Aspartame Metabolism in Normal Adults, Phenylketonuric Heterozygotes, and Diabetic Subjects

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This study reviews clinical studies testing the effects of various doses of aspartame on blood levels of phenylalanine, aspartate, and methanol in normal subjects and known phenylketonuric heterozygotes. The effect of aspartame on the phenylalanine-to–large neutral amino acid ratio under various feeding situations is shown. The clinical studies of aspartame in diabetic subjects are limited to observations of its effects on blood levels of glucose, lipids, insulin, and glucagon. These studies clearly demonstrate the safety of this high-intensity sweetener for use by humans. *Diabetes Care* 12:67–74, 1989

In the United States the prevalence of diabetes, both insulin dependent (IDDM) and non–insulin dependent (NIDDM), involves 2.7% of women and 2.0% of men (1). In 1976, it was projected that the incidence of diabetes was increasing at a rate of 6%/yr (2). The association of NIDDM with the degree and duration of obesity suggests one reason why high-intensity sweeteners, nutritive and nonnutritive, may be a component of foods eaten by diabetic individuals. The natural interest of humans in the sweet taste modality provides another rationale for incorporation of high-intensity sweeteners into the diet of diabetic individuals. Currently, the most widely consumed high-intensity sweetener is aspartame, a dipeptide methyl ester (L-aspartyl-L-phenylalanine methyl ester).

On the basis of total pounds of aspartame sold to food and beverage processors, it has been estimated that aspartame replaces 15 lb of the ~132 lb of total sweeteners consumed per person per year. Because aspartame is 180–200 times sweeter than sucrose, this is equivalent to 38 g of aspartame per person per year. Daily intake can be calculated and amounts to 104 mg/day or 1.5 mg/kg body wt for a 70-kg individual. Aspartame is rarely consumed alone but is usually ingested in conjunction with varying proportions of carbohydrate, protein, and fat. Unless a person drinks an aspartame-sweetened beverage, carbonated or still, as a refreshment, the intake usually involves other foods. Aspartame-containing carbonated soft drinks provide 150–200 mg of aspartame per serving (12 oz or 360 ml). Noncarbonated beverages usually contain 140 mg per serving (8 oz or 240 ml). For the average 70-kg adult or 20-kg 4-yr-old, aspartame intake under these amounts would approximate 3–10 mg/kg body wt. The Market Research Corporation of America (MRCA) has projected the 99th percentile of daily intake of aspartame at 34 mg/kg body wt (3).

Accordingly, the clinical studies highlighted in this review bracket aspartame intakes that range from 4 to 200 mg/kg body wt. These studies largely represent single-bolus doses of aspartame given to normal adult subjects, known adult phenylketonuric (PKU) heterozygotes, or normal 1-yr-olds. Aspartame was administered in orange juice, in a noncarbonated beverage, as part of a hamburger and milk shake meal, or in a beverage ingested at repeated intervals. Aspartame doses >50 mg/kg body wt were considered to represent abuse doses; i.e., 100–200 mg/kg body wt. Based on the relative sweetness of aspartame to sucrose, abuse intakes of this magnitude represent an acute intake of sweetness equivalent to 3–6 lb of sucrose. Participants in the latter clinical studies found these high doses of aspartame excessively sweet.

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Each of these studies was conducted in a randomized crossover design to an appropriate placebo. In most studies, it was difficult to blind the subjects as to the identity of the aspartame-containing solutions due to aspartame's intense sweetness.

On the basis of these extensive studies, it is possible to develop dose-response curves for plasma amino acid concentrations after aspartame administration to normal subjects and individuals known to be PKU heterozygotes and to determine pharmacokinetic relationships predictive of the half-life ($t_{1/2}$) and average steady-state concentrations for plasma phenylalanine.

Comparable studies on the metabolism of aspartame in diabetic subjects have not been carried out. Of the few clinical studies involving diabetic subjects, observations have been limited to determination of the effects of aspartame loading on blood glucose, lipids, serum insulin, plasma glucagon, and glycosylated hemoglobin concentrations (4–8).

MATERIALS AND METHODS

Gut. In the gut, aspartame is subject to the action of esterases and peptidases that release methanol, L-aspartyl-L-phenylalanine, phenylalanine, and aspartate. Matthews (9) has provided evidence that aspartame or its dipeptide is transported into the cytosol of the enterocyte. Cystoplasmic enzymes in the enterocyte readily hydrolyze aspartame or aspartyl phenylalanine to aspartate and phenylalanine, and the resulting amino acids enter the portal circulation via a poorly understood transport mechanism within the basolateral membrane (10). Thus, in the gut, aspartame is subject to the same physiologic processes of digestion and transport as ingested protein or protein hydrolysates.

Plasma and erythrocyte free–amino acid pools. Phenylalanine enters the plasma free–amino acid pool from the portal blood after being subjected to the action of liver phenylalanine hydroxylase, resulting in its partial conversion to tyrosine. Within the enterocyte, aspartate is subject to transamination with other α-ketoacids, producing oxaloacetate, thereby attenuating the quantity of aspartate entering the portal circulation and plasma free–amino acid pool (11). It has not been established if the concurrent ingestion of carbohydrate and aspartate by humans will result in a further lowering of plasma free-aspartate concentration (12).

Methanol is not subject to metabolic degradation within the enterocyte and rapidly passes into the portal circulation to equilibrate with total body water. The circulating erythrocytes represent another organ system that can accumulate and transport free amino acids. Accordingly, we also measured the concentration of phenylalanine, aspartate, and other amino acids in erythrocytes.

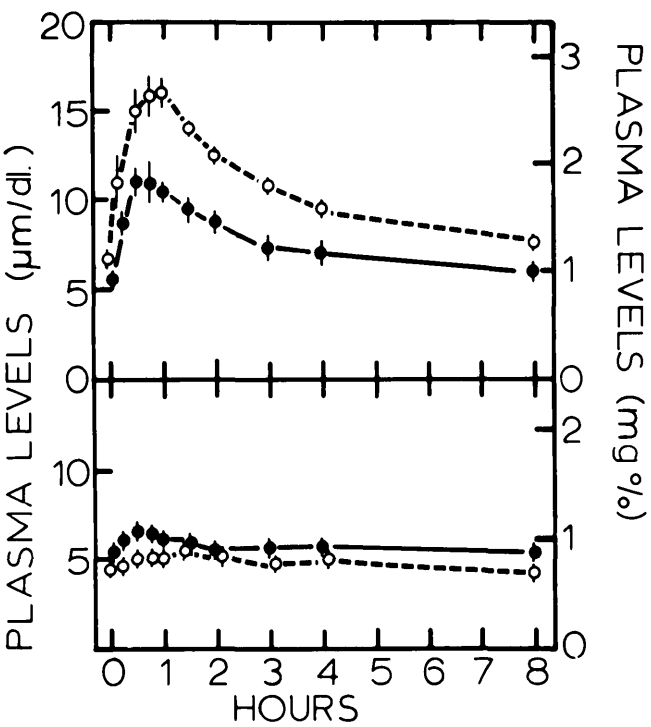

FIG. 1. Mean ± SE plasma phenylalanine (*top*) and tyrosine (*bottom*) concentrations in normal adults (●) and phenylketonuric heterozygotes (○) administered aspartame at 34 mg/kg body wt. [Reprinted with permission from *J Nutr* 109:708–17, 1979 (13). Copyright 1979.]

RESULTS

Phenylalanine. Twelve normal adults (6 men, 6 women) and 8 women known to be heterozygous for PKU were given 34 mg/kg body wt aspartame dissolved in 300 ml of orange juice after an overnight fast (3). Blood samples, collected at frequent intervals, were separated into plasma and erythrocyte fractions, and free–amino acid concentrations were determined on deproteinized samples. Plasma phenylalanine and tyrosine levels for these subjects are shown in Fig. 1. After the aspartame load, plasma phenylalanine concentrations peaked in 60 min at 11 and 16 μmol/dl for normal and PKU heterozygous subjects, respectively. Plasma phenylalanine levels in PKU heterozygotes were significantly higher, and the plasma phenylalanine concentration-time curve was broader than noted in normal subjects. Plasma tyrosine levels were higher in normal subjects 60 min after aspartame ingestion than in PKU heterozygotes. Erythrocyte phenylalanine and tyrosine levels showed a similar pattern (Fig. 2). These data clearly indicate that PKU heterozygotes metabolize the phenylalanine portion of aspartame slower than normal adults. However, peak plasma phenylalanine values in heterozygous subjects given aspartame at the 99th percentile of projected daily intake (34 mg/kg) are well below those associated with toxic effects (Table 1). Thus, the 99th percentile of projected daily intake of aspartame, given as a single-bolus dose to the PKU heterozygote, poses no significant risk.

Aspartame doses of 100, 150, and 200 mg/kg body wt were administered as a single bolus in orange juice to normal adult volunteers (3). Such intakes represent situations of abuse or accidental ingestion comparable with a daily intake of >20 L of an aspartame-sweetened beverage or a 10-kg 1-yr-old ingesting the entire contents of an aspartame coffee-sweetener bottle (100 tablets of 20 mg each). Peak plasma phenylalanine levels were proportional to dose (Fig. 3).

Comparable studies were carried out in PKU heterozygotes where the maximum bolus dose of aspartame studies was 100 mg/kg body wt (14). PKU heterozygotes given this dose metabolize the phenylalanine portion of aspartame as rapidly as normal adults metabolize aspartame doses of 200 mg/kg body wt (Fig. 4). These observations are compatible with the observations of Bremer and Neuman (15) and Woolf et al. (16).

The dose-response curves plotted from these studies are shown in Fig. 5. This curve predicts that peak plasma phenylalanine levels in normal subjects should increase ~1 μmol/dl above fasting level at an aspartame intake of 4 mg/kg body wt and ~2–3 μmol/dl above fasting levels at an intake of 10 mg/kg body wt.

Pharmacokinetic analysis of these dose-response data enables the prediction of the average steady-state concentration of plasma phenylalanine after repeated doses of aspartame (L.J. Fischer, personal communication). The calculated $t_{1/2}$ for disappearance of phenylalanine from plasma under the conditions of study was 1.7 h (Table 2), with a first rate constant (K_e) of 0.41. The first-order rate input for phenylalanine in plasma (K_1) is dose dependent, ranging from 1.26 to 3.7 μmol · dl^{-1} · h^{-1}. The variation in this constant might be due to the fact that the rate of hydrolysis of aspartame in the enterocyte is rate limiting.

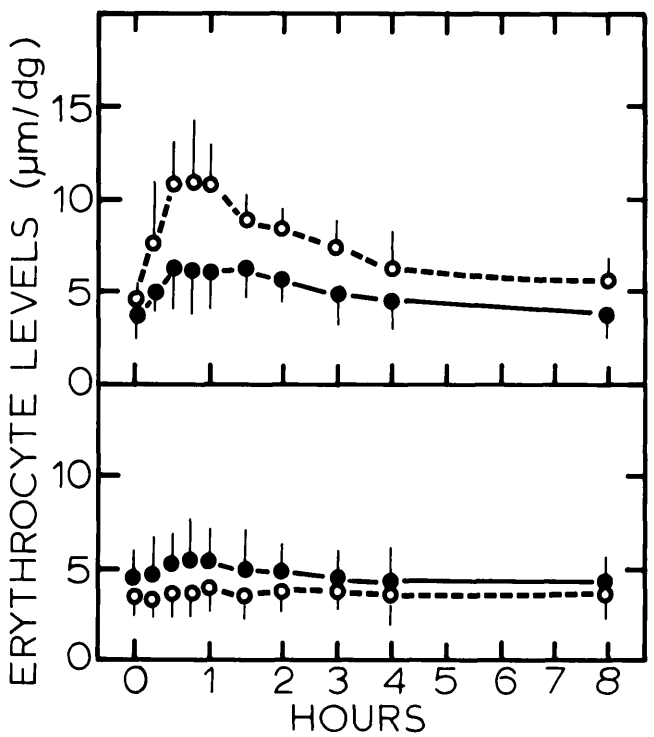

FIG. 2. Mean ± SD erythrocyte phenylalanine (*top*) and tyrosine (*bottom*) concentrations in normal adults (●) and phenylketonuric heterozygotes (○) administered aspartame at 34 mg/kg body wt. [Reprinted with permission from *J Nutr* 109:708–17, 1979 (13). Copyright 1979.]

TABLE 1
Plasma phenylalanine levels under various conditions

	Concentration (μmol/dl)
Normal subjects	
Fasting	6
Postprandial	12
Phenylalaninemia	
Classic phenylketonuria	120–600
Questionable variant	60–120
Benign variant	24–48
After 34 mg/kg body wt aspartame	
Normal	11
PKU heterozygote	16
After 100 mg/kg body wt aspartame	
Normal	20
PKU heterozygote	42

PKU, phenylketonuric.

Calculated average steady-state concentrations of phenylalanine after oral doses of aspartame ranging from 34 to 200 mg/kg body wt repeated at intervals of 1–8 h are given in Table 3. Administration of aspartame at the 99th percentile of projected daily intake at 2-h intervals will produce an average steady-state concentration of 12 μmol/dl in normal adults. These calculations illustrate the abnormal situations required to achieve plasma phenylalanine concentrations in excess of 60 μmol/dl, an upper limit for managing patients with hyperphenylalaninemia.

Studies of aspartame metabolism in 1-yr-olds indicate that blood levels of phenylalanine in children are lower than those observed in adults given an equivalent dose per kilogram of body weight (17). This probably reflects the fact that growing children incorporate phenylalanine into newly synthesized protein.

The effect of successive doses of aspartame on plasma levels of phenylalanine was studied in eight healthy adults (18). Twelve-ounce servings of an aspartame-containing beverage providing 10 mg/kg body wt aspartame per serving were given at 2-h intervals on three occasions. The observed increase in plasma phenylalanine concentration after individual doses ranged from 1.6 to 2.1 μmol/dl when compared with baseline values observed before dosing (Fig. 6). Baseline plasma phenylalanine concentrations increased slightly during the course of the study when the three successive beverage servings contained aspartame.

Aspartate. Unlike plasma phenylalanine concentrations, plasma aspartate levels do not increase proportionally to dose. No changes were noted in plasma or

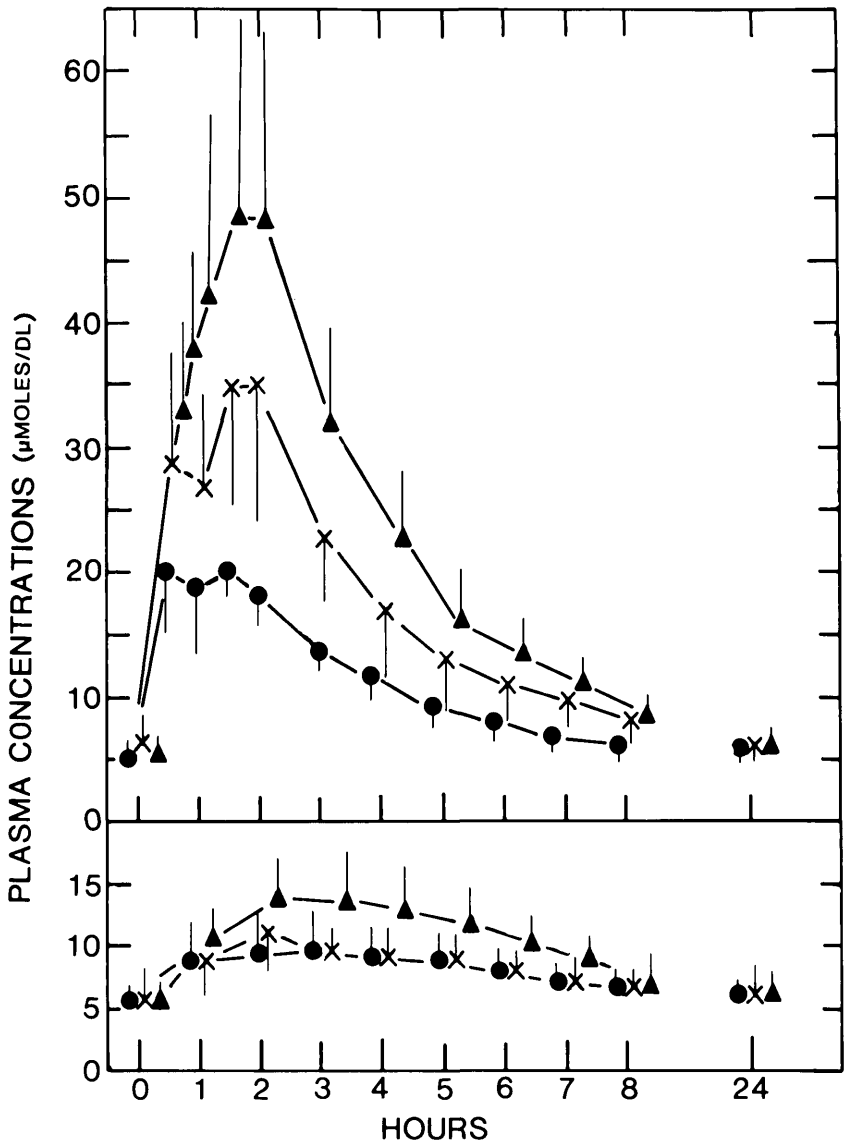

FIG. 3. Mean ± SD plasma phenylalanine (*top*) and tyrosine (*bottom*) concentrations (μmol/dl) in normal adults administered aspartame at 100 (●), 150 (X), or 200 (▲) mg/kg body wt. [Reprinted with permission from Stegink LD (3), New York, Dekker. Copyright 1984.]

erythrocyte aspartate concentrations when aspartame was given at ≤50 mg/kg body wt. Doses of aspartame between 100 and 200 mg/kg body wt produced a rise in plasma aspartate that was less than that observed postprandially in infants or adults fed a protein-containing meal. PKU heterozygotes and infants handled the aspartate portion of aspartame similarly to normal adult subjects.

Methanol. At an aspartame intake of 34 mg/kg body wt, blood methanol concentrations were below the sensitivity of the method (0.35–0.4 mg/dl). At abuse dose intakes of aspartame, 100–200 mg/kg body wt, peak blood methanol concentrations ranged from 1.3 to 2.6 mg/dl (3). Blood methanol levels returned to baseline within 8 h after an aspartame dose of 100 mg/kg body wt and within 24 h for higher levels of intake.

The methanol content of aspartame amounts to 10% of ingested dose. Thus, the maximum intake of methanol in these studies was 20 mg/kg body wt. There is ample evidence that dietary sources of methanol are only partial contributors to the total-body pool of methanol. Protein methylation through the action of protein methyl esterases also results in the formation of methanol as the end product. In addition, there are many widely consumed beverages that provide greater concentrations of methanol per liter than aspartame-containing beverages (Table 4).

Tephly and McMartin (19) have indicated that the toxic effects of methanol in the nonhuman primate are due to formate accumulation rather than formaldehyde or methanol. Accordingly, blood and urine samples from subjects administered the highest aspartame dose were assayed for formate content. No significant changes in blood formate concentration were noted after aspartame administration at 200 mg/kg body wt; however, urinary formate excretion was significantly increased for 8 h after dosing (Table 5). These urinary excretion data indicate conversion of methanol to formate. Because blood

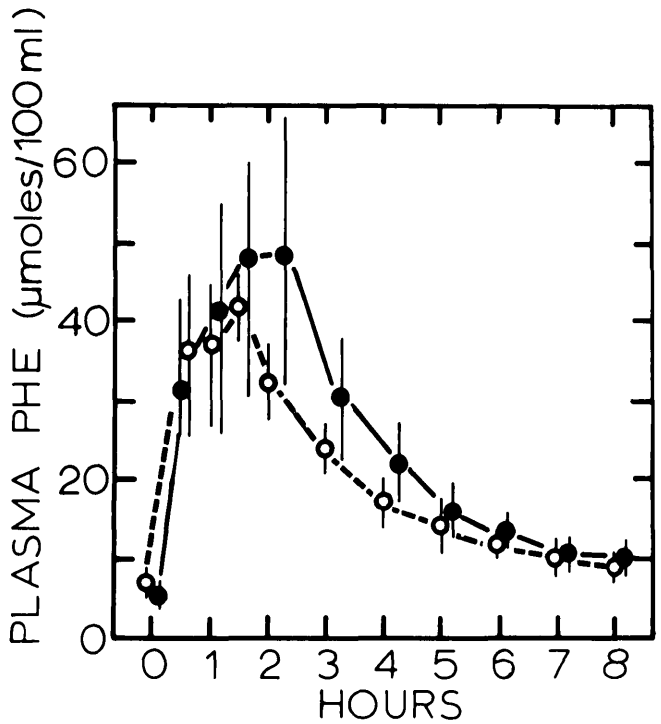

FIG. 4. Mean ± SD plasma phenylalanine concentrations in normal adults administered aspartame at 200 mg/kg body wt (●) and phenylketonuric heterozygotes administered aspartame at 100 mg/kg body wt (○). [Reprinted with permission from *J Nutr* 110:2216–24, 1980 (14). Copyright 1980.]

formate levels were not elevated, the rate of formate synthesis apparently did not exceed the rate of formate excretion.

Phenylalanine-to–large neutral amino acid ratio (Phe/LNAA). Studies in rats have shown that phenylalanine is transported from plasma into the brain via an amino acid transport site that is shared by a number of other large neutral amino acids (methionine, isoleucine, leucine, valine, tyrosine, and tryptophan). This mechanism is near or at saturation at normal plasma levels of these amino acids. Thus, the quantity of a specific amino acid transported into the brain increases as its level in the plasma increases. However, because each amino acid in the group competes for transport with other members of the group, the transport of a specific amino acid increases in proportion to its plasma level only if the levels of other amino acids sharing the transport site remain constant.

For example, plasma phenylalanine levels increase after ingestion of a protein meal, reflecting the phenylalanine content of the protein. However, the rate of phenylalanine transport into the brain does not increase because the protein also contains methionine, isoleucine, leucine, valine, tyrosine, and tryptophan. Plasma levels of these amino acids also increase postprandially in proportion to their content in the meal, resulting in increased competition of these amino acids with phenylalanine for the transport site.

In an attempt to quantitate the changes in brain transport rates relative to changes in plasma levels, Wurtman and Fernstrom (20) and Fernstrom and Faller (21) proposed the use of the ratio of the plasma concentration of the amino acid in question to the sum of the plasma concentrations of all the other amino acids sharing this transport site. Fernstrom et al. (22) have reported Phe/LNAA values as high as 0.13 ± 0.05 (mean ± SD) in normal adults under a variety of dietary conditions. Mean plasma Phe/LNAA values after aspartame ingestion are summarized in Table 6. A plasma Phe/LNAA value 2SD above the high mean value reported by Fernstrom et al. (22) would be 0.23. The Phe/LNAA values shown in Table 6 indicate that ingestion of three successive doses of aspartame at 10 mg/kg body wt at 2-h intervals has only a small effect on plasma Phe/LNAA. A single-bolus

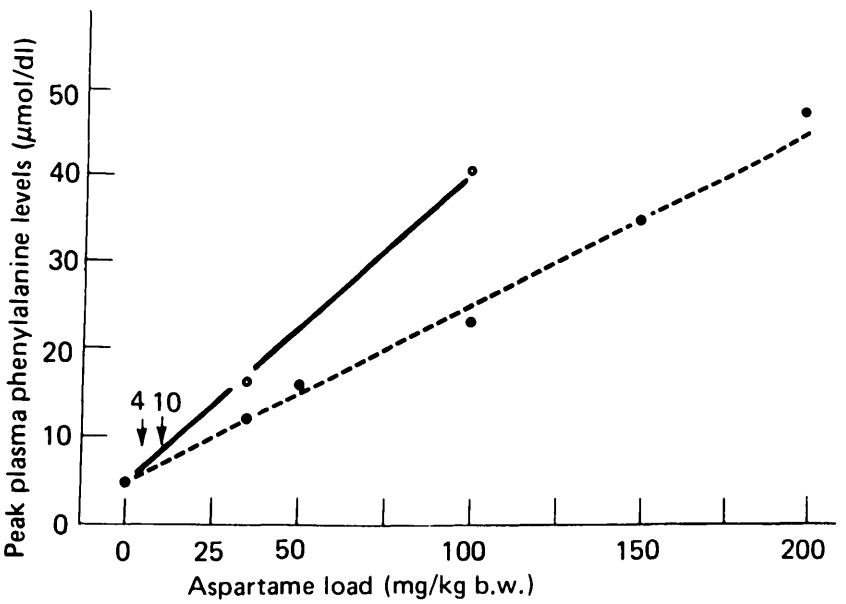

FIG. 5. Correlation of mean peak plasma phenylalanine concentrations with aspartame dose in normal subjects (●) and phenylketonuric heterozygotes (○). [Reprinted with permission from Steginк LD (3), New York, Dekker. Copyright 1984.]

TABLE 2
Plasma phenylalanine pharmacokinetics after aspartame dosing

Aspartame dose (mg/kg body wt)	$t_{1/2}$ (h)	K_e (μmol · dl^{-1} · h^{-1})	K_1 (μmol · dl^{-1} · h^{-1})
34	1.65	0.420	3.47
100	1.7	0.408	2.72
200	1.7	0.408	1.26

K_e, first rate constant; K_1, first-order constant.

dose of aspartame in orange juice at the 99th percentile for projected intake (34 mg/kg body wt) results in a mean Phe/LNAA of 0.23, a value within the range experienced under normal dietary conditions. Aspartame at 34 mg/kg body wt taken as part of a hamburger and milk shake meal has minimum effect on Phe/LNAA.

Adverse reactions. Several individuals have reported adverse effects from aspartame ingestion. In general, these reports are anecdotal. The Food and Drug Administration (FDA) and the Centers for Disease Control continue to receive and review reports of adverse reactions, but their reviews indicate little evidence of aspartame-related effects (24,25). The situation is best summarized by quoting the summary paragraph of Tollefson et al. (25)

> In summary, the adverse reactions that have been reported to the FDA regarding aspartame, and which have been extensively reviewed, do not establish reasonable evidence of possible public health harm. There is currently no consistent or unique pattern of symptoms reported with respect to aspartame that can be causally linked to its use. Because the information reported to the FDA is anecdotal and often not accompanied by complete medical records, the agency has been unable to eliminate factors other than aspartame consumption as reported causes for the adverse effects.

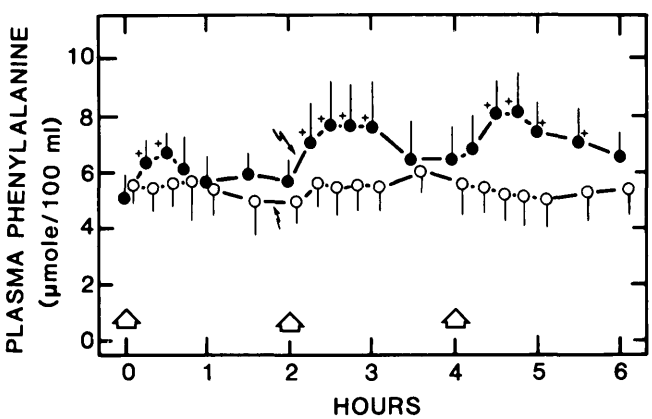

FIG. 6. Mean ± SD plasma phenylalanine concentrations in normal adults ingesting repeated servings of either unsweetened beverage (○) or beverage providing 10 mg/kg body wt aspartame (●). +P < .05 vs. baseline values. [Reprinted with permission from Stegink LD (3), New York, Dekker. Copyright 1984.]

TABLE 3
Plasma phenylalanine concentration in average steady-state concentration

Interval between doses (h)	Plasma phenylalanine levels at aspartame dose (mg/kg body wt)		
	34	100	200
		(μmol/dl)	
1	18	73	162
2	12	40	84
3	10	28	58
4	9	23	45
8	6	14	25

Values are in micromoles per deciliter.

Aspartame studies in diabetic subjects. Stern et al. (4) fed 69 adult NIDDM subjects, aged 21–70 yr, 1.8 g of aspartame or a placebo control daily for 13 wk. Subjects were randomly assigned in a double-blind study design. Two aspartame or placebo-containing capsules were given 3 times daily. There was no evidence that aspartame influenced the control of diabetes. Furthermore, there were no significant differences between treatment groups in mean body weight or blood pressure. Plasma phenylalanine and tyrosine concentrations did not differ by treatment group.

Paccalin et al. (5) studied 177 persons given 2–15 aspartame tablets (20 mg) daily for 3–15 mo. They reported that aspartame had no effect on blood glucose, triglycerides, and total lipids. No interactions with antidiabetic treatment were noted.

Horwitz et al. (6) and Nehrling et al. (7) fed 2.7 g of aspartame, equivalent to 1.2 lb of sugar, or an appropriate placebo control daily for 18 wk to 63 diabetic subjects without effect on fasting plasma glucose, glycosylated hemoglobin, glucagon, cholesterol, or high-density lipoprotein cholesterol (HDL-chol) levels. A slight increase in serum insulin concentration was noted among those subjects given aspartame. In an acute loading study of normal and diabetic subjects, Horwitz determined insulin, glucagon, and blood glucose responses to 400 mg of aspartame or 135 mg of saccharin. Aspartame

TABLE 4
Methanol content of various natural products and aspartame-containing beverages

Product	Methanol concentration (mg/L)
Tomato juice	180–218
Grape juice	12–680
White wines	20–36
Red wines	99–271
Brandy	181–2425
Soft drink (aspartame)	55

TABLE 5
Urinary formate excretion in normal adults given 200 mg/kg body wt aspartame

Urine sample collection interval (h)	Formate excretion (μg/mg creatinine)
Preload 8	34 ± 22
0–4	101 ± 30*
4–8	81 ± 22*
8–24	38 ± 12

*Differs from baseline value, $P < .01$.

and saccharin had no effect on insulin, glucagon, or blood glucose concentrations (26).

Okuno et al. (8) have reported similar results in diabetic subjects given 500-mg doses of aspartame. These investigators also fed a group of diabetic subjects 125 mg aspartame daily, the sweetness equivalent of daily sugar intake from the Japanese diet for 2 wk. No changes were noted in blood glucose, cholesterol, HDL-chol, or triglycerides. Glucose tolerance testing remained unchanged.

Glucose metabolism and the glucoregulatory hormones insulin and glucagon have been measured in 59 adolescents given 300 mg aspartame or placebo during weight reduction (27). Plasma glucagon concentrations increased in both groups throughout the 13-wk period of weight reduction. Insulin levels decreased in the group receiving aspartame during the first 7 wk of the study and then returned to baseline values. The authors concluded that weight reduction in these subjects caused a detectable metabolic shift in carbohydrate metabolism that was not affected by aspartame.

Diabetic subjects have been given aspartame under chronic and acute dosing situations. Whereas studies of plasma free–amino acid response to aspartame loading have not been carried out, examination of the effects of acute or chronic loads of aspartame in diabetic subjects indicate that it is without effect on blood glucose, lipid, insulin, or glucagon concentrations.

On the basis of these observations, we conclude that aspartame may be safely ingested at projected levels of use.

DISCUSSION

Whereas some high-intensity sweeteners may have been subjected to more extensive animal testing for the purpose of demonstrating safety for use in the food supply, it is doubtful if any additive has received more clinical study than aspartame. As noted in this study, aspartame has been fed under a variety of conditions to normal adults, known PKU heterozygotes, 1-yr-olds, and IDDM and NIDDM subjects. Clinical tests have focused on doses of aspartame compatible with its use in the food supply in addition to its use under abuse situations. Administration

TABLE 6
Mean plasma phenylalanine-to–large neutral amino acid (Phe/LNAA) values after aspartame ingestion by normal subjects

Dietary condition	Phe/LNAA ± SD	Ref.
Fasting	0.10 ± 0.01	23
Protein meal, 1 g protein/kg body wt	0.10 ± 0.02	18
Kool-Aid + aspartame		
4 mg/kg body wt	0.10 ± 0.02	23
10 mg/kg body wt	0.14 ± 0.02	23
10 mg/kg body wt × 3 doses	0.16 ± 0.02	18
Orange juice + aspartame		
34 mg/kg body wt	0.23 ± 0.04	18
Protein meal + aspartame		
34 mg/kg body wt	0.13 ± 0.03	18

of aspartame to humans occurred in the fasting state, as part of a meal, or in repeated loading studies. Pharmacokinetic data developed for plasma phenylalanine concentrations indicate that a bolus dose of 34 mg/kg body wt, the 99th percentile of projected daily intake, repeated at intervals of 2 h does not increase plasma phenylalanine concentrations above those levels experienced after ingesting a protein-containing meal. Aspartate and methanol released from aspartame under the conditions of these clinical studies did not constitute an excessive metabolic load.

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