Toxicity of Methionine in Humans\textsuperscript{1}

Peter J. Garlick\textsuperscript{2}

Department of Animal Sciences, University of Illinois, Urbana, IL 61801

ABSTRACT The literature has been searched to identify evidence relating to the possible toxicity of the amino acid methionine in human subjects. Nutritional and metabolic studies have employed amounts of methionine, including the D and DL isomers, both below and above the requirement and have not reported adverse effects in adults and children. Although methionine is known to exacerbate psychopathological symptoms in schizophrenic patients, there is no evidence of similar effects in healthy subjects. The role of methionine as a precursor of homocysteine is the most notable cause for concern. A "loading dose" of methionine (0.1 g/kg) has been given, and the resultant acute increase in plasma homocysteine has been used as an index of the susceptibility to cardiovascular disease. Although this procedure results in vascular dysfunction, this is acute and unlikely to result in permanent damage. However, a 10-fold larger dose, given mistakenly, resulted in death. Longer-term studies in adults have indicated no adverse consequences of moderate fluctuations in dietary methionine intake, but intakes higher than 5 times normal resulted in elevated homocysteine levels. These effects of methionine on homocysteine and vascular function are moderated by supplements of vitamins B-6, B-12, C, and folic acid. In infants, methionine intakes of 2–5 times normal resulted in impaired growth and extremely high plasma methionine levels, but no adverse long-term consequences were observed. J. Nutr. 136: 1722S–1725S, 2006.

KEY WORDS: • methionine • toxicity • human

Previous reviews of methionine toxicity have relied largely on data derived from animals and have led to the belief that methionine is the most toxic amino acid (1). In humans, however, despite the use of methionine to detoxify acetylamophen (paracetamol) and its role as a precursor of homocysteine, an indicator of cardiovascular risk, there appear to have been no systematic studies with toxicity or adverse effects as the primary focus. The aim of this paper is, therefore, to examine the literature for evidence that might enable the safety of methionine in humans to be derived. For this purpose, literature searches were performed including journals from the fields of nutrition and metabolism (including amino acid requirements), physiology, pharmacology, psychology, and clinical medicine.

Nutritional and metabolic studies. During the 1960s and 1970s, there were several studies of the dietary requirement for sulfur amino acids, which employed ranges of intakes of methionine (with or without cysteine) from below to above the estimated requirement (2–7). The highest intakes given to adults were almost three times the current estimates of the requirement, derived from studies of graded intake levels in volunteers (8), but no adverse effects were reported. Nutritional studies of sulfur amino acids in healthy and malnourished children (9–14) have not employed such large excesses over requirement, so they might not be expected to show any adverse effects.

In some of the above studies, the methionine was given as DL-methionine, D-methionine, or N-acetyl-methionine rather than L-methionine (6,7,12,14). These L-methionine analogs seem to have been well tolerated, except that DL-methionine in infant feeds resulted in high tissue concentrations of D-methionine, with unknown consequences (15). However, no other adverse effects were noted. It has also been shown that intake of D-methionine, but not L-methionine, caused high excretion of 3-methyl propionate (16).

Methionine has also been given to induce acidosis. In a study to investigate whether the acidosis induced by the metabolism of an oral dose of 11.3 g of methionine would modify ketosis during starvation or ketogenic dieting, the fall in blood pH was similar to that produced by an equivalent dose of ammonium chloride (17). This could be detrimental to the subjects if continued for extended periods, as metabolic acidosis has been shown to result in an inhibition of muscle protein synthesis in animals (18). Moreover, in human volunteers, acidosis resulted in negative nitrogen balance and decreased synthesis of muscle protein and serum albumin (19,20), which could be detrimental to body protein homeostasis if continued. The acidosis induced by methionine could be the rationale for the prevention of recurrent urinary tract infections by L-methionine (21). In another clinical study, methionine (5 or 10 g/d) was given to patients as a treatment for rheumatoid polyarthritis (22). No serious adverse effects were reported, although nausea, vomiting, constipation, and halitosis were frequent.

Methionine is an indispensable amino acid for humans, but there is evidence that if given in excess, it can interfere with the

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\textsuperscript{2} To whom correspondence should be addressed. E-mail: pgarlick@uiuc.edu.
utilization of nitrogen from dispensable amino acids. In studies of nitrogen balance in subjects receiving low-protein diets, nitrogen balance was improved in subjects receiving low protein plus urea or low protein plus glycine, but not with diets containing low protein plus methionine or low protein plus both methionine and urea (23). Also, the urinary excretion of 5-L-oxoproline, a marker of glycine availability, was significantly lower when the diets contained low protein plus urea or low protein plus urea and methionine. There was a significant correlation between the excretion of 5-L-oxoproline and excretion of sulfate. The interpretation was that glycine was consumed to detoxify the excess methionine, with the result that the availability of glycine for other metabolic processes became limiting (23).

Neuropsychiatric diseases. In 1952 Osmond and Smithies (24) proposed the “transmethylation theory” of schizophrenia, based on the knowledge that methyl donors such as methionine cause exacerbation of psychopathological symptoms (25). They suggested that schizophrenia occurs as a result of a disturbance of methylation, leading to the conversion of catecholamines released under conditions of stress-induced anxiety to psychotic mesencephaline-like compounds. Large doses of methionine (5–40 g/d of L- or DL-methionine), with or without a monoamine oxidase inhibitor, given over periods of 1 wk to 2 mo, have resulted in striking exacerbations of psychotic symptoms in chronic schizophrenic patients (see ref. 26 for further information). However, in healthy subjects doses of 10 g of methionine have been shown to have no effect (27).

Methionine and homocysteine. The first step in the metabolism of methionine is its conversion to homocysteine via the intermediate, Sadenosylmethionine. Homocysteine is then removed by combination with serine to produce cystathionine, which is cleaved to form α-ketobutyrate and cysteine. As long ago as 1969, it was noticed that children with the inherited disorder homocysteinuria suffered from vascular abnormalities and frequent arterial and venous thromboses (28). Because the homocysteinemia was associated with arteriosclerotic plaques in individuals with mutations of 3 different enzymes involved in the conversion of methionine to homocysteine, it was concluded that the homocysteine itself is atherogenic (28,29).

Since that time the role of homocysteine in the development of vascular disease has been extensively researched and clarified. In 1985, "methionine intolerance" was cited as "a possible risk factor for coronary artery disease" (30), and it was also suggested that patients with hyperhomocysteinemia have a 50% probability of a vascular accident before age 30 (31).

Since 1985, there has been a large amount of research into the relationships between methionine intake in normal subjects in relation to plasma homocysteine and vascular disease. In particular, this research has yielded a considerable amount of information regarding both the acute and chronic effects of methionine intake on indices of cardiovascular disease. Moreover, because methionine has been given to many subjects in these studies, the incidence of adverse effects can be used to derive information on other possible aspects of toxicity. A "methionine-loading test" has been employed in a large number of subjects to produce an increase in plasma homocysteine. After the methionine is given orally, there is an increase in plasma homocysteine concentration, which is then used as an index of the susceptibility of the individual to cardiovascular disease. This is believed to be a more sensitive index than the fasting homocysteine concentration alone (32). The dose given is usually 100 mg/kg body weight, which is approximately 7 times the average daily requirement for total sulfur amino acids (methionine plus cysteine) (8).

The methionine-loading test not only produces a rise in homocysteine concentration but also mimics homocysteinemia in other respects. For example, in a study of the effect of an oral dose of methionine (100 mg/kg) in healthy volunteers, plasma homocysteine doubled at 2 h after methionine ingestion, with a further increase at 4 h (33). Flow-mediated dilatation fell at 2 h, with a further fall at 4 h. In particular, there was an inverse relation between homocysteine concentration and flow-mediated dilatation. In a similar study, the same authors showed that physiological increments in plasma homocysteine resulting from the intake of graded amounts of methionine, or of animal protein, induced endothelial dysfunction. However, an amino acid mixture lacking methionine had no effect (34). Conversely, arterial stiffness, as measured by pulse wave analysis, does not appear to be altered by methionine loading (35).

An important question relating to the possible toxicity of methionine is whether the responses to the methionine-loading test are responses to methionine directly or responses to the rise in homocysteine level. This question has been answered by comparing the response of forearm blood flow to oral doses of methionine and homocysteine that by design gave the same increase in plasma homocysteine concentration (36). The 2 treatments resulted in similar responses of forearm blood flow, indicating that the active agent is homocysteine, not methionine per se.

Methionine-loading test: potential for adverse effects. As described above, the methionine-loading test results in an increase in homocysteine level and vascular endothelial dysfunction. However, these effects are acute and therefore seem unlikely to be harmful after a single test. Various smaller doses of methionine have been examined in relation to their potential as an additive to acetaminophen (paracetamol), for which it is the antidote (37). There was no significant difference in plasma homocysteine concentrations at 1 h after a single dose of methionine (250 mg) or after 1 mo of methionine, 250 mg daily, but after 1 wk of methionine, 100 mg/kg body weight daily, there was an increase in plasma homocysteine. With each of these dose regimens, there were no changes in endothelial-dependent or endothelial-independent responses. The conclusion was that the lower dose regimens were safe but that the dose of 100 mg/kg for 1 wk could not be declared safe.

The safety of the methionine-loading test has been examined in an epidemiological study of 296 patients with coronary or peripheral artery disease and 591 controls (38). There were acute complications in 33% of the female and 17% of the male patients, with no difference between patients and controls. However, these complications were relatively mild, with dizziness being the most common symptom, which was attributed to the methionine. Isolated sleepiness, nausea, polyuria, and decreased or increased blood pressure were also observed. None of the 887 patients died within a 30-d period. The conclusion was that the test frequently causes transient complications, impairing perception and vigilance, but it does not have serious adverse effects on vasculature and may be considered safe.

From a limited survey of the literature, it appears that methionine-loading tests have been performed on at least 600 adults without any serious adverse effects being reported, with 1 exception (39). A control (non-Alzheimer’s disease) subject in a study of the relation between homocysteine and Alzheimer’s disease was given the test, apparently with the usual dose of methionine. However, after 2 h 40 min, she began to vomit and continued for several hours, during which prochlorperazine and diphenhydramine were given. At about 8 h after the methionine was given, she was taken to the emergency room, subsequently became apneic and pulseless, and was admitted to an intensive care unit. After various other complications, she died 30 d after the methionine load was administered. Retrospective measurements of plasma methionine showed it to be about 200 times the baseline value at 2 h.
after the dose, even higher at 4 h, and 10 times the baseline value after 2 d. Although there was no direct evidence that the dose of methionine was incorrect, the blood analysis data are consistent with a dose approximately 10 times what was intended (i.e., ~70 times the dietary requirement) (8). This is, however, an extreme case, which does not give much indication of the potential for toxicity of methionine at more moderate intakes.

**High methionine intake in infants.** There seem to be no direct studies of the effects of methionine intake in infants that give information relating to toxicity. However, a cluster of 10 infants with hypermethioninemia and hyperhomocysteinemia was identified in 1999–2001, with no obvious cause, as cystathionine β-synthase deficiency and other known reasons for elevated blood methionine were ruled out. A detailed analysis of this occurrence was described by Mudd et al. (40), who concluded that the hypermethioninemia was the result of being given formula with a very high methionine content. Nine of the infants had received 1 formula that had recently been modified to contain more methionine, and the other infant also received formula with a high methionine content. The intakes of methionine were estimated retrospectively to be in the range 125–507 mg/kg per day, compared with the estimated average of 62–97 mg/kg per day. Plasma methionine concentrations were disproportionately elevated, rising as high as 6830 μmol/L, compared with the normal range of 10–40 μmol/L. Despite the severe hypermethioninemia during infancy, no long-term adverse clinical effects of methioninemia were identified among these cases (40).

**Dietary methionine intake and plasma homocysteine.** Methionine is an indispensable amino acid and must be supplied from the diet. It is therefore appropriate to ask whether dietary methionine intake affects homocysteine concentration and cardiovascular risk. In a study by Ward et al. (41), healthy men were screened for methionine intake by a food-frequency questionnaire. Those who were in the top quartile of intake were randomly assigned to receive a low-methionine diet for 1 week followed by a control diet for 1 week, or vice versa. Those in the bottom quartile of intake received a high methionine intake for 1 week followed by the control diet, or vice versa. Thus, those subjects in the top quartile of intake reduced their intake by 79%, and those in the lowest quartile doubled their intake. However, the homocysteine concentrations did not alter in response to the changes in dietary methionine intake. The conclusion was that homocysteine concentrations are not responsive to moderate fluctuations in dietary methionine intake. In another study, the same authors measured the response of plasma homocysteine to increasing intakes of methionine (42). A significant increase in plasma homocysteine was seen only when the methionine intake was increased to 5 times the normal intake. These studies provide evidence that moderately high methionine intakes will not lead to hyperhomocysteinemia and subsequent risk of cardiovascular disease. However, the effects of methionine loading are also markedly influenced by vitamin status. For example, although treatment with vitamin C before the study did not influence the rise in homocysteine concentration, there was a reduction of the effect on fluid-mediated dilatation, suggesting that oxidative stress was involved in the mechanism (33). Similarly, folic acid been shown to be beneficial in reducing the endothelial dysfunction but did not affect the homocysteine concentration (42). Studies have also shown correlations between pre- and post-methionine-load homocysteine levels with vitamin B-12 and folate (43,44).

**Conclusions.** Although methionine was labeled as being the most toxic amino acid in relation to growth in animals (1), the evidence in humans does not point to serious toxicity, except at very high levels of intake. Despite the function of methionine as a precursor of homocysteine, and the role of homocysteine in vascular damage and cardiovascular disease, there is no evidence that dietary intake of methionine within reasonable limits will cause cardiovascular damage. A single dose of 100 mg/kg body weight has been shown to be safe, but this dose is about 7 times the daily requirement for sulfur amino acids, and repeated consumption for 1 wk was shown to result in increased homocysteine levels (37,42). Daily doses of 250 mg (i.e., 4 mg/kg per day) are only 25% of the daily requirement and have been shown to be safe. Overall, the literature suggests that the single dose which is typically given in the methionine loading test (100 mg/kg/d) does not cause any serious complications, except in the extreme case when a 10-fold excess of methionine appears to have been given, and in patients who have schizophrenia or inborn errors of sulfur amino acid metabolism, such as hypermethioninemia.

**LITERATURE CITED**