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Use of Aspartame in Pregnancy

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ABSTRACT: The low-calorie sweetening agent, aspartame, is broken down in the small intestine into three moieties: aspartic acid, methanol and phenylalanine. Acute loading studies have been performed in human beings who received up to six times the 99th percentile of the projected daily intake (6 x 34 = 200 mg/kg). No evidence of risk to the fetus was developed. Aspartate does not readily cross the placenta. Small elevations of blood methanol following such abuse doses of aspartame did not lead to measurable increases of blood formic acid, which is the product responsible for the acidosis and ocular toxicity in methanol poisoning. Phenylalanine is concentrated on the fetal side of the placenta. Aspartame in abuse doses up to 200 mg/kg in normal subjects, or to 100 mg/kg in PKU heterozygotes, did not raise blood phenylalanine levels to the range generally accepted to be associated with mental retardation in the offspring. It is concluded that, under foreseeable conditions of use, aspartame poses no risk for use in pregnancy.

INTRODUCTION

ASPARTAME (NUTRASWEET®, SEARLE) IS A low-calorie sweetening agent discovered in 1965 by Searle chemist James M. Schlatter.[1] It is 180-200 times sweeter than sucrose. The use of aspartame in certain foods was approved by the U.S. Food and Drug Administration (FDA) in 1974, but the approval was subsequently stayed pending deliberations of a Public Board of Inquiry,[2] which eventually took place in 1980. Thereafter, the FDA approved the use of aspartame in certain dry foods in 1981[3] and, later, in carbonated beverages in 1983.[4] Since that time, the sweetener has been marketed world-wide in a variety of products.

Chemically, aspartame is L-aspartyl-L-phenylalanine methyl ester. The dipeptide ester is metabolized into three moieties in the small intestine,[5] so that studies on the safety of aspartame are essentially studies of aspartic acid, phenylalanine and methanol.

Any discussion of safety must refer to the concept of dose. It has been estimated that an aspartame dose of 34 mg/kg represents the 99th percentile of the projected intake for an entire day when aspartame replaces all dietary sucrose and saccharin on a sweetness basis.[6] An aspartame dose of 34 mg/kg yields the following approximate amounts: aspartic acid 14 mg/kg, phenylalanine 17 mg/kg, methanol 3.3 mg/kg. The allowable or acceptable daily intake (ADI) of aspartame, based upon animal and human safety studies, has been set by the FDA at 50 mg/kg.[7] For a 50-kg individual,[4] this ADI represents a dozen 12-ounce cans of 100%-sweetened soda or approximately 62 cans of soda sweetened with a blend of aspartame plus saccharin. The ADI also represents the aspartame content of approximately 71 packets of Equal® for a 50-kg person (one packet contains 35 mg of aspartame, which is equivalent in sweetness to two teaspoons of sucrose).

With the foregoing considerations in mind, it is of interest to review each of the three digestion products of aspartame as they relate to safety in pregnancy.

DIGESTION PRODUCTS AS RELATED TO PREGNANCY

Aspartic Acid

Neither aspartic acid nor glutamic acid, the two dicarboxylic amino acids, readily crosses the placenta.[8] In human beings administered aspartame, dissolved in orange juice, at single doses up to 200 mg/kg, plasma aspartate levels rose during the two hours after ingestion, but were still well below normal postprandial aspartate levels.[9] This dose, administered at a single sitting, is approximately six times the 99th percentile of the estimated projected daily intake. In near-term, pregnant rhesus monkeys, aspartate was given intravenously for one hour at a rate of 100 mg/kg/h.[10] While maternal plasma aspartate levels increased to approximately 90 μmole/dl, fetal levels rose only to 1 μmole/dl, thus demonstrating the relative impermeability of the placenta to aspartate.[8] It has been concluded that "it is virtually impossible for humans to ingest aspartame in quantities sufficient to increase maternal plasma aspartate levels to values that would allow transfer of significant quantities of aspartate to the fetal circulation."[6]

Methanol

The methanol resulting from the hydrolysis of aspartame is oxidized in primates to formaldehyde by alcohol dehydrogenase.[11] The formaldehyde is then very rapidly oxidized to formic acid, which is responsible for the metabolic acidosis and ocular toxicity when intoxicating doses of methanol are given.[12] When a single oral dose of aspartame, 200 mg/kg (equivalent to 20 mg methanol per kg), was administered to human beings, blood methanol rose to only 2.6 mg/dl at 2 h, which is significantly below any level associated with toxicity,[13] and had returned to baseline by 24 h.[14] Blood formate was unchanged, while urine formate was significantly increased, indicating that the rate of formate synthesis did not exceed the rate of its excretion. "Thus there appears to be little risk from aspartame's methanol component at the doses studied."[6] The aspartame dose of 200 mg/kg is equivalent to the consumption of a single sitting of fifty 12-ounce cans of soda formerly sweetened with aspartame, or of 250 cans sweetened with an aspartame-saccharin blend. The methanol from 100% aspartame-[illegible] mg/l,[4] is generally less than provided for fruit juices[15,16] and

Phenylalanine

In contrast to aspartic acid, phenylalanine is concentrated on the fetal side of the placenta, with a ratio of 1.3 to 1.[18] Maternal blood phenylalanine levels below 60 μmole/dl have not been associated with decreased intelligence in the offspring, while levels above 110 μmole/dl usually have been associated with mental retardation.[19] The latter is the situation in phenylketonuria (PKU), where maternal blood levels range from 120 to 600 μmole/dl.[6] An important factor to remember is that it is a *sustained* high blood level of phenylalanine that causes mental retardation in the offspring, not merely acute elevations.

When normal subjects were given aspartame at a dose of 10 mg/kg every 2 h for a total of three doses, peak phenylalanine levels did not exceed the normal postprandial range.[6] The same was true for a single dose of 34 mg/kg.[6] PKU heterozygotes displayed peak levels of 14 and 16 μmole/dl, following the 30 mg/kg divided dose and the 34 mg/kg single dose, respectively. Following aspartame at 100 mg/kg, the blood level of normal subjects peaked at 20 and that of PKU heterozygotes peaked at 42 μmole/dl. With a dose of 200 mg/kg, only normal individuals were tested. Their peak levels averaged 49 μmole/dl.[6] Thus, all of these acute blood levels fell far short of the 110 μmole/dl sustained blood level at which evidence suggests a risk of mental damage to the offspring.[19]

In actual use, aspartame usually would be consumed together with natural protein, which would also contribute phenylalanine. In experiments involving the administration of aspartame, 34 mg/kg, with a hamburger-milk shake meal (1 g protein/kg), peak phenylalanine levels were somewhat less than expected and still far below the safety limit.[6,20]

It should be noted that changes in erythrocyte phenylalanine paralleled the changes in plasma phenylalanine in the foregoing studies.

Pitkin[8] has concluded that, "it seems highly unlikely that customary intakes [of aspartame] in normal pregnancy could raise fetal levels close to a neurotoxic range. Theoretically, abuse levels of intake [e.g., 200 mg/kg] in a PKU heterozygote might approach a zone where fetal toxicity would be possible" [i.e., >60 μmole/dl], were such levels to be sustained.

CONCLUSIONS

At intake levels at least three times the 99th percentile of the projected daily intake of aspartame, there is no experimental evidence to suggest a risk to the fe-

tus from the aspartic acid, methanol or phenylalanine moieties resulting from digestion of the aspartame molecule.

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