Anesthesiology
58:11–17, 1983

Sodium Thiosulfate Disposition in Humans: Relation to Sodium Nitroprusside Toxicity

Anthony D. Ivankovich, M.D., Berton Braverman, Ph.D.,† Thomas S. Stephens, M.D.,‡ Morton Shulman, M.D.,§ Harold J. Heyman, M.D.§*

Thiosulfate concentrations and pharmacokinetics were studied in relation to sodium nitroprusside before, during, and after anesthesia. Normal thiosulfate concentrations were 1.13 ± 0.11 mg/dl and 0.28 ± 0.02 mg/dl in plasma and urine, respectively. Cholecystectomy patients had similar concentrations during surgery, with bile thiosulfate concentration of 13.72 ± 2.95 mg/dl. Fasting patients and children had significantly higher plasma and urine thiosulfate concentrations. Over 99% of endogenous filtered thiosulfate was reabsorbed by the kidney in the average case. Coronary bypass patients had decreased plasma thiosulfate levels and increased excretion postoperatively. Disappearance of injected thiosulfate was biphasic; the distribution phase was dependent on the initial rate of injection, and the elimination phase depended on extracellular fluid turnover and renal excretion. Cholecystectomy patients on diurectics had a markedly increased rate of excretion, 56% within 100 min, *versus* normal subjects who excreted less than 50% in up to 18 h. In children, plasma thiosulfate did not change significantly, while blood cyanide concentration increased significantly during sodium nitroprusside administration and surgery. Thiosulfate did not change during recovery while cyanide decreased. Normal production of thiosulfate in humans may be limited; hence, continuous thiosulfate infusion may be required during sodium nitroprusside administration. (Key words: Anesthetic techniques: hypotension, induced. Pharmacokinetics: sodium thiosulfate. Pharmacology: nitroprusside. Toxicity: cyanide; nitroprusside.)

SODIUM NITROPRUSSIDE (SNP; Nipride, Roche), a potent, short-acting vasodilator, is widely used for the treatment of hypertensive emergencies and various forms of myocardial dysfunction, and also for deliberate induction of hypotension during anesthesia.[1] The formation of the toxic byproduct cyanide (CN),[2,3] however, severely limits the dosage and duration of SNP treatment and necessitates careful monitoring of blood gases and acid-base balance. Several cases of toxicity and death due to high doses of SNP, especially in children, have been reported.[1] Cyanide is detoxified to thiocyanate in the body by the mitochondrial enzyme rhodanese (thiosulfate: cyanide sulfurtransferase, EC 2.8.1.1) and a sulfur donor.[4] Since sufficient rhodanese activity is present in the body, especially in the liver, to convert many times the toxic dose of CN to thiocyanate,[5] the rate-limiting factor in the reaction appears to be the availability of the sulfur donor.

With the renewed interest in CN detoxification and in the possibility of extending the dosage of SNP in clinical situations, we studied various CN antidotes and found sodium thiosulfate to be effective in preventing CN lethality without deleterious side effects.[6] We also found little data on thiosulfate metabolism or endogenous concentration in the body.

Thiosulfate serves as a sulfur donor both *in vitro*,[5] and *in vivo*,[7] and as a substrate for the isolation and purification of rhodanese.[8–10] It has been isolated in urine[11] and appears to be an endogenous intermediate product of sulfur-containing amino acid metabolism.[12] Vassel and associates[13] observed in dogs that during fasting, the excretion of thiosulfate in urine ceases; this would suggest that the major source of thiosulfate is from food, implying that fasting patients may have low endogenous thiosulfate levels and would have decreased CN-detoxifying capability and increased risk of CN toxicity during SNP administration.

The purpose of the present study was to determine the available thiosulfate pool and pharmacokinetics of administered thiosulfate in normal volunteer subjects and in patients likely to receive SNP, to help determine the most efficacious method of thiosulfate administration during SNP infusion.

Materials and Methods

Protocols were reviewed and approved by the Committee on Experimental Drugs and Procedures. Informed consent was obtained from each subject or patient, or his parent or guardian.

Endogenous thiosulfate concentration was determined in refrigerated plasma obtained from volunteer blood samples collected by venipuncture in heparinized tubes and centrifuged. Urine samples from volunteers were freshly voided, refrigerated, and analyzed within 24 h of collection. Samples were collected without regard to time of day. In a group of normal male volunteers, 24-h urine specimens were collected on each of three consecutive days, and blood samples were taken between 0800 and 0900 h at the beginning of each 24-h period. Otherwise, these volunteers went about their normal daily activities and consumed their usual diet of food and liquids *ad lib*.

* Professor and Chairman, Anesthesiology.
† Director of Research, Anesthesiology.
‡ Clinical Assistant Professor, Pathology.
§ Clinical Associate Professor, Anesthesiology.

Received from the Department of Anesthesiology, Illinois Masonic Medical Center, and the Abraham Lincoln School of Medicine, University of Illinois, Chicago. Accepted for publication June 16, 1982.

Address reprint requests to Dr. Ivankovich: Chairman, Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, 1753 W. Congress Parkway, Chicago, Illinois 60612.

0003-3022/83/0100/0011 $01.15 © The American Society of Anesthesiologists, Inc.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/58/1/11/306521/0000542-198301000-00003.pdf by guest on 10 April 2024

Nitroprusside is routinely used in children to induce hypotension for hemostasis and in adults during aorto-coronary bypass surgery to control hypertension. In addition, cholecystectomy patients provide a unique opportunity to obtain bile samples and assess liver production of thiosulfate. Therefore, patients in whom endogenous thiosulfate was determined included two groups of children, one group ranged in age from 8 to 16 years, and come to surgery for correction of scoliosis, and the other aged 4 to 10 years, in general surgery; coronary bypass patients were 51 to 80 years old; and cholecystectomy patients were 48 to 65 years old, from whom bile samples could be collected. In children, NPO (nothing by mouth) 8–12 h, thiosulfate samples were collected before and during surgery, during SNP administration, and during a 3-h recovery period. In bypass patients, thiosulfate samples were collected before and during surgery, during bypass perfusion, and during a 72-h recovery period. Since the liver may be the principal site of CN detoxification and thiosulfate utilization, samples were obtained from cholecystectomy patients, NPO for three to several days, during recovery from surgery.

Thiosulfate disappearance curves were measured after an iv injection of sodium thiosulfate (Torigian Laboratories, Inc, Queensvillage, New York) at the therapeutic dose (for CN toxicity) of 150 mg/kg in the male volunteers at 0800 h, NPO 8–12 h, and in cholecystectomy patients postoperatively.

The methylene blue method for measuring thiosulfate was derived from an assay previously used to measure trace amounts of thiosulfate in photographic films, plates, and archival-quality prints,¶ analyzed directly on 0.5 ml of heparinized plasma or on 1 ml of urine. Zeolite (Technicon Corp., Terrytown, New York) (0.5 g) was added to bile samples, 0.5 ml diluted with 5 ml of H_2O, to absorb interfering pigments. Samples were cleared by centrifuging and the supernatant analyzed for thiosulfate. Two sets of standardized solutions, one in H_2O only and one in H_2O with added Zeolite, were analyzed with bile samples to correct for thiosulfate absorbed onto the Zeolite. Initially, when 0.5 g of Zeolite was used, recovery of thiosulfate was between 60 and 80%. After initial studies showed that the amount of Zeolite could be reduced to 0.25 g, recoveries were consistently 90 to 95% of the standards in H_2O. While bile pigment interfered with observation of color formation, urine and plasma rarely presented any problems, and recovery of added thiosulfate was above 90%. The standard range was between 1 and 10 μg/ml; concentrated samples were diluted with H_2O in this range.

¶ American National Standard Methylene Blue Method for Measuring Residual Chemicals in Films, Plates, and Papers: A.N.S.I. PH 4.8:1–12, 1971.

Five milliliters of diluent which consisted of 0.006 M KI, 0.17 M KBr, and 0.007 M KH_2PO_4 were added to each sample of plasma, urine, or diluted bile. To this was added five drops of K borohydride (0.556 M in 0.2/N NaOH, prepared fresh weekly) with stirring, 10 drops of acetone with stirring, five drops of 0.07 M $Fe_2(SO_4)_3 \cdot xH_2O$ in 2.6 M H_2SO_4, and five drops of N,*N*-dimethyl-p-phenylenediamine sulfate (1 g in 104 ml of 2.6 M H_2SO_4). The mixture was capped and vortexed for 30 s, vented, and vortexed for another 30 s. The solution was allowed to stand 10 min as the blue color developed and then the absorbance was measured at 665 nm. Thiosulfate concentration was calculated from a new standard curve determined with each analysis.

This method was found more convenient than the starch-iodometric titration method,[14] which requires deproteinization and filtration of each sample. In addition, the starch-iodometric method is subject to interference by nonspecific reducing substances, such as sulfite, in solution. The methylene blue method, which is specific for thiosulfate, was sensitive to 1 μg/ml. The coefficient of variation for repeated measurements on the same sample (10 μg/ml standard; n = 15) was 5.08%.

Creatinine and blood urea nitrogen (BUN) were measured on an SMAC (Technicon) by routine chemical analysis. Data were compared by one-way and two-way analysis of variance for repeated measurements in the same subject,[15] and individual groups were compared by the Student-Newman-Keuls technique[15] when statistical significance was observed ($P < 0.05$). Pharmacokinetic data of the plasma thiosulfate disappearance curve were fitted to a double exponential equation using a programmable calculator and the tail-subtraction method.[16] The coefficients were corrected for slow infusions by the method of Loo and Riegelman[17] and the volume of distribution and metabolic clearance rate were calculated by the method of Sapirstein *et al.*[18]

Results

Endogenous Thiosulfate Concentration (Table 1)

Plasma thiosulfate concentration, sampled from healthy volunteers ranging in age from 25 to 45 years, was 1.13 ± 0.11 mg/dl (mean ± SE; n = 26) with a range of 0.43 to 2.54 mg/dl.

Urine thiosulfate concentration was 0.28 ± 0.02 mg/dl (n = 24) with a range of 0.1 to 0.5 mg/ml. Plasma concentration in six cholecystectomy patients during surgery was the same as in nonsurgical volunteers, while the bile samples obtained during surgery

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/58/1/11/306521/0000542-198301000-00003.pdf by guest on 10 April 2024

TABLE 1. Endogenous Thiosulfate Concentration in Humans

Patient	Plasma		Urine		Bile	
	mg/dl	N	mg/dl	N	mg/dl	N
Volunteers	1.1 ± 0.1	26	0.3 ± 0.1	24	——	
Cholecystectomy						
During surgery	1.1 ± 0.1	6	——		13.7 ± 3.0	4
Postoperative	1.6 ± 0.3	4	0.3 ± 0.1	4	25.7 ± 8.8	4
Ascites or infected gall bladder	0.9 ± 0.2	5	——		2.4 ± 0.5‡	5
NPO (One to three weeks)	2.2 ± 0.6*	5	0.6 ± 0.1†	5		
Pediatric	2.3 ± 0.3†	8	0.8 ± 0.1†	8		

Values are means ± SE.
Significantly different from normal volunteers: * $P < 0.01$ and † $P < 0.001$.
‡ Significantly different from other cholecystectomy groups, $P < 0.02$.

contained 13.72 ± 2.95 mg/dl. Four different patients who had common duct drainage with a T-tube postoperatively had slightly elevated plasma thiosulfate concentrations, normal urine concentrations, and bile concentrations that were nearly twice that found in patients sampled during surgery. In five patients with either ascites or an infected gall bladder, plasma thiosulfate levels were decreased slightly, while the bile concentration was significantly lower than in the other two groups sampled.

In a variety of adult patients who had received no oral nourishment for 1 to 3 weeks, both plasma and urine had significantly higher thiosulfate concentrations than in the volunteers. Pediatric patients, ranging in age from 4 to 10 years, also had significantly increased thiosulfate concentrations in plasma and urine compared to normal values.

THIOSULFATE EXCRETION DURING 24-HOUR COLLECTIONS

Plasma thiosulfate concentration, measured in five healthy adult males on *ad lib* food and water intake, was consistent for the first 2 days of collections, but on the third morning, a significant decrease was observed (table 2). Nonsignificant changes were found in urine thiosulfate concentration, thiosulfate excretion rate, and creatinine clearances, while significant increases were found in total thiosulfate excreted and renal thiosulfate clearance on the third day of collection. The increase in thiosulfate excretion seen in the third day may have been because of apparent increased urine output (though not significant), which could have been the result of an evening social function attended by all five subjects at which wine (which contains thiosulfate) was imbibed. From the combined data, the thiosulfate tubular load (plasma thiosulfate concentration × creatinine clearance) was calculated to be approximately 1.18 mg/min. The overall thiosulfate excretion rate (urine concentration × urine flow) was 2.04 μg/min, the net excretion of thiosulfate accounting for approximately 0.17% of the tubular load, while 99.83% was reabsorbed, which would suggest active transport of thiosulfate out of the tubule.

Thiosulfate excretion and plasma and urine levels before surgery measured in four patients undergoing coronary bypass surgery were similar to normal levels (table 3). During anesthesia induction and fluid loading, plasma thiosulfate concentration decreased while urine concentration, urine flow, excretion rate, and clearance of thiosulfate increased. During cardiopulmonary bypass perfusion, the plasma concentration decreased even more while urine flow and thiosulfate excretion markedly increased. During recovery from surgery, thiosulfate excretion, renal clearance, and urine flow tended to decrease but were still higher than preoperative values (table 3). On the third postoperative day the plasma thiosulfate increased markedly above the levels of day 2 ($P < .05$), while urine flow, thiosulfate clearance, and thiosulfate excretion appeared to have stabilized at preoperative levels.

KINETICS OF THIOSULFATE

Thiosulfate, 150 mg/kg, was injected iv through indwelling venous catheters in five normal male volun-

TABLE 2. Thiosulfate Excretion in Normal Volunteers (N = 5)

	Day 1	Day 2	Day 3
Plasma (mg/dl)	1.0 ± 0.1	1.1 ± 0.2	0.7 ± 0.1*
Urine (mg/dl)	0.3 ± 0.1	0.2 ± 0.1	0.3 ± 0.1
Total urine thiosulfate (mg/24 h)	2.6 ± 0.5	2.2 ± 0.3	3.9 ± 0.6†
Thiosulfate excretion rate (μg/min)	1.8 ± 0.3	1.6 ± 0.2	2.7 ± 0.4
Thiosulfate clearance (ml/min)	0.2 ± 0.1	0.2 ± 0.1	0.4 ± 0.1*
Creatinine clearance (ml/min)	121 ± 10	137 ± 10	149 ± 13
Urine flow (ml/min)	0.7 ± 0.1	0.7 ± 0.1	0.9 ± 0.1

Values are means ± SE.
* $P < 0.05$.
† $P < 0.02$.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/58/1/11/306521/0000542-198301000-00003.pdf by guest on 10 April 2024

TABLE 3. Thiosulfate in Cardiopulmonary Bypass (CB) Patients

	Thiosulfate				
	Plasma (mg/dl)	Urine (mg/dl)	Excretion Rate (μg/min)	Clearance (ml/min)	Urine flow (ml/min)
Day 1					
Prep	1.1 ± 0.2	0.1 ± 0.02	1.1 ± 0.2	0.1 ± 0.03	0.8 ± 0.1
Anesthesia	0.8 ± 0.2	0.1 ± 0.02	3.1 ± 1.1	0.4 ± 0.1	2.5 ± 1.1*
Before bypass	0.6 ± 0.1	0.4 ± 0.03*	12.3 ± 4.5	2.1 ± 0.9	3.2 ± 1.2
60 Min on bypass	0.7 ± 0.1	0.6 ± 0.1*	36.3 ± 7.9*	6.6 ± 2.1*	6.7 ± 1.7*
End bypass	0.5 ± 0.1*	0.5 ± 0.02*	44.1 ± 7.2*	10.0 ± 2.4*	8.6 ± 1.2*
End surgery	0.8 ± 0.1	0.4 ± 0.03*	11.7 ± 3.5*	1.8 ± 0.4*	3.2 ± 0.7*
PM	0.7 ± 0.1	0.5 ± 0.03*	13.0 ± 2.5*	1.9 ± 0.3*	2.6 ± 0.2*
Day 2					
AM	0.8 ± 0.2	0.5 ± 0.1*	9.3 ± 2.7*	1.6 ± 0.5*	1.9 ± 0.3*
PM	0.5 ± 0.1	0.3 ± 0.03*	1.8 ± 0.4	0.3 ± 0.1	0.7 ± 0.1
Day 3					
AM	2.0 ± 0.7	0.2 ± 0.04	2.1 ± 0.7	0.2 ± 0.1	0.8 ± 0.2
PM	1.2 ± 0.3	0.5 ± 0.1*	5.0 ± 1.6	0.4 ± 0.2	1.1 ± 0.5
Day 4					
AM	1.0 ± 0.1	0.4 ± 0.03*	6.1 ± 2.1	0.6 ± 0.3	1.8 ± 0.6
PM	1.3 ± 0.5	0.6 ± 0.1*	9.9 ± 3.1*	1.1 ± 0.8	1.9 ± 0.5

Values are means ± SE; n = four patients. * $P < 0.05$.

teers. The preparation of 1 g/10 ml was hyperosmolar, and caused nausea and vomiting on rapid injection; thus, the material was injected over several minutes. At five minutes after injection, the plasma concentration was 101.2 ± 8.85 mg/dl in venous blood sampled from the opposite arm (fig. 1). The plasma thiosulfate concentration decreased rapidly until 180 min after injection, when the concentration was 12 ± 1 mg/dl, and then the rate of disappearance decreased so that by 18 h the concentration was 7 ± 1 mg/dl. The half-life of the distribution phase was 23 min, while that of the elimination phase was 182 min. The calculated volume of distribution was 151 ml/kg body weight, and the metabolic clearance rate, using the two-compartment model,[18] was −1.39 ml/min.

Urine concentration, clearance, and rate of thiosulfate excretion increased markedly after injection (figs. 1 and 2). Total excretion was 42.6 ± 3.5% of the injected dose at 180 min (fig. 2), but after the onset of the elimination phase, total excretion increased to only 47.4 ± 2.4% at 18 hours after injection.

Thiosulfate was injected into three patients during recovery from cholecystectomy. Since these patients were sedated, they appeared able to tolerate a more rapid iv injection (2–3 min) of 150 mg/kg, without the transient nausea experienced in normal volunteers. The maximum plasma concentration was 226 ± 45 mg/dl at 5 min after injection (table 4). These patients had an increased half-life of the distribution phase of 1.3 min, and an increased half-life of the elimination phase of 48 min, compared with the volunteers. These faster components were probably the result of increased fluid turnover produced by fluid loading and diuretic therapy during surgery. Urine flow, thiosulfate excretion, and thiosulfate clearance were increased compared with normals, so that 56% of the injected thiosulfate had been excreted by 100 min. In addition, thiosulfate clearance remained high after injection. Even with increased fluid turnover, bile flow was very slow, about 0.1 ml/min, and bile thiosulfate concentration did not change after thiosulfate injection. Bile excretion of thiosulfate accounted for less than 0.1% of total thiosulfate excretion.

THIOSULFATE DISAPPEARANCE DURING SNP ADMINISTRATION IN CHILDREN

Eight children, aged 8–16 years, NPO for 8–12 h, were anesthetized as follows: induction with thiopental; intubation with succinylcholine; maintenance with fentanyl–N_2O–O_2. Deliberate hypotension (systolic blood pressure of 70 to 80 mmHg) for hemostasis was induced during posterior spinal fusion and Harrington rod or Luque Instrumentation by a microdrip infusion of SNP, 0.01% in 5% dextrose, with continuous monitoring of arterial blood pressure via an intra-arterial catheter. The plasma thiosulfate concentration did not change significantly (fig. 3). Whole-blood CN concentrations increased during this time and reached the maximum level when SNP (46 ± 5 mg) infused over approximately 200 min, had stopped. Plasma thiocyanate concentrations (not shown in fig. 3) increased significantly during the recovery period, from 348 ± 74 μg/dl before surgery to 565 ± 45 μg/dl at two hours postoperatively.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/58/1/11/306521/0000542-198301000-00003.pdf by guest on 10 April 2024

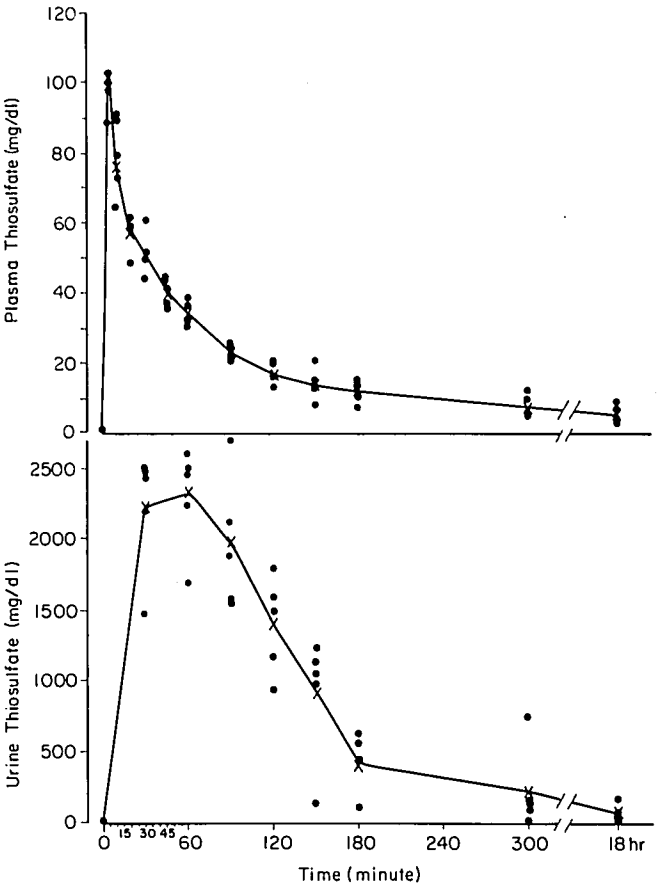

FIG. 1. Venous plasma (upper graph) and urine (lower graph) thiosulfate concentration before injection (time 0) to 300 min after iv injection of sodium thiosulfate, 150 mg/kg, in five normal volunteers. Injection began immediately after 0 time and ended before 5 min when the first plasma sample was taken. Urine samples were obtained every 30 min to 180 min. (Curve connects means for each period.)

Discussion

Our study shows that independent of dietary intake, thiosulfate is present in plasma of normal males in concentrations of about 1 mg/dl with an excretion of about 3 mg/day. Since thiosulfate is one of the end products of the metabolism of sulfur-containing amino acids such as cysteine and methionine,[12] it is probable that the elevated levels found in starving patients and children were the result of increased protein utilization. The previous study,[13] which found little or no thiosulfate in urine from fasting dogs, may have had analytical problems, that masked the thiosulfate increase.

In the present study, clearance of endogenous thiosulfate in normal males was 0.26 ± .04 ml/min, and net excretion accounted for only 0.17% of the filtered load. The majority of thiosulfate was actively reabsorbed. That these relatively low levels of thiosulfate are actively regulated by the kidney was shown by previous work in which thiosulfate was both secreted into and reabsorbed out of the tubule at separate sites, while the drug carinamide inhibited secretion without affecting reabsorption.[19,20] Micropuncture studies have confirmed these earlier observations.[21]

Thiosulfate is utilized as a sulfur donor for various reactions, including detoxifying CN which is normally present in very low concentrations, from 0 to 5 μg/dl in nonsmokers and up to 15 μg/dl in smokers.[22] Only a small amount of thiosulfate is excreted in the bile, and tissue thiosulfate metabolism appears to be relatively slow. In view of our data that normal males excrete only 3 mg/day, the normal production of thiosulfate by the body may be quite small and its ability to produce increased amounts in response to toxic substances may be limited. Further evidence of this limited production was found in children given SNP; endogenous plasma thiosulfate levels did not change significantly while CN levels were increasing, thus suggesting limited utilization of extracellular thiosulfate for CN detoxification and the children's inability to handle a CN load by mobilizing thiosulfate stores. Since thiosulfate levels remained near baseline levels even two hours after SNP was discontinued, and since some intracellular thiosulfate was utilized for CN detoxification as indicated by the in-

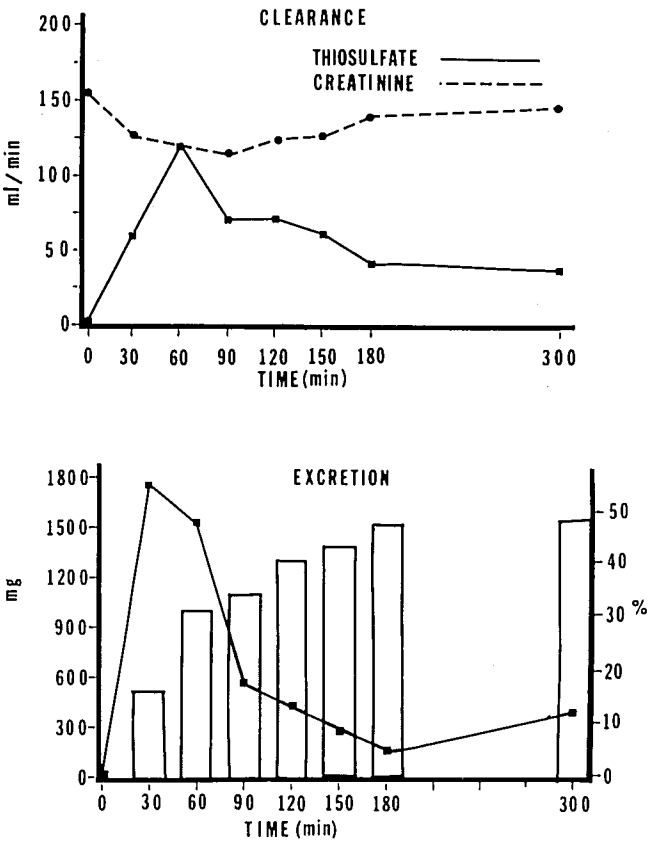

FIG. 2. Upper graph: Standard renal clearances of thiosulfate and creatinine measured in five volunteers (fig. 1) before (time 0) and after thiosulfate injection. Lower graph: Curve represents total excretion of thiosulfate for each time period; histogram depicts cumulative excretion as per cent of injected dose.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/58/1/11/306521/0000542-198301000-00003.pdf by guest on 10 April 2024

TABLE 4. Thiosulfate Kinetics in Normal Volunteers and Cholecystectomy Patients*

Minutes	Plasma (mg/dl)	Urine (mg/dl)	Bile (mg/dl)	Thiosulfate Clearance (ml/min)	Thiosulfate Excretion (mg/min)	Excretion/Injection % (ratio)	Urine Flow ml/min
Normal Volunteers; n = 5							
Control	1.0 ± 0.1	0.1 ± 0.03	—	0.1 ± 0.01	0.001 ± 0	—	0.6 ± 0.1
5	101 ± 6	—	—	—	—	—	—
10	76 ± 6	—	—	—	—	—	—
20	57 ± 3	—	—	—	—	—	—
30	51 ± 3	2,236 ± 281	—	59.1 ± 17.7	37.7 ± 11.0	15 ± 4	1.7 ± 0.4
45	40 ± 2	—	—	—	—	—	—
60	35 ± 1	2,311 ± 166	—	119.5 ± 18.5	48.6 ± 7.7	28 ± 2	2.2 ± 0.4
90	23 ± 0.7	1,982 ± 222	—	70.8 ± 17.5	18.5 ± 9.1	33 ± 3	0.9 ± 0.2
120	17 ± 1	1,400 ± 152	—	71.1 ± 7.3	14.6 ± 1.9	36 ± 3	1.1 ± 0.1
150	14 ± 2	894 ± 207	—	61.0 ± 10.8	9.6 ± 1.8	39 ± 4	1.0 ± 0.1
180	12 ± 1	429 ± 121	—	41.5 ± 5.8	5.3 ± 0.7	43 ± 4	1.0 ± 0.1
300	8 ± 1	239 ± 134	—	36.9 ± 24.6	2.4 ± 1.6	43 ± 3	0.8 ± 0.1
18 hours	7 ± 1	46 ± 45	—	3.2 ± 3.1	0.2 ± 0.2	47 ± 2	0.8 ± 0.2
Cholecystectomy Patients; n = 3							
Control	1.6 ± 0.3	0.3 ± 0.1	25.7 ± 8.8	0.8 ± 0.4	0.014 ± 0.35	—	7.5 ± 2.7
5	226 ± 45	229 ± 83	—	12.7 ± 2.9	31.2 ± 12.3	1 ± 0.4	13.3 ± 1.2
10	142 ± 22	1,280 ± 426	—	88.4 ± 29.8	138.3 ± 61.9	7 ± 3	9.8 ± 1.6
20	126 ± 28	1,534 ± 15	—	136.8 ± .5	171.7 ± 39.0	21 ± 6	11.3 ± 2.7
40	73 ± 10	1,230 ± 9	22.4 ± 2.6	113.3 ± 9.5	80.0 ± 4.9	34 ± 7	6.5 ± 1.4
70	59 ± 14	828 ± 141	—	94.6 ± 8.1	53.0 ± 8.4	47 ± 8	7.2 ± 2.2
100	38 ± 11	629 ± 91	18.8 ± 8.5	104.5 ± 4.1	38.8 ± 10.3	56 ± 11	7.0 ± 2.7

* Injections of thiosulfate were given in doses of 150 mg/kg.

crease in plasma thiocyanate, replenishment of thiosulfate stores is probably a slow process. How much SNP can be detoxified by endogenous thiosulfate? The volume of distribution of thiosulfate was found to be 150 ml/kg, which agrees with previous work by Gilman's group.[23] A 70-kg man would have a total extracellular thiosulfate content of approximately 126 mg, or 1.12 mM. Since SNP contains five potential CN molecules, 66 mg of SNP can be detoxified under ideal conditions. However, thiosulfate must be present at three times higher than theoretic concentrations to act as a substrate for the mitochondrial rhodanese,[8] indicating that even less than 50 mg of SNP, the standard vial content, can be safely detoxified by endogenous thiosulfate. The rec-

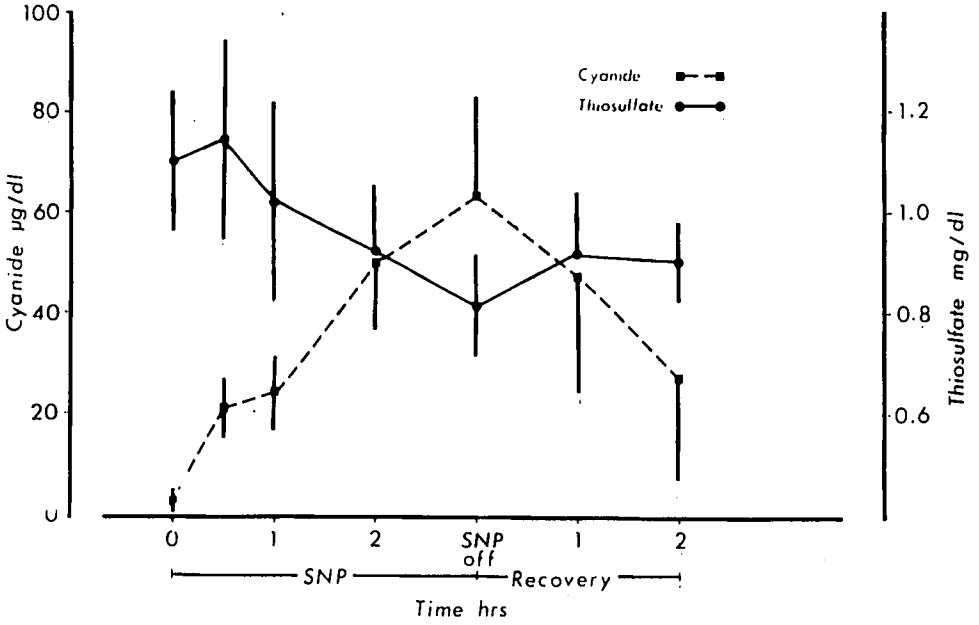

FIG. 3. Whole-blood cyanide and plasma thiosulfate concentrations in eight children, aged 8 to 16 years, before (time 0), during, and after surgery. During surgery they received an infusion of sodium nitroprusside (SNP) to reduce systolic blood pressure to 70–80 mmHg. Left ordinate and broken curve represent CN. Right ordinate and solid line represent thiosulfate. Vertical bars represent standard errors.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/58/1/1/306521/0000542-198301000-00003.pdf by guest on 10 April 2024

ommended maximum safe dose of SNP, based upon clinical experience, is 1–1.5 mg/kg.[1]

When volunteer subjects or patients were given a therapeutic-dose bolus iv injection of thiosulfate, plasma concentration increased rapidly and then decayed exponentially as the result of distribution and equilibration in the ECF and also as a result of rapid renal excretion. In fact, 60 min after injection, thiosulfate clearance increased until it equalled creatinine clearance. In our three, well-hydrated cholecystectomy patients with high urine flows, thiosulfate clearance appeared to remain elevated, so that in these patients the majority of injected thiosulfate was eliminated by 100 min.

At therapeutic doses thiosulfate plasma concentration increases approximately 100 times. Since thiosulfate is a large divalent anion that does not readily enter the cell, and is rapidly excreted,[23] such high extracellular concentrations may be needed to increase the intracellular concentration, with detoxification of CN probably taking place at the mitochondrial membrane where rhodanese is present.

From these data it is apparent that the body does not have enough endogenous thiosulfate to cope with increased CN loads. In addition, the rapid distribution and renal excretion of thiosulfate suggest that bolus injections during SNP infusion will not maintain the high plasma concentrations of thiosulfate necessary for detoxification.[6,24,25] Previous work has shown that a constant infusion of thiosulfate will prevent lethality from SNP-derived CN[24,25] and that thiosulfate can act rapidly enough to prevent lethality from infused CN directly.[6] In recent studies with dogs,[25] we found that in addition to its ability to rapidly detoxify CN, thiosulfate administration did not appear to produce any deleterious side effects and was not antagonistic to the desired hemodynamic effects of SNP. Therefore, our observations of low endogenous stores of thiosulfate suggest that thiosulfate definitely should be administered when infusion of SNP will be prolonged over several hours. Since thiosulfate is cleared rapidly from the plasma, maintenance of the high plasma concentrations of thiosulfate necessary for CN detoxification can best be accomplished by continuous infusion.

The authors thank Dr. Frank Selini, M.D., Chairman, Department of Anesthesiology, Children's Memorial Hospital, Chicago, for his cooperation and Mr. Ninos Joseph for his expert technical assistance.

References

1. Ivankovich AD, Miletich DJ, Tinker JH: Sodium nitroprusside: Metabolism and general considerations. Int Anesthesiol Clin 16:1–29, 1978
2. Page IH, Corcoran AC, Dustan HP, Koppanyi T: Cardiovascular actions of sodium nitroprusside in animals and hypertensive patients. Circulation 11:188–198, 1955
3. Michenfelder JD: Cyanide release from sodium nitroprusside in the dog. ANESTHESIOLOGY 46:196–201, 1977
4. Lang K: Die Rhodanbildung im Tierkorper. Biochem Z 250:243–256, 1933
5. Saunders JP, Himwich WA: Properties of the transulfurase responsible for the conversion of cyanide to thiocyanate. Am J Physiol 163:404–409, 1950
6. Ivankovich AD, Braverman B, Kanuru RP, Heymen HJ, Paulissian R: Cyanide antidotes and methods of their administration in dogs: A comparative study. ANESTHESIOLOGY 52:210–216, 1980
7. Chen KK, Rose CL, Cloves GHA: Comparative values of several antidotes in cyanide poisoning. Am J Med Sci 188:767–781, 1934
8. Sörbo BH: Crystalline rhodanese. I. Purification and physicochemical examination. Acta Chem Scand 7:1129–1136, 1953
9. Horowitz PM: Purification of thiosulfate sulfurtransferase by selective immobilization on blue agrose. Anal Biochem 86:751–753, 1978
10. Horowitz PM, Patel K: Some comparisons between solution and crystal properties of thiosulfate sulfurtransferase. Biochem Biophys Res Commun 94:419–423, 1980
11. Fromageot C, Royer A: La presence constante du thiosulfate dans l'urine des animaux superieurs et sa signification physiologique. Enzymologia 45:361–372, 1943–1945
12. Kun E: The metabolism of sulfur-containing compounds, Metabolic Pathways. Edited by Greenberg DM. New York, Academic Press, 1961, pp 237–259
13. Vassel B, Patridge R, Crossley ML: The chemistry of infectious diseases: VII. An investigation of the excretion of certain urinary constituents during type I pneumococcal pneumonia in dogs. Arch Biochem 4:59–74, 1944
14. Brun C: Thiosulfate as a measure of the glomerular filtration rate in normal and diseased human kidneys. Acta Med Scand (Suppl) 234:63–70, 1946
15. Winer BJ: Statistical Principles in Experimental Design. First edition. New York, McGraw-Hill Book Co, 1972, pp 298–318
16. Riggs DS: The Mathematical Approach to Physiological Problems. Cambridge, The M.I.T. Press, 1963, pp 120–167
17. Loo JCK, Riegelman S: Assessment of pharmacokinetic constants from postinfusion blood curves obtained after I.V. infusion. J Pharm Sci 59:53–55, 1970
18. Sapirstein LA, Vidt IG, Mandel MJ, Hanusek G: Volume of distribution and clearances of intravenously injected creatine in the dog. Am J Physiol 181:330–336, 1955
19. Lebrun J: Etude de la clearance de l'hyposulfite de soude chez l'homme a basse concentration sanguine. J Urol 55:745–757, 1949
20. Bucht H: On the tubular excretion of thiosulfate and creatinine under the influence of carinamide. Scand J Clin Lab Invest 1:270–276, 1949
21. Ullrich KJ, Rumrich G, Kloss S: Bidirectional active transport of thiosulfate in the proximal convolution of the rat kidney. Pfluegers Arch 387:127–132, 1980
22. Feldstein M, Klendshoj NC: Determination of cyanide in biologic fluids by micro-diffusion analysis. J Lab Clin Med 44:166–170, 1954
23. Gilman A, Philips FS, Koelle ES: The renal clearance of thiosulfate with observations on its volume of distribution. Am J Physiol 146:348–357, 1946
24. Michenfelder JD, Tinker JH: Cyanide toxicity and thiosulfate protection during chronic administration of sodium nitroprusside in the dog. Correlation with a human case. ANESTHESIOLOGY 47:441–448, 1977
25. Ivankovich AD, Braverman B, Klowden AJ, Heyman HJ: Prevention of nitroprusside toxicity with thiosulfate in dogs. Anesth Analg (Cleve) 61:120–126, 1982

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/58/1/11/306521/0000542-198301000-00003.pdf by guest on 10 April 2024