodium (Nitropress. NDC 0409-3024-01. Concentration 50 mg/2 mL. Hospira, Inc, Lake Forest, IL. Lot number: 76790DD) and 2 mL of a 250 mg/mL sodium thiosulfate pentahydrate (sodium thiosulfate. NDC 0517-5019-01. Concentration 250 mg/mL. American Regent, Shirley, NY. Lot number: 8472) to each of seven 250 mL 0.9% sodium chloride (NS) bags (Baxter Healthcare Corp, Deerfield, IL. Various lot numbers) and seven 250 mL 5% dextrose and water (D5W) bags (Baxter Healthcare Corp, Deerfield, IL. Various lot numbers), yielding a label claim of 0.2 mg/mL and 2 mg/mL, respectively.

These bags contained a standard 10% overfill and therefore contained actual concentrations of 0.18 mg/mL nitroprusside and 1.8 mg/mL thiosulfate. Three bags of each type were stored at ambient conditions and protected from light. One bag of each type was stored at each of the following conditions: 25ºC/60% relative humidity (RH), 30 C/65% RH, and 5ºC, all of which were protected from light. The remaining bag was stored at ambient conditions exposed to ambient light. Initial samples for analysis were removed from one of the ambient/no-light NS bags and one of the ambient/no-light D5W bags.

HPLC Analytical Method

A high performance liquid chromatography (HPLC) method was developed for measuring nitroprusside, thiosulfate, and thiocyanate in single analysis. The conditions used for sample analysis were:

- Column: Zorbax Eclipse XDB-C8 4.6x150 mm, 5µm, Agilent Part No. 993967-906
- Column Temperature: 25ºC
- Injection volume: 10 µL
- Flow Rate: 1.0 mL/min
- Detector: UV at 210 nm
- Mobile Phase: 0.005 M (1.698 g/L) Tetrabutylammonium hydrogen sulfate (TBAHS) dissolved in a solution of methanol-phosphate buffer (15:85). The phosphate buffer consists of 10 mM KH_2PO_4 with a pH of approximately 7.1.

HPLC Method Verification

The appropriateness of the chromatographic method conditions were evaluated by assessing the following method performance parameters.

- *Linearity*

For each compound, standard mixtures were prepared in water at concentrations ranging from 0.02 mg/mL to 0.5 mg/mL for nitroprusside, 0.12 mg/mL to 2.1 mg/mL for thiosulfate, and 0.01 mg/mL to 1.0 mg/mL for thiocyanate. For each compound, a standard curve was prepared by plotting peak area versus standard concentrationand the correlation coefficient must be ≥ 0.995.

- *Repeatability*

For each compound, the repeatability of the method was assessed by calculating the %RSD of peak areas from triplicate standard injections. The %RSD of triplicate injections must be ≤ 2%.

- *Accuracy Assessment*

Samples containing known amounts of nitroprusside, thiosulfate, and thiocyanate were prepared separately in normal saline and D5W. Each solution was assayed using the HPLC method. The resulting peak areas were compared to standards prepared in water to determine the % recovery.

Physical Stability

Physical stability was assessed using a visual inspection technique previously defined and determined to be more reliable than turbidimetric methods.[6] Four 250 mL infusion bags were prepared using aseptic technique. The first bag contained 50 mg nitroprusside and 500 mg thiosulfate in D5W, the second contained only D5W and no drug, the third contained 50 mg nitroprusside and 500mg thiosulfate in NS, while the fourth contained only NS and no drug. All bags were wrapped in the nitroprusside manufacturer supplied opaque wrapping and labeled with letters A through D. Nine licensed pharmacists investigated the bags on a white and black background and identified evidence of incompatibility after preparation and at 48 and 72 hours. Examples of incompatibility included color change, formation of haze or precipitate, or evolution of a gas. If an incompatibility was found, the investigator graded the incompatibility as slight, moderate, or gross. The bags were stored in the light-protective covering, at 22ºC.

Economic Analysis

The potential economic impact of nitroprusside/thiosulfate admixture was compared to nicardipine hydrochloride and clevidipine butyrate, two calcium channel blockers currently used for the treatment of hypertension in critically ill patients. Nicardipine and clevidipine costs were based on a conservative estimate of usual adult maintenance dose specified in the prescribing information: nicardipine 3 mg/hr and clevidipine 5 mg/hr. Nitroprusside and thiosulfate admixture costs were based on maximum doses recommended for prolonged IV therapy: 4:40 mcg/kg/min. All calculations used a hypothetical 70 kg patient with good renal function. Average wholesale prices were calculated based on 2009 values published by our wholesaler (nitroprusside $19.43 per 50 mg; thiosulfate $0.86 per 500 mg; nicardipine $135 per 20 mg; clevidipine $168 per 50 mg).

Figure 1

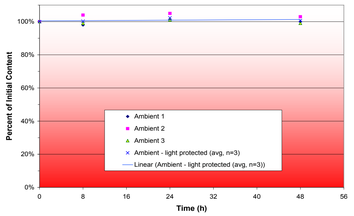


Figure 2

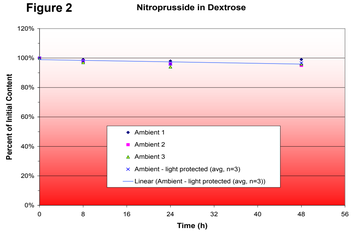


Figure 3

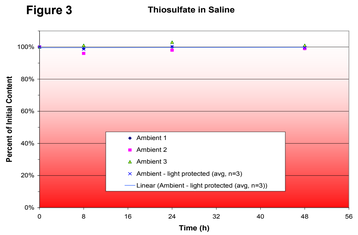
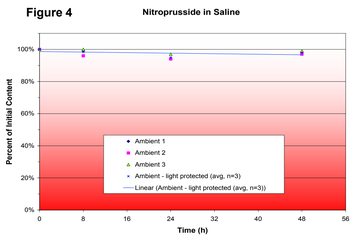


Figure 4



Results

Chemical Stability

The HPLC method was verified as linear, repeatable, and accurate. HPLC analysis revealed that chemical stability is retained upon initial mixing of nitroprusside and thiosulfate. Upon mixing, the mean nitroprusside concentration was within 97% of calculated content and the mean thiosulfate concentration was greater than 89% of calculated content in both D5W and NS. The concentration of both nitroprusside and thiosulfate remained greater than 95% of the initial concentration at all subsequent time points through 48 hours (Figures 1-4) when protected from light.

When exposed to high temperature and high relative humidity, degradation occurs at a faster rate. At eight hours, only 88% of nitroprusside and thiosulfate remained when stored at 30°C and 65% relative humidity (Figure 5). Refrigeration of the admixture seemed to provide improved stability, as 97% and 94% of initial concentrations of nitroprusside and thiosulfate remained at the end of 48 hours (Figure 6). Under both conditions, both drugs appeared to be more stable in saline than dextrose.

As expected, exposure to light resulted in increased degradation of nitroprusside, with only 85% of the initial nitroprusside concentration remaining after 48 hours of fluorescent light exposure (data not shown). Thiocyanate was not found in a measurable quantity in the admixture. As the formation of thiocyanate requires the enzymatic activity of rhondase, this is to be expected.

Physical Stability

One hundred percent (100%) of the compounded admixture bags were given a compatible rating at all time points in the study, which demonstrates the physical stability of the nitroprusside/thiosulfate admixture.

Economic Analysis

Results of the economic analysis of hypertensive agent options indicate that a substantial savings can be realized by increasing the use of nitroprusside/thiosulfate admixture (Table 1). Based on actual annual drug usage, both nitroprusside and nicardipine were used for approximately 270 days. The use of this compounded admixture could result in a projected annual savings of $87,480 compared to nicardipine use.

Table 1

Drug	Usage[a] (mg/day)	AWP	Daily Cost	Daily Cost Savings	Days of therapy in FY08[b]	Projected Annual Cost[c]	Projected Annual Saving
NPS/TS admixture	400/4000	$20/50mg	$160	($326)	274	$43,740	($87,480)
Nicardipine	72	$135/20mg	$486	NA	269	$131,220	NA
Clevidipine	120	$168/50mg	$404	($82)	0	$109,080	(22,140)

Figure 5

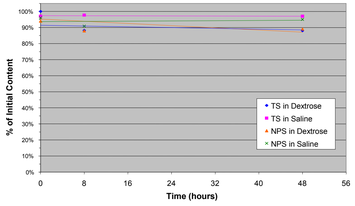
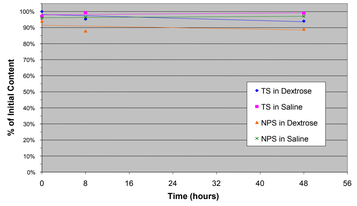


Figure 6



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Conclusions

Nitroprusside and thiosulfate 1:10 IV admixture is chemically and physically stable for up to 48 hours when stored at room temperature and protected from light. The admixture is an alternative anti-hypertensive agent and provides a more economical option than nicardipine or clevidipine[7].

Acknowledgements

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