Bioavailability and Lack of Toxicity of S-Adenosyl-L-Methionine (SAMe) in Humans

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Study Objective. To determine if S-adenosyl-L-methionine (SAMe), a widely used dietary supplement with antidepressant properties, is significantly bioavailable, and whether toxic methylated compounds are produced with oral SAMe administration in humans. Serum homocysteine levels were also measured since alterations in these levels have been theorized in association with SAMe.

Design. Unblinded pharmacokinetic trial.

Subjects. Fifteen healthy volunteers.

Setting. Clinical research unit in a psychiatric hospital.

Intervention. Subjects received oral SAMe for 4 weeks; the dosage was titrated over 5 days to 1600 mg/day. Serum levels of SAMe, toxic methylated compounds (methanol, formaldehyde, and formic acid), and homocysteine were measured at baseline and at weeks 2 and 4. At baseline, a structured clinical interview for axis I disorders (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) was completed to assess for any undiagnosed psychiatric disorders. Mood was rated at baseline and at weeks 2 and 4 using the Zung Depression Rating Scale, Young Mania Rating Scale, Montgomery-Asberg Depression Rating Scale, Clinical Global Impression Scale, and the Global Assessment of Function Scale.

Measurements and Main Results. After oral administration, SAMe levels were significantly elevated. Slight, likely insignificant, elevations in serum formaldehyde levels were detected in three subjects. No subject exhibited elevated homocysteine levels during SAMe treatment. One subject developed a transient mixed manic state with suicidal ideation within 2 weeks of starting SAMe; she recovered fully within 3 days of discontinuing the compound.

Conclusion. Oral dosages of 1600 mg/day of SAMe appear to be significantly bioavailable and nontoxic, at least regarding toxic methylated metabolites and homocysteine. However, the risk of mania in vulnerable individuals remains a serious concern.

Key Words: S-adenosyl-L-methionine, bioavailability, formaldehyde, homocysteine, bipolar disorder, methanol, formic acid, mania, switch process.

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S-adenosyl-L-methionine (SAMe) is an endogenous compound that functions as a methyl donor in many cellular processes.[1–7] It is not an essential dietary supplement, as humans can synthesize it from methionine and adenosine triphosphate (ATP).[2] Since SAMe synthesis is dependent on vitamin B_{12} and folate metabolism, deficiencies in these vitamins may lead to

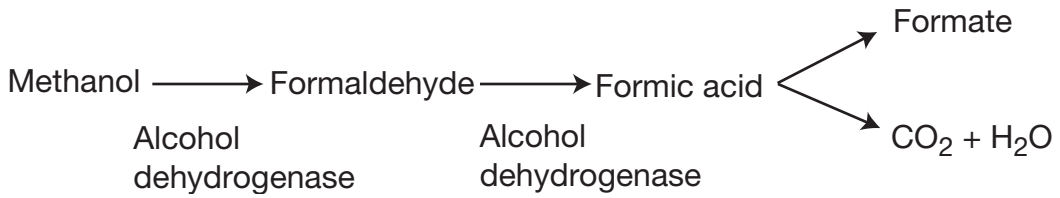

Figure 1. The metabolic pathway of methanol shows the formation of toxic methylated compounds in vivo.

decreased SAMe levels.[3]

S-adenosyl-L-methionine is commercially available as a dietary supplement and is being used for the treatment of many medical disorders, including depression. Reports on the antidepressant activity of SAMe date back more than 20 years. A critical review of the literature indicates that intravenous SAMe is almost certainly a mood-elevating substance[1, 3–10]; however, debate continues as to whether definitive data exist regarding the antidepressant effects of oral SAMe. The compound crosses the blood-brain barrier. Potential explanations for its role as an antidepressant likely include decreased serotonin and norepinephrine uptake, dopamine turnover, and enhanced signal transduction through improved receptor-effector coupling by way of increased membrane fluidity.[5–7]

Exogenous SAMe has a low bioavailability due to first-pass effects, rapid metabolism, chemical instability of the molecule, and past problems with tablet dissolution in some commercial preparations.[5, 8, 11] An enteric-coated formulation is in widespread use, which reaches a peak plasma level within 5 hours and has a half-life of 1–2 hours.

Since SAMe is metabolized to S-adenosylhomocysteine and ultimately to homocysteine, it is theoretically possible that SAMe administration could lead to hyperhomocysteinemia.[12–14] Elevated homocysteine levels are an established risk factor for cardiovascular and renal disease.[12, 13] In contrast, due to SAMe-associated elevations in 5-methyltetrahydrofolate, a cofactor of homocysteine metabolism, SAMe has been postulated to be effective in treating elevated homocysteine levels.[12]

A 1972 report indicated that rats produced substantial amounts of methanol after administration of SAMe.[14] Thus, a theoretical but particularly hazardous consequence of SAMe use is the formation of toxic methylated compounds in vivo (Figure 1). These small methylated molecules may be formed by enzymatic action on SAMe and water. Very high levels of methanol, and related molecules, such as formaldehyde and formic acid, are systemically toxic and may cause death. Lower levels may lead to blindness through destruction of the optic nerve.[2, 14]

It is not known if humans form methanol or other toxic methylated compounds in response to SAMe administration. Rats differ somewhat from humans in the relative activities of the various enzymes used in methylation reactions and in the degradation of small methylated compounds, such as methanol. Although it is unlikely that SAMe supplementation in humans is associated with the formation of acutely toxic concentrations of methanol, formaldehyde, or formic acid, small or moderate amounts of these toxic methylated molecules may be formed. Whether the subacute or chronic presence of low or moderate levels of such methylated compounds is toxic is also not known.

As it is a dietary supplement, SAMe has never undergone the rigorous safety testing required for prescription drugs, and although short-term trials have suggested that SAMe is safe, no long-term data exist. Enthusiastic media reports of SAMe have ignored documented hazards and adverse effects, particularly mania induction in patients with a bipolar diathesis.[5, 10, 15] Other potential adverse effects include flatulence, diarrhea,

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headache, and nausea.[4, 5, 10]

The widespread use of SAMe and the unanswered questions regarding toxicity led us to study the bioavailability and safety of oral SAMe by measuring serum levels of SAMe, homocysteine, methanol, formic acid, and formaldehyde.

Methods

The institutional review boards of McLean Hospital and Northeastern University approved the clinical research protocol. Written, informed consent was obtained from all subjects. Subjects completing the study received modest remuneration for their participation.

Subjects

Subjects were recruited through fliers posted around McLean Hospital or by word of mouth. Exclusion criteria were a personal or family history of a psychiatric disorder, drug therapy other than oral contraception, and any active medical disorders. Women who were pregnant or unwilling to practice reliable contraception were also excluded.

Study Drug

Subjects received a 4-week supply of SAMe (Nature Made, Mission Hill, CA) in 200-mg caplets. The dosage was titrated over 5 days, starting with 200 mg twice/day for 2 days, then 400 mg twice/day for 2 days, followed by 800 mg twice/day thereafter, for a total of 4 weeks.

Laboratory Studies

Each subject's blood was drawn at approximately the same time at each visit and 12 hours after the last dose. Blood samples for SAMe, methanol, formaldehyde, formic acid, and homocysteine levels were obtained at baseline and at weeks 2 and 4. A commercial laboratory (Quest Diagnostics, Cambridge, MA) performed all of the analyses except for the SAMe assay, which was performed at Northeastern University by one of the authors (JLG). S-adenosyl-L-methionine was extracted from blood with use of previously established methods and was measured by high-performance liquid chromatography (HPLC).[16–18] Samples (20 µl) were injected into a Waters 510 Spectrosphere HPLC system (Lambda Max 480; Waters Corporation, Milford, MA) equipped with an Econosphere C-18 measuring 25 x 4.6 mm and a 5-µm particle size column (ultraviolet detector level 254 nm). The mobile phase was prepared with use of 10 mM of the sodium salt of heptansulfonic acid and 50 mM of sodium dihydrogen phosphate in 16% methanol. The pH was adjusted to 4.38 with phosphoric acid, and the flow rate was set at 1.5 ml/minute.

Before and after sample analysis, the column was equilibrated and standard samples of SAMe (range 0.25–5 µg/ml) in 0.1 mM hydrochloric acid were analyzed. Assay sensitivity was 0.1 nmol/ml, and the intrassay and interassay coefficients of variation were 1.2% and 3.6%, respectively. Minimum levels of detection were methanol 10 mg/L, formaldehyde < 1:4 titer, formic acid 1.0 µg/ml, and homocysteine 0.5 µmol/L.

Clinical Assessments

During the baseline visit, a detailed psychiatric and medical history was obtained, and the following scales were used to assess diagnoses and to rate symptoms: Structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, axis I disorders,[19] Zung Depression Scale,[20] Young Mania Rating Scale[21] (11-item structured-interview version), Montgomery-Asberg Depression Rating Scale,[22] Clinical Global Impression scale,[23] Global Assessment of Function,[23] and a brief adverse-effect rating scale. Patients returned for office visits at weeks 2 and 4, and assessments were performed using the same rating scales. The detailed rating scales for bipolar disorder symptoms were used because of SAMe's capacity to induce mania in vulnerable individuals. Since this was a healthy population, psychiatric rating scales were used only to assess potential psychiatric adverse events.

Statistical Analysis

Laboratory results were analyzed with use of a repeated-measures analysis of variance (ANOVA). A Tukey test for pairwise multiple comparisons was used to assess individual group differences when ANOVA demonstrated a significant difference between groups (SigmaStat 2.03; SPSS Inc., Chicago, IL). A p value less than 0.05 was considered to indicate a statistically significant difference.

Results

Fifteen healthy adults (10 women, 5 men), mean ± SD age 26 ± 4.5 years, completed the 4-

Table 1. Serum Concentrations of SAMe and Toxic Methylated Compounds in the 15 Subjects

Sex, Age (yrs)	SAMe (nmol/ml)	Methanol (mg/L)	Formaldehyde IgG[a]	Formaldehyde IgM[a]	Formic Acid (µg/ml)	Homocysteine (µmol/L)
F, 27						
Baseline	0.62	0.00	0.25	0.00	3.50	7.90
Week 2	0.65	0.00	0.00	0.00	2.50	7.40
Week 4	0.67	0.00	0.00	0.00	2.30	7.30
F, 30						
Baseline	0.72	0.00	0.00	0.00	1.30	7.80
Week 2	0.73	0.00	0.00	0.25	1.90	6.90
Week4	0.73	0.00	0.00	0.00	2.80	6.90
F, 23						
Baseline	0.68	0.00	0.00	0.00	0.00	5.40
Week 2	0.70	0.00	0.25	0.00	2.20	5.50
Week 4	0.73	0.00	0.00	0.00	2.10	4.40
F, 24						
Baseline	0.60	0.00	0.00	0.00	2.20	6.60
Week 2	0.65	0.00	0.00	0.00	2.40	6.40
Week 4	0.64	0.00	0.00	0.00	2.00	5.70
M, 23						
Baseline	0.90	0.00	0.00	0.00	2.40	6.80
Week 2	0.98	0.00	0.00	0.00	NA	8.90
Week 4	0.97	0.00	0.25	0.00	2.70	7.20
M, 22						
Baseline	0.83	0.00	0.00	0.00	1.10	9.70
Week 2	0.90	0.00	0.00	0.00	2.80	9.40
Week 4	0.91	0.00	0.00	0.00	2.20	8.40
M, 25						
Baseline	0.80	0.00	0.00	0.00	1.90	10.3
Week 2	0.85	0.00	0.00	0.00	2.30	13.5
Week 4	0.85	0.00	0.25	0.00	1.80	12.0
F, 25						
Baseline	0.73	0.00	0.00	0.00	2.90	5.70
Week 2	0.75	0.00	0.00	0.00	3.10	7.10
Week 4	0.77	0.00	0.25	0.00	2.10	NA
F, 39						
Baseline	0.69	0.00	0.00	0.00	2.10	4.50
Week 2	0.69	0.00	0.00	0.00	1.50	4.20
Week 4	0.69	0.00	0.25	0.00	2.90	4.70
F, 22						
Baseline	0.80	0.00	0.25	0.00	2.40	6.10
Week 2	0.87	0.00	0.00	0.00	0.00	7.00
Week 4	0.87	0.00	0.00	0.00	0.36	7.80
M, 26						
Baseline	0.70	0.00	0.25	0.00	2.20	6.30
Week 2	0.78	0.00	0.25	0.00	2.40	8.20
Week 4	0.78	0.00	0.00	0.00	3.30	9.00
F, 23						
Baseline	0.99	0.00	0.00	0.00	2.60	6.90
Week 2	1.06	0.00	0.00	0.00	1.10	7.00
Week 4	NA	0.00	0.00	0.00	2.70	5.80
M, 23						
Baseline	0.86	0.00	0.00	0.00	2.70	7.00
Week 2	0.90	0.00	0.00	2.50	7.40	NA
Week 4	0.91	0.00	0.00	0.00	1.40	7.20
F, 30						
Baseline	0.66	0.00	0.00	0.00	2.00	6.20
Week 2	0.72	0.00	0.00	0.00	2.80	6.20
Week 4	0.70	0.00	0.00	0.00	1.70	7.80

Table 1. (continued)

Sex, Age (yrs)	SAMe (nmol/ml)	Methanol (mg/L)	Formaldehyde IgG	Formaldehyde IgM	Formic Acid (µg/ml)	Homocysteine (µmol/L)
F, 29						
Baseline	0.60	0.00	0.00	0.00	1.40	6.70
Week 2	0.68	0.00	0.00	0.00	1.50	8.50
Week 4	NA	0.00	0.00	0.00	1.60	7.90
All subjects (10 F/5 M, mean ± SD age 25 ± 4.5 yrs)						
			Mean ± SD			
Baseline	0.75 ± 0.12				2.05 ± 0.84	6.93 ± 1.52
Week 2	0.79 ± 0.13 (p<0.001)				2.08 ± 0.82 (p=0.89)	7.58 ± 2.10 (p=0.05)
Week 4	0.78 ± 0.12 (p=0.002)				2.35 ± 0.64 (p=0.26)	7.29 ± 1.91 (p=0.115)

SAMe = S-adenosyl-L-methionine; IgG = immunoglobulin G; IgM = immunoglobulin M; NA=not available.
[a]Minimum level of detection was < 1:4 titer.

week study (Table 1). Mean ± SD SAMe plasma levels were significantly different from baseline (0.75 ± 0.12 nmol/ml) at week 2 (0.79 ± 0.13 nmol/ml, p<0.001) and week 4 (0.78 ± 0.12 nmol/ml, p=0.002). A Tukey test demonstrated that SAMe levels at baseline were significantly less than at weeks 2 and 4 (p<0.001 for both) but not significantly different between weeks 2 and 4. Inclusion of data from two subjects for whom SAMe levels were not available at week 4 did not significantly alter these results. Methanol levels were not detected in any study participant at any time during the study. Formaldehyde was detected in three subjects at baseline, in three at week 2, and in four at week 4. No subject had elevated formaldehyde levels at both weeks 2 and 4. A formic acid level was not available for one subject at week 2. Mean ± SD formic acid levels were not significantly different from baseline (2.05 ± 0.84 µg/ml) at week 2 (2.08 ± 0.82 µg/ml, p=0.89) or week 4 (2.35 µg/ml ± 0.64, p=0.26). Mean ± SD homocysteine levels increased only slightly and were not significantly different from baseline (6.93 ± 1.52 µmol/L) at week 2 (7.58 ± 2.10 µmol/L, p=0.05) or week 4 (7.29 ± 1.91 µmol/L, p=0.115).

One woman developed a transient mixed manic state with suicidal ideation within 2 weeks of starting SAMe. The compound was stopped immediately, and she was clinically evaluated by a psychiatrist (ALS). She recovered fully within 3 days of discontinuing SAMe. She had no prior history of a mood disorder; however, after the study she recalled that one of her siblings had experienced a single psychotic, likely manic, episode as a teenager.

Table 2. Frequency of SAMe Adverse Effects in the 15 Subjects

Adverse Effect	No. (%) of Subjects	
	Mild	Moderate-to-Severe
Central nervous system		
Baseline	4 (27)	0
Week 2	4 (27)	2 (13)
Week 4	5 (33)	2 (13)
Cold or flu-like symptoms		
Baseline	8 (53)	6 (40)
Week 2	6 (40)	1 (7)
Week 4	3 (20)	2 (13)
Dry mouth		
Baseline	1 (7)	1 (7)
Week 2	2 (13)	0
Week 4	3 (20)	0
Gastrointestinal		
Baseline	2 (13)	1 (7)
Week 2	4 (27)	2 (13)
Week 4	10 (67)	3 (20)

No psychiatric changes were noted in any other participant. Adverse effects were generally mild (Table 2). Central nervous system adverse effects, consisting primarily of headache and dizziness, occurred with slightly greater frequency at weeks 2 and 4 than at baseline. However, gastrointestinal side effects, primarily diarrhea and flatulence, did increase to a clinically significant level with SAMe administration. No participant discontinued SAMe due to adverse effects.

Discussion

In general, SAMe was well tolerated. The supplement chosen for this study increased SAMe plasma levels significantly. Although the percentage increase in SAMe concentration was small, SAMe is highly reactive and most of a dose is not expected to be present in serum or tissue. Therefore, small changes in serum levels are likely to be clinically significant. Other studies administering lower dosages of SAMe intravenously have found similar elevations that correlated with increased SAMe levels in cerebrospinal fluid.[4, 24, 25]

No statistically significant changes in serum levels of toxic methylated compounds or homocysteine were observed with oral SAMe administration. The small changes observed in the laboratory are unlikely to be clinically significant. However, this can only be determined with a much larger number of subjects. Although SAMe and its methylated compounds are rapidly metabolized, it is theoretically possible that SAMe given for longer periods of time could lead to greater changes in methyl compounds, although the metabolism of SAMe and its effects on methylated compounds are rapid.

Since compliance was assessed by pill count only, it is possible that participants did not take the SAMe as prescribed, which could have confounded our results.

Three participants were taking oral contraceptives, which could interfere with the metabolism of SAMe. However, a literature search revealed no reports of such a drug interaction. Although it is unlikely that oral contraceptives accounted for a significant difference, the small number of participants taking those agents precludes meaningful subanalysis.

Our finding of minimal adverse effects is consistent with the published literature. Studies in approximately 20,000 patients with osteoarthritis found no serious gastrointestinal effects in association with SAMe administration.[26] Other studies have also concluded that adverse effects of SAMe are mild and consist primarily of transient nausea and diarrhea.[26]

It is important to note the risk of mania induction with SAMe, as experienced by one of our subjects. This well-known phenomenon was reported in 9 of 11 patients from various studies who had bipolar disorder and who switched to hypomania or mania when given SAMe intravenously or orally; in contrast, no patient with unipolar disorder experienced such a switch.[15]

Conclusion

Our results suggest that short-term oral administration of SAMe at the dosages studied is a safe and effective way to increase endogenous SAMe levels and that it may be useful for further study in patients with depression. Because of the risk of mania, caution should be used when prescribing SAMe to patients with a personal or family history of bipolar symptoms.

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