Published in final edited form as:
Hosp Pharm. 2010 October 1; 45(10): 779–784. doi:10.1310/hpj4510-779.

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

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Abstract

Purpose—Thiosulfate has been shown to reduce the risk of cyanide toxicity during nitroprusside administration. Admixtures containing both agents may provide a safe and effective alternative to more expensive agents used to reduce blood pressure in the critically ill patient. This study determined the physical and chemical stability of a 1:10 nitroprusside:thiosulfate admixture, stored up to 48 hours. The economic consequences of a shift toward using thiosulfate and nitroprusside, and away from higher cost alternatives, are considered.

Methods—Seven samples of 50 mg nitroprusside and 500 mg thiosulfate were prepared and stored away from light, at room temperature, and in a refrigerator prepared in D5W and NS. Each sample was analyzed via a novel high-performance liquid chromatographic (HPLC) method at time 0, 8, 24, and 48 hours. The method was tested and passed specifications for linearity, reproducibility, and accuracy. A visual inspection by 9 licensed pharmacists was used to demonstrate physical stability. A cost evaluation comparing nitroprusside and thiosulfate to alternative agents was completed.

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Results—The concentration of both nitroprusside and thiosulfate remain greater than 95% of the initial concentration through 48 hours. Physical compatibility was confirmed in all samples tested through 72 hours.

Conclusion—The combination of nitroprusside and thiosulfate is chemically and physically stable as a single compounded dose for up to 48 hours when stored at room temperature and protected from light. The admixture represents an inexpensive option to other higher cost alternatives such as nicardipine or clevidipine.

Keywords

drug stability; high-pressure liquid chromatography; pharmacoeconomics

Sodium nitroprusside is a potent vasodilator used in critical care and perioperative patients. Due to its chemical composition and metabolic pathways, it has the potential to cause cyanide and thiocyanate toxicity.[1–3] Malnourished patients, post-surgical patients, patients receiving diuretic therapy, and smokers are predisposed to lower thiosulfate stores and may be more prone to early toxicity.[3] Patients with compromised renal function are also at risk for toxicity because 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.[4] 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 can be administered with nitroprusside, which has been demonstrated to have equal efficacy in the treatment of hypertensive crises [5] and cerebral vasospasm,[6] with no adverse events reported. A recent prospective randomized trial demonstrated equal blood pressure control between nicardipine and nitroprusside in neurosurgery patients.[4] In light of the current literature, nitroprusside is equally effective as more expensive alternative agents. While the literature reports equal efficacy, it is unknown whether the nitroprusside and thiosulfate combination is chemically stable. Schulz et al demonstrated the efficacy of nitroprusside/thiosulfate admixture was maintained after 14 days of storage at room temperature, and reduced efficacy was associated with a visible color change.[5]

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

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 mLs 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: 25°C/60% relative humidity (RH), 30°C/65% RH, and 5°C, 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 Preparation and Calibration—Previously identified methods of detection and quantification of independent samples of nitroprusside and thiosulfate were unable to detect and quantify nitroprusside and thiosulfate in an admixture; therefore, a new HPLC method was created and validated.

Chromatographic analysis was achieved using a reverse-phase column (*ZORBAX Eclipse XDB-C8* 4.6×150 mm, 5μm, Agilent part no. 993967-906), neutral pH mobile phase, and UV detector (Dionex *UltiMate* 3000 HPLC with PDA-3000 photodiode array detector). Separation of target compounds occurred on a C8 column (5 μm particle size, 150 × 4.6 mm) at 25°C. The mobile phase consisted of 0.005 M (1.698 g/L) tetrabutylammonium hydrogen sulfate (TBAHS; Acros Organics Cat. No. 420100100, lot no. A0253968) dissolved in a solution of methanol-phosphate buffer (15:85). The phosphate buffer was 10 mM potassium dihydrogen phosphate (KH_2PO_4; Fisher Chemical Cat. No. P285-500, lot no. 035653) with a pH of approximately 7.1. The flow rate was set at 1.0 mL/min with a 10 μL injection volume. Nitroprusside, thiosulfate, and thiocyanate were monitored via ultraviolet light at 210 nm.

HPLC Method Validation—The appropriateness of the chromatographic method conditions were evaluated by assessing linearity, repeatability, and accuracy parameters.

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 concentration. The correlation coefficients of the thiosulfate, thiocyanate, and nitroprusside standard curves were 0.999986, 0.999916, and 0.999973, respectively. These results satisfy the protocol linearity criteria that states that the correlation coefficient must be ≥0.995.

For each compound, the repeatability of the method was assessed by calculating the percent relative standard deviation (%RSD) of peak areas from triplicate standard injections. The standard concentrations ranged from 0.041 mg/mL to 0.062 mg/mL for nitroprusside, 0.14 mg/mL to 0.22 mg/mL for thiosulfate, and 0.086 mg/mL to 0.13 mg/mL for thiocyanate. The %RSDs of triplicate peak areas for thiosulfate, thiocyanate, and nitroprusside were 0.04% to 0.2%, 0.16% to 0.44%, and 0.51% to 0.61%, respectively. These results satisfy the protocol repeatability criteria that states that the %RSD of triplicate injections must be ≤2%.

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 described previously. The resulting peak areas were compared to standards prepared in water to determine the percent recovery. The results (not shown) demonstrated that this method is accurate for measuring these 3 compounds in normal saline and D5W ± 10%.

Physical Stability

Physical stability was assessed using a visual inspection technique previously defined and determined to be more reliable than turbidimetric methods.[7] 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 500 mg thiosulfate in NS, and 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. 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 pharmacists were asked to complete follow-up investigations at 48 and 72 hours. The bags were stored in a locked drawer, in the light-protective covering, at 22 °C.

Economic Analysis

The potential economic impact of nitroprusside/thiosulfate admixture was compared to nicardipine hydrochloride and clevidipine butyrate, 2 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/h and clevidipine 5 mg/h. Nitroprusside and thiosulfate admixture costs were based on maximum doses recommended for prolonged intravenous (IV) therapy: 4:40 mcg/kg/min. All calculations used a hypothetical 70 kg patient with good renal function. Medication costs were calculated based on published average wholesale prices (AWP; representing published catalogue or list prices for medications). AWP values used were as follows: nitroprusside, $22.88 per 50 mg; thiosulfate, $0.86 per 500 mg; nicardipine (*Sandoz*), $268.80 per 20 mg; clevidipine, $348.00 per 50 mg.[8]

RESULTS

The results of chromatographic studies, expressed as the mean ± *SD* percentage of the initial concentration, are found in Table 1.

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 expected and the mean thiosulfate concentration was greater than 89.4% of expected in both D5W and NS. The concentration of both nitroprusside and thiosulfate remained greater than 95% of the expected concentration at all subsequent time points through 48 hours.

Degradation data at extreme conditions are presented in Table 2. When exposed to high temperature and high relative humidity, degradation occurs at a faster rate. At 8 hours, only 88% of nitroprusside and thiosulfate remained when stored at 30°C and 65% relative humidity. 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. Refrigeration of the admixture appeared to convey some stability, as 97% and 94% of initial concentrations of nitroprusside and thiosulfate remained at the end of 48 hours.

One hundred percent 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.

Results of the economic analysis of hypertensive agent options are found in Table 3. A substantial savings can be realized by increasing the use of the nitroprusside/thiosulfate admixture. Based on actual annual institution drug usage, both nitroprusside and nicardipine were used for approximately 270 days. The use of the compounded admixture could result in a projected annual savings of $210,514 compared to nicardipine use.

DISCUSSION

The results of this study provide quantitative evidence of the chemical stability of nitroprusside and thiosulfate combined in a 1:10 ratio in both D5W and NS when protected from light at room temperature for at least 48 hours. The physical compatibility of this mixture was also re-confirmed and is consistent with the previous literature.[5] A novel quantitative HPLC method for the determination of nitroprusside, thiosulfate, and thiocyanate in solution is also presented.

The HPLC method is linear, repeatable, and accurate. The HPLC data for thiocyanate are not presented because 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. Ideally, cyanide quantification could be performed simultaneously with nitroprusside, thiosulfate, and thiocyanate; however, our attempts to separate cyanide required an acidic mobile phase, during which cyanide was lost. We hypothesized that the acidic environment resulted in hydrolysis of the cyanide molecule secondary to creation of hydrogen cyanide, a dangerous compound prone to vaporization.

The existence of greater than a 95% concentration of nitroprusside and thiosulfate remaining in the admixture is promising. The presence of high concentrations of thiosulfate, which was added to provide a layer of protection from cyanide toxicity, is particularly reassuring. The current ratio of 1 mg nitroprusside to 10 mg thiosulfate provides an ample safety margin to account for any excess or unmeasured cyanide molecules.[1,5]

Physical compatibility was confirmed using a previously defined visualization method[7] and is similar to previously published results.[5] Although this portion of the study was blinded, it was limited by 1 factor: an extended time course of 72 hours where observers were asked to identify incompatibilities based, in part, on color change. This required the observer to identify a change in the reddish-brown color of nitroprusside that may have occurred more than 72 hours prior. The dilution of nitroprusside into a 250 mL container sufficiently diluted the reddish-brown color of this drug (thiosulfate is a colorless solution). However, the presence of distinct blue-green degradation products was clearly detectable upon light exposure after the 72-hour mark.

The economic analysis demonstrates substantial savings potential with the transition to the low cost alternative nitroprusside and thiosulfate admixture. This analysis is a cost-minimization analysis and does not reflect the variability in patient response to the respective agents. Projected annual costs and savings are based on an estimated 270 days of therapy for each agent, and this method is used purely as a method to compare economic impact across agents. A complete shift to nitroprusside/thiosulfate admixture is unrealistic, but a portion of the projected $210,000 savings may be realized with adoption of nitroprusside/thiosulfate admixture.

CONCLUSION

Nitroprusside and thiosulfate is chemically and physically stable as a single infusion for up to 48 hours when stored at room temperature and protected from light. The admixture is an

alternative antihypertensive agent and provides a more economical option than nicardipine or clevidipine.

Acknowledgments

The authors would like to thank Jeffrey B. Williams, MS, Research Specialist with the Zeeh Pharmaceutical Experiment Station, and Don Wiebe, PhD, and Gary Lensmeyer, PhD, with the Clinical Laboratory at the University of Wisconsin Hospital and Clinics for their assistance in the development of this project.

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Table 1

Stability of nitroprusside and thiosulfate 1:10 intravenous admixture preparation at room temperature

Preparation	Storage conditions	Initial experimental concentration, mg/mL		% Initial experimental nitroprusside (NTP) concentration			% Initial experimental thiosulfate (TS) concentration		
		NTP	TS	8 hours	24 hours	48 hours	8 hours	24 hours	48 hours
Dextrose	Ambient	0.182 ± 0.003	1.963 ± 0.057	97.8 ± 0.7	96.2 ± 2.3	96.8 ± 2.0	100.4 ± 3.1	102.2 ± 2.7	100.8 ± 2.1
Saline	Ambient	0.186 ± 0.004	1.994 ± 0.047	98.2 ± 1.8	95.2 ± 2.0	97.9 ± 1.2	98.6 ± 2.1	100.5 ± 2.3	99.7 ± 1.5

Note: Values shown are mean ± *SD*. HPLC = high-performance liquid chromatography.

Table 2

Stability of nitroprusside and thiosulfate 1:10 intravenous admixture preparation at extreme conditions

Preparation	Storage conditions	Initial experimental concentration, mg/mL[a] Mean ± *SD*		% Initial experimental nitroprusside (NTP) concentration			% Initial experimental thiosulfate concentration		
		NTP	TS	8 hours	24 hours	48 hours	8 hours	24 hours	48 hours
Dextrose	25°C/60%RH	0.182 ± 0.003	1.963 ± 0.057	91	96	91	89	89	88
	30°C/65%RH			88	NA[b]	89	88	NA	88
	5°C			96	NA	97	95	NA	94
	Light exposed			92	NA	85	93	NA	90
Saline	25°C/60%RH	0.186 ± 0.004	1.994 ± 0.047	93	98	94	98	99	98
	30°C/65%RH			88	NA	92	98	NA	97
	5°C			93	NA	94	99	NA	99
	Light exposed			84	NA	83	97	NA	94

Note: RH = relative humidity.

[a] Mean of triplicate assay and 3 separate high-performance liquid chromatography (HPLC) analyses.

[b] NA = not applicable. The assay was not performed on extreme condition samples at 24 hours, only 0, 8, and 48 hours.

Hosp Pharm. Author manuscript; available in PMC 2011 May 26.

Table 3

Economic analysis of nitroprusside/thiosulfate (NTP/TS) admixture, nicardipine, and clevidipine

Drug	Usage,[a] mg/d	AWP[b]	Daily cost	Daily cost savings	Days of therapy in FY08[c]	Projected annual cost[d]	Projected annual saving
NTP/TS admixture	400/4000	$23.74/50 mg	$188	($779.68)	274	$50,760	($210,514)
Nicardipine	72	$268.80/20 mg	$967.68	N/A - reference	269	$261,274	N/A - reference
Clevidipine	120	$348/50 mg	$835.20	($132.48)	0	$225,504	($35,770)

[a] Each patient was assumed to use: either nitroprusside/thiosulfate at 4 mcg/kg/min, nicardipine at 3 mg/h, or clevidipine at 5 mg/h for 24 hours.

[b] AWP = average wholesale price.

[c] Days of therapy based on actual institution usage statistics for fiscal year 2008.

[d] The annual cost for each drug is based on an average of 270 days of therapy.

Hosp Pharm. Author manuscript; available in PMC 2011 May 26.