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Letters to the Editor

Intravenous ascorbic acid infusions and oxalate production

To the Editor:

Robitaille et al [1] studied the extent of the autooxidation of ascorbate to oxalate after the intravenous administration of megadoses of ascorbic acid to patients with advanced cancers of a variety of types. They found that when 100 g of ascorbate was delivered over 1.5 to 2 hours, urinary oxalate excretion reached an average of 81 mg over a 6-hour period. A portion of this oxalate increase was due to the 26 mg present in the infusate. They concluded that this increase in oxalate excretion would not be clinically significant. This degree of oxalate excretion for the 6-hour period is higher than that of most patients with primary hyperoxaluria and is compatible with that seen with ethylene glycol toxicity [2], the latter being an acute event usually after a single oral dose. Severe renal oxalosis can follow ethylene glycol toxicity in some instances and can lead to renal failure. We feel that the authors should temper their conclusion that this amount of oxalate excretion is only of moderate risk until they have longer follow-up on a larger number of subjects, especially examining parameters of renal function and injury.

Their study does raise additional points. The oxalate generated in vivo from ascorbate could occur intracellularly or extracellularly. One might hypothesize that ascorbate oxidation to oxalate occurs in cells and tissues when ascorbate is exposed to a peroxidative environment. Alternatively, the mild alkaline environment of the extracellular compartment may promote oxidation of ascorbate. The observation that significant breakdown (18%) of ascorbate at a concentration of 5.7 mmol/L apparently occurred in urine stored at room temperature for 24 hours at pH 1.7 is a cause for concern for the analysis of oxalate in 24-hour urine collections. This clouds the interpretation of several recent studies that reported that the oral ingestion of 2 g of ascorbate significantly increased urinary oxalate excretion [3-6].

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Reply: Oxalic acid excretion after intravenous ascorbic acid administration

To the Editor:

These correspondents suggest that we were intemperate in considering that the amount of oxalic acid excreted after the intravenous infusion of approximately 100 g ascorbic acid may create only a moderate risk in people with normal renal function. Whether the risk of oxalate stone formation (or acute nephropathy) from high-dose intravenous ascorbic acid is small, moderate, or large in a given situation is a clinical judgment that most physicians would balance against the benefit of the treatment. Undoubtedly, intravenous

vitamin C is an unproven treatment. Our report is useful because it describes a method for overcoming the technical problem of analyzing oxalic acid in the presence of extremely high ascorbic acid concentrations and because of the surprisingly small fractional conversion of ascorbic acid to oxalic acid under the conditions of our study.

We cannot agree with the claim that intravenous vitamin C is equivalent to ethylene glycol poisoning simply because urinary oxalic acid concentrations may be only moderate after suicidal ethylene glycol ingestion. In such cases, the rapid development of oxalate nephropathy prevents the kidneys from excreting the large amounts of oxalic acid generated from ethylene glycol. In contrast, our data indicate that very little oxalic acid is formed after rapid intravenous ascorbic acid in people with normal renal function, a very different situation.

The possibility that oxalic acid can be formed intracellularly as well as extracellularly is speculative, and the data in our article do not address it. We agree that urine samples containing ascorbic acid should be acidified and refrigerated at pH less than 2.0 as soon a possible to avoid ex vivo formation of oxalic acid. Our observation of oxalic acid formation at pH 1.7 was in samples with extremely high ascorbic acid concentrations left at room temperature for 24 hours.

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The effect of phytophenols in alcoholic beverages on alcohol dehydrogenase 1: is there really evidence for an inhibition of metabolic toxicity of alcohol?

To the Editor:

We read with great interest the article by Haseba et al [1] on the influence of polyphenols in whisky on the alcohol metabolism, specifically, the reduction of acetaldehyde levels through inhibition of liver alcohol dehydrogenase (ADH). The findings could be important because the authors conclude that the intake of alcohol together with phytophenols may not only diminish the metabolic toxicity of alcohol by reducing both the blood acetaldehyde level and oxidative stress, but also help limit the amount of alcohol a person drinks by depressing alcohol metabolism. However, we have major concerns that both conclusions cannot be derived from the experimental data and are purely conjectural.

The major restriction of the study is the interpolation of results gathered using experimental animals (mice) to humans, the potential problems of which are not even mentioned. We have no evidence to date regarding if and how the results from mice can be transferred to humans. Thus, conclusions on the link between phytophenols in whisky or other foods and the metabolic toxicity of alcohol due to acetaldehyde and oxidative stress are simply not supported. There is a general lack of data on bioavailability of polyphenols in humans [2]. Concentrations of the nonvolatile whisky fraction in the percentage range as used in the in vitro experiment on liver extract are highly unlikely to occur in vivo in the human liver. The in vivo animal experiments with blood acetaldehyde concentration between 20 and 50 μmol/L also appear to be outside of the parameters of human alcoholic beverage consumption, which seldom leads to measurable blood acetaldehyde concentrations. It is generally accepted that no significant (>0.5 μmol/L) acetaldehyde concentrations occur in venous blood during normal conditions, that is, with no deficiency in, or inhibition of, aldehyde dehydrogenase [3,4]. The in vivo experiments also used a concentrate of the whisky nonvolatile fraction (10:1), which was added to ethanol solution in 10% or 20% amounts leading to considerably higher dosages than those expected in humans drinking whisky. All in all, we think that the situation used in mice is not directly comparable with humans. The short-term design of the animal experiments was also problematic because chronic-toxic effects (eg, carcinogenic effects) of ethanol and acetaldehyde are evident only in long-term or lifetime studies [5,6].

Thus, phytophenols may or may not have a positive effect on health. As explained above, this currently is a hypothesis without empirical evidence; however, hypothetically, if phytophenols really had an effect on ADH1 in humans, then ethanol would be expected to stay in the blood and other tissues longer and at higher concentrations. One of the well-established major pathways for carcinogenesis of ethanol in the gastrointestinal tract is the local formation of acetaldehyde by the microbial flora in the oral cavity and colon [7,8]. With reference to genetic-epidemiologic evidence available from humans with reduced ADH1 activity, the ADH1B*1/*1 genotype (activity only 1/40 of the normal) was reported to increase relative risk for head and neck cancers [9], which was in fact explained by a longer exposure time to the microbially formed salivary acetaldehyde after alcohol consumption [10]. The same effect would be expected by the inactivation of ADH1 through polyphenols.

The conclusion that the effect of polyphenols on ADH1 reduces the likelihood of binge drinking by depressing alcohol metabolism is completely unfounded. First, the study did not include a component investigating the behavioral effects of the experimental animals. Second, there is no evidence in humans that such an effect may even arise. Although there is evidence that the pharmacokinetics of