Comparison of S-Adenosyl-l-methionine and N-Acetylcysteine Protective Effects on Acetaminophen Hepatic Toxicity

Marcus V. Terneus, K. Kelley Kiningham, A. Betts Carpenter, Sarah B. Sullivan, and Monica A. Valentovic

Department of Pharmacology, Physiology and Toxicology (M.V.T., K.K.K., S.B.S., M.A.V.); Department of Pathology (A.B.C.); and Marshall University, Joan C. Edwards School of Medicine, Huntington, West Virginia

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ABSTRACT

Nutraceuticals are widely used by the general public, but very little information is available regarding the effects of nutritional agents on drug toxicity. Excessive doses of acetaminophen (APAP, 4-hydroxyacetanilide) induce hepatic centrilobular necrosis. The naturally occurring substance S-adenosyl-l-methionine (SAMe) has been reported to reduce the hepatic toxicity of APAP. The present study was designed to investigate the hepatoprotective effects of SAMe in comparison to the clinically used antidote N-acetylcysteine (NAC). Male C57BL/6 mice were injected intraperitoneally (i.p.) with an equimolar dose (1.25 mmol/kg) of either SAMe or NAC just before APAP, and the groups were denoted SAMe/H11001 APAP and NAC/H11001 APAP, respectively. Mice were immediately injected i.p. with 300 mg/kg APAP, and hepatotoxicity was evaluated after 4 h. SAMe was more hepatoprotective than NAC at a dose of 1.25 mmol/kg as liver weight was unchanged by APAP injection in the SAMe+APAP group, whereas liver weight was increased in the NAC+APAP group. SAMe was more hepatoprotective for APAP toxicity than NAC, because alanine aminotransferase levels were lower in the SAMe+APAP. Pretreatment with SAMe maintained total hepatic glutathione (GSH) levels higher than NAC pretreatment before APAP, although total hepatic GSH levels were lower in the SAMe+APAP and NAC+APAP groups than the vehicle control values. Oxidative stress was less extensive in the SAMe+APAP group compared with the APAP-treated mice as indicated by Western blots for protein carbonyls and 4-hydroxynonenal-adducted proteins. In summary, SAMe reduced APAP toxicity and was more potent than NAC in reducing APAP hepatotoxicity.

Acetaminophen (APAP) or N-(4-hydroxyphenyl acetamide) is a commonly used over the counter medication contained in more than 125 products within the United States. APAP is widely used as an antipyretic and analgesic agent. APAP in excessive doses can induce hepatic centrilobular necrosis (Davidson and Eastham, 1966; McJunkin et al., 1976). Acute administration in animals can induce similar damage to the liver within the centrilobular region (Mitchell et al., 1973a,b; Jollow et al., 1973).

APAP hepatotoxicity requires cytochrome P450-mediated formation of the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI) (Mitchell et al., 1973b). Glutathione (GSH) is crucial in detoxification of NAPQI. However, when excessive amounts of APAP are ingested, the formation of NAPQI is greater than the supply of GSH resulting in depletion of intracellular stores of GSH and hepatic damage.

S-Adenosyl-l-methionine (SAMe) has been shown to reduce APAP hepatotoxicity by our laboratory (Valentovic et al., 2004) as well as others (Stramentinoli et al., 1979; Bray et al., 1992; Carrasco et al., 2000; Song et al., 2003). SAMe administration just before APAP treatment greatly diminished the extent of centrilobular necrosis in C57BL/6 male mice compared with animals given APAP (Valentovic et al., 2004). SAMe has also shown beneficial effects in reducing and reversing hepatic damage induced by alcohol in humans (Lieber, 2002) and in intrahepatic cholestasis (Frezza et al., 1990).

SAMe is a naturally occurring substance present in plasma and most tissues. SAMe is commercially available and marketed worldwide as a nutritional supplement that is readily available in vitamin and health food stores. SAMe is the principal methyl donor within the body for transmethylation.
reactions. The major site of transmethylation reactions is the liver. SAMe is also a vital precursor for the trans-sulfuration pathway. The final product of the trans-sulfuration pathway is glutathione. SAMe is metabolized to S-adenosylhomocysteine (SAH) and then to homocysteine by a hydrolyase enzyme. Homocysteine is converted to cystathionine by cystathionine β-synthase, and cystathionine is subsequently converted to cysteine, a precursor for GSH, by γ-cystathionase (Lu, 1998). Cysteine is subsequently converted by glutamate-cysteine ligase (EC 6.3.2.2), the rate-limiting enzyme in GSH synthesis, to γ-glutamylcysteine, which is finally converted by GSH synthetase to GSH.

N-Acetylcysteine (NAC) is the current clinical treatment for APAP overdose. Hepatic GSH depletion is a critical component in the development of hepatic necrosis resulting in an increase in NAPQI (Nelson and Bruschi, 2003), which reacts with protein macromolecules and causes cell damage. NAC reduces APAP hepatic toxicity by increasing GSH levels and maintaining thiol status (Corcoran and Wong, 1986). NAC reduces APAP hepatic damage by providing cysteine as a precursor for GSH (Lauterburg et al., 1983; Corcoran et al., 1985a,b).

As mentioned above, NAC is the standard clinical antidote for APAP hepatic overdose. Evaluation of a potential antidote, such as SAMe, would necessitate a comparison to NAC. The current study was designed to evaluate the protective effect of SAMe on APAP hepatic toxicity in comparison to the current antidote NAC. The potential beneficial effect of SAMe to reduce APAP hepatic toxicity can be properly evaluated only after comparison to the standard antidote of NAC. Comparisons were made of the protective effect of an equimillimole dose of NAC and SAMe on APAP hepatic toxicity to evaluate the potency of SAMe. The present study further explored the potential property of SAMe to modify APAP-mediated oxidative stress.

Materials and Methods

Materials. SAMe was used in all studies as the toluenesulfonate salt (Sigma Chemical Co., St. Louis, MO). Malondialdehyde was purchased from Aldrich Chemical Company (St. Louis, MO). Glutathione, NADPH, 2-vinylpyridine, thiobarbituric acid, and all other reagents were purchased from Sigma Chemical Co. The ALT reagent kit (TR-71021) was purchased from Thermo Electron Corporation (Louisville, CO).

Animals. All studies were conducted in 4 to 5-week-old male C57BL/6 mice weighing 16 to 20 g, which were obtained from Hilltop Lab Animals Inc. (Scottsdale, PA). The protocol was approved by the University Committee on Animal Care and Use. Mice were housed in a facility accredited by the American Association for Accreditation of Laboratory Animal Care. Mice were maintained under a controlled ambient temperature (21–23°C), humidity (40–55%), and 12-h light cycle (lights on 6:00 AM to 6:00 PM). Mice were acclimated for 7 days before initiation of any procedures. Animals had free access to water and Purina rodent chow before initiation of any treatment. However, mice were fasted before treatment with APAP as indicated below.

SAme and NAC Treatments Just before APAP. Mice were randomly divided into the following groups: vehicle-treated (VEH); APAP-treated (APAP), SAMe-treated (SAMe), SAMe-pretreated plus APAP (SAMe+APAP), NAC (NAC), and NAC-pretreated plus APAP (NAC+APAP). Each group contained five to 10 different mice/group. Mice were fasted for 16 h before injection of APAP beginning with the removal of food at 5:00 PM on the previous day. Mice in the SAMe and SAMe+APAP groups were injected i.p. with 1.25 mmol/kg (5 ml/kg) SAMe at 9:00 AM. Mice in the NAC and NAC+APAP groups were injected i.p. with 1.25 mmol/kg (5 ml/kg adjusted to pH 7) NAC. Immediately after treatment with SAMe or NAC, mice in the APAP, SAMe+APAP, and NAC+APAP groups were injected i.p. with 300 mg/kg APAP (15 ml/kg in warm water). The VEH group was injected i.p. with water at an equivalent volume (15 ml/kg). Mice were anesthetized with carbon dioxide 4 h after APAP administration. Blood was collected by cardiac puncture using heparin-rinsed 1-ml syringes (20-gauge needles) for determination of ALT activity, a biomarker of liver injury. The livers were isolated, collected on ice, rinsed in ice-cold Krebs buffer, blotted, and weighed.

NAC High-Dose Treatment Given Just before APAP. Studies were done with a higher dose of NAC reported by other investigators to provide complete protection (Corcoran et al., 1985a,b; James et al., 2003) to validate our model. Mice were divided into the following groups: VEH, APAP, NAC (NAC-H), and NAC-pretreated plus APAP (NAC-H+APAP). Each group contained five to 10 different mice/group. Animals were fasted overnight for 16 h. Mice were injected with 7.35 mmol/kg NAC (5 ml/kg in water adjusted to pH 7). Immediately after injection of NAC-H, mice were injected i.p. with 300 mg/kg APAP. Mice were anesthetized with carbon dioxide 4 h after APAP. Blood was collected via cardiac puncture. The liver was quickly excised and rinsed in ice-cold buffer.

Serum Enzyme Assay. Blood was collected for measurement of ALT levels. Plasma was collected following centrifugation of blood for 15 min at 9000g in a microcentrifuge. Plasma was stored at 4°C until ALT levels were measured. ALT levels were measured using an enzymatic kit (TR-71021) obtained from Thermo Electron Corporation.

Glutathione Determination. Tissues (200 mg) were homogenized in 500 μl of 0.5% sulfosalicylic acid and adjusted to a 1-ml volume. Total glutathione was determined using a glutathione reductase and NADPH-coupled reaction with 5,5'-dithiobis(2-nitrobenzoic acid) (Griffith, 1980; Andersen, 1985) and expressed as nanomole/gm tissue. Glutathione disulfide (GSSG) was measured following 2-vinylpyridine derivatization (Griffith, 1980) and expressed as nanomole/gm tissue.

Lipid Peroxidation. Liver (200 mg) was homogenized in 1 ml of Krebs buffer, and the homogenizer probe was rinsed with an additional 1 ml of Krebs buffer. Lipid peroxidation was measured as described previously (Valentovic et al., 2002). The amount of malondialdehyde (MDA) was calculated based on a standard curve (range 1–40 nmol) using MDA (Aldrich Chemical Company) and expressed as micromoles of MDA/milligram of protein.

4-Hydroxynonenal Adducts. Western blot was used to analyze for the presence of 4-hydroxynonenal (4-HNE) protein adducts. For each sample, 150 μg of protein was analyzed following a boiling period of 5 min. Samples and standards were run on polyacrylamide gel (12.5% acrylamide). The gel was then transferred to a nitrocellulose membrane. To verify efficiency of transfer, the membrane was placed in Ponceau S stain for visualization. The membrane was then rinsed with H2O at room temperature under constant shaking to remove stain. Nonspecific protein binding was blocked with milk at room temperature under constant shaking for 1 h. Rabbit polyclonal antibody to (E)-4-hydroxynonenal (anti-HNE polyclonal antibody) (ALX-210-767, 1:1000; Alexis Biochemicals, San Diego, CA) was added and incubated overnight at 4°C under constant shaking. The membrane was then rinsed three times in Tris-buffered saline plus Tween 20. The secondary antibody, goat anti-rabbit linked with horseradish peroxidase (1:3000), in blocking buffer was added and incubated at room temperature under constant shaking for 90 min. The membrane was rinsed three times in Tris-buffered saline plus Tween 20 and developed using enhanced chemiluminescent substrate for visualization of 4-HNE-adducted proteins.

Protein Carbonyl. Protein carbonyls were evaluated to assess whether SAMe reduced APAP-mediated oxidative stress relative to
No differences were observed in the body weights between groups.

S staining was used on all gels to ensure that protein additions were comparable among all samples. The protein carbonyls were run with DNP-derivatized molecular weight standards.

**Histological Preparation.** A segment of liver was fixed in 15 ml of neutral buffered formalin solution. The tissues were embedded in Paraplast and processed. The tissue was sectioned into approximately 4-µm thickness and stained with hematoxylin and eosin (H&E). The tissues were viewed with a Nikon light microscope for evidence of hepatic necrosis.

**Statistical Analysis.** Values represent Mean ± S.E.M. with n = 5–10 animals/group. Differences between groups were analyzed using an analysis of variance followed by a Tukey’s test (SigmaStat; SPSS Inc. Chicago, IL). All statistical analyses were conducted using a 95% confidence interval.

### Results

#### Liver Weight, Plasma ALT, and Liver Histological Evaluation

Body weights were comparable between all treatment groups (Table 1). APAP increased liver weight within 4 h compared with the VEH group (Table 1). Treatment with NAC or SAMe had no affect on liver weight, because values were comparable to the VEH group. Liver weight was not elevated in the SAMe + APAP group after APAP injection (Table 1), as liver weight was similar to the VEH and SAMe groups. Treatment with an equimolar dose of NAC just before APAP injection (NAC + APAP) resulted in elevated liver weight compared with the VEH and NAC groups. Liver weight values were similar between the APAP and NAC + APAP groups. These findings indicated that, when comparing equimolar (1.25 mmol/kg) treatment of SAMe and NAC just before APAP injection, SAMe provided better protection than NAC. Administration of a higher dose (7.35 mmol/kg) NAC resulted in the best protection of liver weight, as the NAC-H + APAP group was similar to the

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No differences were observed in the body weights between groups.

NAC. Hepatic tissue was weighed and homogenized in 1 ml of Krebs buffer pH 7.4, and the homogenizer probe was rinsed with 1 ml of Krebs buffer. The homogenate was adjusted to 2 ml. An aliquot (200 µl) was used for protein determination using a Coomassie Blue spectrophotometric method. The appearance of protein carbonyls was measured using a protein carbonyl Protein Oxidation OxyBlot kit (Chemicon). The principle of the method is that modification of proteins by the addition of carbonyl side chains due to oxidative stress are derivatized to 2,4-dinitrophenylhydrazine (DNP) following addition of 2,4-dinitrophenylhydrazine. The antibody is specific for the DNP moiety on a protein.

Tissue samples were adjusted to ensure equivalent protein, and volumes were added to gels. Samples and standards were run on polyacrylamide gel (12.5% acrylamide). The gel was then transferred to a nitrocellulose membrane. To verify efficiency of transfer, the membrane was placed in Ponceau S stain for visualization. Ponceau S staining was used on all gels to ensure that protein additions were comparable among all samples. The protein carbonyls were run with DNP-derivatized molecular weight standards.

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No differences were observed in the body weights between groups.
NAC-H group. Experiments were not conducted with an equimolar 7.35 mmol/kg dose of SAMe due to solubility issues and the cost of SAMe.

Normal morphology was observed in the VEH, SAMe, and NAC groups following light microscopic examination of H&E-stained hepatic tissues (Figs. 1, A and B, and 2, A and B). Examination of the VEH group indicated 10/10 mice had no evidence of hepatic necrosis. Examination of the SAMe and NAC groups showed that 10/10 mice for each group had <5% cells with hepatic necrosis. Extensive zonal centrilobular necrosis was evident in the APAP group (Fig. 1C). Examination of APAP-treated tissue indicated that 5/5 animals had marked centrilobular necrosis as indicated by >40% necrotic cells. The extent of centrilobular necrosis was less severe in the SAMe+APAP group (Fig. 1D) compared with the APAP-treated mice. The SAMe+APAP group had less centrilobular necrosis as 1/5 had mild degeneration (10–25% necrotic cells), 3/5 had moderate lesions (25–40% necrotic cells), and only 1/5 with >40% necrotic cells. An equimolar dose of 1.25 mmol/kg NAC given just before APAP resulted in some protection, but necrotic lesions were apparent around the centrilobular region (Fig. 2C). The NAC+APAP group exhibited 3/5 with marked centrilobular necrosis (>40% necrotic cells) and 2/5 with moderate lesions (25–40% necrotic cells). Thus, the protection by 1.25 mmol/kg NAC (NAC+APAP) was not as extensive as SAMe+APAP. As a positive control, treatment with 7.35 mmol/kg NAC (NAC-H) just before APAP resulted in the best protection, because the NAC-H+APAP mice exhibited normal structure and 5/5 mice had very moderate degeneration (10–25% necrotic cells) of the centrilobular region (Fig. 2D).

ALT levels were evaluated in plasma collected 4 h after vehicle or APAP injection. ALT values were similar in the VEH, SAMe, and NAC groups (Table 2), suggesting normal hepatic function. APAP administration resulted in the highest increase in ALT levels, which were approximately 100-fold higher than VEH values. The 1.25 mmol/kg NAC dose given just before APAP did not reduce ALT levels in the NAC+APAP group compared with the APAP group. Treatment with 1.25 mmol/kg SAMe did provide partial protection from APAP toxicity because ALT levels were reduced in the SAMe+APAP group treatment relative to the APAP and NAC+APAP group, providing support for the conclusion that SAMe does reduce APAP hepatic toxicity.

**Glutathione and Glutathione Disulfide after APAP Treatment.** Total hepatic GSH levels were comparable among VEH, SAMe, and NAC groups (Figs. 3–6), which suggest that total hepatic GSH levels were not increased by
SAMe or NAC treatment. Total hepatic GSH was extensively diminished within 4 h after APAP injection (Figs. 3–6) as GSH levels were decreased over 90% in the APAP group compared with VEH, SAMe, or NAC values. SAMe administration just before APAP partially reversed the depletion of total hepatic GSH (Fig. 3). GSH levels were higher in the SAMe/H11001 APAP group than in the APAP group but were lower than the SAMe and VEH groups, suggesting that the 1.25 mmol/kg dose of SAMe was able to partially maintain hepatic thiol levels in APAP-treated mice.

Total hepatic GSH levels in the 1.25 mmol/kg NAC+APAP group were comparable to mice treated with APAP (Fig. 4). A comparison of hepatic GSH values between groups showed that SAMe+APAP were higher than NAC+APAP values (Fig. 5) and that SAMe+APAP was able to provide a higher GSH level. These results suggest that, at the 1.25 mmol/kg dose, SAMe was more potent than NAC at protecting the liver from APAP-mediated GSH depletion (Fig. 5).

As a positive control, experiments were conducted to validate NAC attenuation of APAP toxicity. Treatment with the higher dose (7.35 mmol/kg) of NAC (NAC-H) just before APAP (NAC-H+APAP) maintained total hepatic GSH at a level comparable to VEH and NAC groups (Fig. 6), confirming that 7.35 mmol/kg NAC was the most effective dose at preventing APAP-mediated hepatic toxicity. These results were also consistent with the normal morphology observed by light microscopy of hepatic tissues.

APAP-mediated oxidative stress resulted in a higher percentage of hepatic GSSG (Figs. 7–9) when measured 4 h after APAP injection. The percentage GSSG was not affected by equimolar dose of either SAMe or NAC, as the levels were similar among the VEH, SAMe, and NAC groups (Figs. 7 and 8). Pretreatment with 1.25 mmol/kg SAMe (SAMe+APAP) or NAC (NAC+APAP) did not alter the percentage of GSSG...
after APAP injection (Figs. 7–8). Although not statistically different, the NAC/H11001 APAP group had a trend of higher GSSG than the APAP group, whereas the levels had a trend of being lower in the SAMe/H11001 APAP group. Treatment with a high dose of NAC (NAC-H) was able to reduce oxidative stress, because the percentage of GSSG in the NAC-H+APAP group was comparable to VEH and NAC-H values (Fig. 9).

Western Blot Analysis of Protein Carbonyls and 4-HNE. The profile for protein carbonyls was similar between VEH and SAMe groups (Fig. 10), as well as VEH and NAC groups (Fig. 11), suggesting that the extent of protein carbonyl formation was similar among VEH, SAMe, and NAC groups. Western blot analysis showed that protein carbonyls were elevated 4 h after APAP treatment, consistent with an induction of oxidative stress. Increased protein carbonyl-positive staining was noted between 37 and 82 kDa compared with VEH, SAMe, and SAMe+APAP groups (Fig. 10). These results suggest that SAMe reduces APAP-mediated oxidative stress in hepatic tissue. NAC treatment at an equimolar dosage of 1.25 mmol/kg just before APAP (NAC+APAP) did not reduce protein carbonyl formation in hepatic tissue (Fig. 11). The lack of a protective effect on protein carbonyls in the NAC+APAP group was consistent with the greater decline in GSH observed in the NAC+APAP compared with the SAMe+APAP group (Fig. 5). Western blots for 4-HNE indicated an increase in 4-HNE antibody-positive stained bands after APAP treatment between 37 and 115 kDa (Figs. 12 and 13). The SAMe+APAP group exhibited less band intensity than the APAP-treated liver tissue at the 37- to 115-kDa bands. The NAC+APAP group was comparable to the APAP group for the profile of bands between 64 and 115 kDa, which were not as apparent in the VEH and NAC groups. These results were in agreement with the hepatic GSH measurements and the protein carbonyl Western blots.
Discussion

The objective of the present study was to compare the protective effects of NAC and SAMe for APAP toxicity. The present study showed that SAMe was effective at a lower dose than NAC when administering an equivalent millimolar dose. These results suggest that 1) SAMe is effective in reducing APAP hepatotoxicity and that 2) SAMe is more potent than NAC in reducing hepatic damage in the mouse model.

NAC is the drug of choice for emergency room treatment of APAP overdose (Kerr et al., 2005). NAC diminishes hepatic APAP toxicity by increasing glutathione levels and reducing the extent of hepatic glutathione depletion (Lauterburg et al., 1983; Corcoran et al., 1985a,b). Glutathione is critical for conjugation with the reactive metabolite of APAP, and treatment with NAC allows generation of sufficient levels of glutathione to react with the toxic intermediate NAPQI and prevent hepatic necrosis (Lauterburg et al., 1983; Corcoran et al., 1985a,b). When hepatic glutathione is depleted by APAP, NAPQI induces cell damage by arylation of hepatic proteins.

Although NAC is the drug of choice for APAP overdose, it is associated with a variety of adverse effects (Kao et al., 2003). NAC is also not entirely protective for APAP toxicity. Therefore, other agents should be examined for their effectiveness. Beneficial protective effects for APAP hepatotoxic-
ity have been reported for clofibrate (Chen et al., 2002), ribose cysteine (Lucas et al., 2000; Lucas Slitt et al., 2005, 1-cysteine glutathione-mixed disulfide (Berkeley et al., 2003), and 2(RS)-n-propylthiazolidine-4(R)-carboxylic acid (Srinivasan et al., 2001). The mechanism of APAP protection may be different between these agents and remains to be completely identified for clofibrate. Ribose cysteine, 1-cysteine glutathione disulfide, ribose cysteine, and 2(RS)-n-propylthiazolidine-4(R)-carboxylic acid act as a provider of cysteine. The cysteine would then provide a sufficient cysteine to the liver to increase GSH synthesis and reduce hepatic GSH depletion after APAP overdose.

SAMe has been previously reported by our laboratory (Valentovic et al., 2004) as well as others (Stramentinoli et al., 1979; Bray et al., 1992; Carrasco et al., 2000) to reduce APAP toxicity. SAMe is a substrate for the trans-sulfuration pathway, which converts homocysteine ultimately to glutathione (Lu, 1998). A potential mechanism for SAMe reduction of APAP hepatotoxicity may involve maintenance of hepatic glutathione levels, which would diminish hepatic glutathione depletion and NAPQI interaction with cellular components to induce necrosis.

In our studies, hepatic glutathione levels were higher in the SAMe+APAP group compared with the APAP-treated mice, suggesting that SAMe was able to reduce the extent of APAP-mediated glutathione depletion. The SAMe+APAP group also had higher hepatic glutathione levels than the NAC+APAP group when comparing the equimolar dose (1.25 mmol/kg SAMe and NAC), suggesting better potency for SAMe. Glutathione levels are essential in preventing APAP toxicity, because the NAC-H+APAP group treated with 7.35 mmol/kg NAC maintained hepatic glutathione levels after APAP treatment at a level comparable to VEH and NAC-H levels.

Oxidative stress has been implicated to have a role in APAP toxicity. 4-HNE is an aldehyde that is generated during lipid peroxidation, which can impair cellular function (Hartley et al., 1999). 4-HNE can attach to cellular proteins by a 1,4-Michael addition to certain amino acids, such as cysteine and lysine (Esterbauer et al., 1991). 4-HNE-positive stained bands between 37 and 115 kDa were apparent within 4 h after APAP treatment (Figs. 12–13). Oxidative stress was reduced by SAMe pretreatment, because the SAMe+APAP group had less 4-HNE (Fig. 12) and less protein carbonyl-positive (Fig. 10) stained bands compared with the APAP groups.

SAMe is present in many tissues in the body and acts as a principal methyl donor for transmethylation reactions, especially within the liver. Transmethylation reactions are essential in maintaining normal cell function, as SAMe is the methyl donor for transmethylation of phospholipids, proteins, nucleic acids, and ultimately DNA (Mato et al., 1997; Lieber and Packer, 2002). Very little is known regarding the effect of exposure to toxicants and alterations in the transmethylation pathway. Imbalances in SAMe and the transmethylation byproduct, SAH, do occur in chronic alcohol models (Lieber, 2002; Lu and Mato, 2005). An imbalance in the relative ratio of SAMe:SAH can lead to impaired transmethylation reactions (Lu and Mato, 2005), which would be predicted to deter tissue repair and cell function. Further studies are needed to determine whether APAP alters the balance of SAMe:SAH and transmethylation reactions as part of its mechanism of toxicity.

In summary, our study is the first to compare SAMe with NAC on effectiveness as an antidote for APAP toxicity. Equimolar administration of 1.25 mmol/kg SAMe or NAC just before APAP injection showed that SAMe was more effective than NAC in reducing APAP hepatic toxicity. NAC administered at a higher dose of 7.35 mmol/kg provided the best protection of APAP toxicity. This study was also the first to provide a comparison of APAP hepatic toxicity when SAMe and NAC were administered just before APAP. These results suggest that SAMe, at least in our model, has some potential as an antidote for APAP toxicity.


Address correspondence to: Dr. Monica A. Valentovic, Department of Pharmacology, Physiology and Toxicology, Marshall University School of Medicine, 1542 Spring Valley Drive, Huntington, WV 25704-9988. E-mail: valentov@marshall.edu