

# Aspartame: neuropsychologic and neurophysiologic evaluation of acute and chronic effects<sup>1-3</sup>

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## ABSTRACT

**Background:** Neurobehavioral symptoms have been reported anecdotally with aspartame.

**Objective:** This study sought to determine whether aspartame can disrupt cognitive, neurophysiologic, or behavioral functioning in normal individuals.

**Design:** Forty-eight healthy volunteers completed a randomized, double-blind, placebo-controlled, crossover study. The first month was aspartame free. Subjects then consumed sodas and capsules with placebo, aspartame, or sucrose for 20 d each. Order was randomized and subjects were assigned to either a high- (45 mg·kg body wt<sup>-1</sup>·d<sup>-1</sup>) or low- (15 mg·kg body wt<sup>-1</sup>·d<sup>-1</sup>) dose aspartame group. Neuropsychologic and laboratory testing was done on day 10 of each treatment period to determine possible acute effects and on day 20 for possible chronic effects.

**Results:** Plasma phenylalanine concentrations increased significantly during aspartame treatment. Neuropsychologic results; adverse experiences; amino acid, insulin, and glucose values; and electroencephalograms were compared by sex and by treatment. No significant differences were found for any dependent measure.

**Conclusion:** Large daily doses of aspartame had no effect on neuropsychologic, neurophysiologic, or behavioral functioning in healthy young adults. *Am J Clin Nutr* 1998;68:531-7.

**KEY WORDS** Aspartame, sucrose, behavior, mood, cognition, adverse experience, side effect, neuropsychology, neurophysiology, humans, artificial sweetener, phenylalanine, large neutral amino acids

## INTRODUCTION

Although aspartame (NutraSweet Corp, Deerfield, IL) is approved for human use in >100 countries, some adverse experiences have been reported anecdotally. These were summarized by the Centers for Disease Control and Prevention in 1986 (1) and some were investigated in a challenge study reported by the National Institutes of Health in 1991 (2). These complaints included several neurobehavioral symptoms, and other anecdotal reports have suggested that aspartame might produce headaches (3), panic attacks (4), or even seizures (5); the possibility of seizures was also evaluated by the Food and Drug Administration (FDA) (6).

The ingredient of possible concern is phenylalanine, a large neutral amino acid (LNAA) that allegedly inhibits serotonin and catecholamine synthesis in experimental animals after high doses (7, 8). No such data exist for humans, however, and several studies showed no evidence of adverse effects in children or adults (9-15). These included assessments of mood, aggression, arousal, and selected cognitive functions. The potential relation between aspartame and neuronal function was reviewed recently (16), but few studies have systematically tested neurobehavioral functioning.

A colleague at Massachusetts Institute of Technology (MIT), RJ Wurtman, received hundreds of unsolicited letters from concerned individuals after the publication of his letter concerning aspartame and seizure susceptibility (17); a protocol was then designed to investigate neurobehavioral, cognitive, or neurophysiologic reactions in these complainants. Before this, the Clinical Research Center's (CRC) Advisory Committee insisted that high-dose aspartame consumption be tested in healthy subjects. In a preliminary pilot study reported elsewhere (18), we were surprised to find a decline in performance on certain cognitive tasks when some subjects consumed aspartame. As a result, we decided to investigate whether healthy subjects have any disruption in mood or cognitive or neurophysiologic functioning when consuming high doses of aspartame. Further, we evaluated any effects on phenylalanine or its ratio to the sum of all other LNAAs (Phe:LNAA), which is a more precise marker for the transport of phenylalanine into the brain.

## SUBJECTS AND METHODS

The study was conducted at the MIT CRC. Electroencephalograms (EEGs) were done at the Beth Israel-Deaconess Medical

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Center (BI-DMC) in Boston. The protocol was approved by the human research committees of both institutions.

## Subjects

Sixty-seven undergraduate or graduate students were screened to obtain 48 (24 male, 24 female), 18–35-y-old subjects. Twenty-three percent were Asian, Eurasian, or African American, and the remainder were white. Subjects were recruited by advertisement. They were screened for medical, neurologic, or psychiatric disorders, phenylketonuria, and learning disabilities. All subjects were right-handed. Pregnant or lactating women were excluded, as were those taking oral contraceptives; all women were screened for severe premenstrual syndrome and seasonal affective depression. Subjects taking psychotropics or with a history of drug or alcohol abuse were excluded.

Subjects were paid for participation and received prorated payment if they did not complete the study. Three subjects discontinued: 2 men moved away and 1 woman required surgery. No subjects dropped out as a result of adverse experiences related to treatment. Dropouts were replaced to preserve the statistical power of the design but any adverse symptoms reported were retained for analysis. Replacements started the protocol from the beginning with the same sequence of treatments as that received by the dropout.

Subjects were pretested to ensure that they were of at least average ( $\geq 50$ th percentile) verbal and nonverbal intelligence, verbal attention, and memory before they proceeded to familiarization with a computer-administered task (ThinkFast; 19) that would be a dependent measure. This program requires the subject to compare, copy, and recall alternating trials of verbal and nonverbal stimuli. Potential subjects also underwent medical screening, which included an electrocardiogram, an EEG, routine hematologic tests, urinalysis, blood chemistry tests, urine and plasma toxin screens, as well as a routine physical and neurologic examination. The cognitive screening results and demographics are presented in **Table 1**. Male and female subjects differed only on the nonverbal reasoning test; men had a slight advantage, consistent with research concerning sex-related differences (20).

**TABLE 1**  
Characteristics of the subjects<sup>1</sup>

	Men (n = 24)	Women (n = 24)	All (n = 48)
Age (y)	22.5 <sup>2</sup>	22.8	3.9 (18–34) <sup>3</sup>
Education (y)	16.2	16.7	2.2 (13–20)
Digit Span, forwards	6.7	6.8	0.5 (5–7)
Digit Span, backwards	5.3	5.6	0.7 (4–6)
WDS/32	30	29.8	1.7 (25–32)
VOC/40	35.7	35.7	2.5 (29–40)
ABS/40	37.6	37.3	2.3 (32–40)
RAV/60	56.9 $\pm$ 2.3 (51–60) <sup>4,5</sup>	54.5 $\pm$ 3.4 (43–59)	—

<sup>1</sup>WDS/32, words recalled in 4 trials with an 8-word list (subject had to recall all 8 by trial 4 to meet criterion); VOC/40, Shipley Vocabulary (40 points possible); ABS/40, Shipley Abstractions (40 points possible); RAV/60, Raven's Progressive Matrices (60 points possible). Tests described in reference 20.

<sup>2</sup> $\bar{x}$ .

<sup>3</sup>SD; range in parentheses.

<sup>4</sup> $\bar{x} \pm$  SD; range in parentheses.

<sup>5</sup>Significantly different from women,  $P < 0.005$  (two-tailed Student's  $t$  test).

## Treatments

There were 3 treatment conditions: aspartame, sucrose, and placebo. Subjects received each treatment in a randomized, double-blind, 3-way crossover design and were assigned to either high- (HIAP: 45 mg·kg body wt<sup>-1</sup>·d<sup>-1</sup>) or low- (LOAP: 15 mg·kg body wt<sup>-1</sup>·d<sup>-1</sup>) dose aspartame. The results of the randomization were known only to the clinical pharmacy (Almedica Services Corp, Waldwick, NJ) that prepared the treatment supplies and to an independent statistician. HIAP approached the FDA's acceptable daily intake for aspartame (50 mg·kg body wt<sup>-1</sup>·d<sup>-1</sup>) and exceeded the acceptable daily intake of Health and Welfare Canada (40 mg·kg body wt<sup>-1</sup>·d<sup>-1</sup>; 22).

Depending on body weight, HIAP was the daily aspartame equivalent of 17–24 diet beverages (355 mL, or 12 oz) for men and 14–19 such beverages for women. Equal numbers of men and women were randomly assigned to the HIAP and LOAP groups. Sucrose treatment (90 g/d) was the same for all subjects. Sucrose delivery required a beverage, however, and a lightly carbonated, lemon-lime flavored soda was formulated. Sodas and capsules were administered for all treatments to maintain the blinding. In the aspartame-treatment period, the bulk of the treatment substance was in the capsules, whereas in the sucrose treatment period the bulk of the treatment substance was in the sodas. Sweetness was equivalent for aspartame and sucrose sodas. For placebo, sodas were unsweetened and capsules contained 300 mg microcrystalline cellulose (Avicel PH 102; FMC Corp, Philadelphia) and 0.9 mg silicon dioxide.

Sodas and capsules were identical in appearance except for being labeled treatment 1, 2, or 3. The number of capsules varied by aspartame dose and body weight but identical numbers of capsules were given each treatment period. Subjects were told the treatment might be contained in either the capsules or the sodas and that taste might not be correlated with treatment. The blinding was tested in a Latin-square design for the first 12 subjects who guessed their order of treatments. Independent statistical analysis showed that the blinding was effective.

Subjects were not permitted to consume dietary aspartame during the study but dietary sucrose was restricted only on test days. Subjects maintained their usual diets except on test days, when meals were provided and they were asked not to snack or consume additional sucrose. Subjects abstained from alcohol and any drugs for 36 h before testing. This was verified by urine and plasma toxin screens. Compliance with treatment was verified by plasma amino acid and glucose analysis.

## Procedures

Participation was for 4 consecutive months with 3 outpatient visits per treatment period: 2 for testing and 1 for monitoring before the next treatment. The first month was baseline, during which subject were asked not to consume aspartame and were not given any treatment. During months 2, 3, and 4, subjects were provided with sodas and capsules, which they took 3 times daily (at 1000, 1500, and 2000) for 20 d. Order was randomized so that each of the 6 orders for the 3 treatments was assigned 8 times.

Neuropsychologic testing was done on days 10 and 20 of each treatment period. For female subjects, testing was scheduled for the 10th and 20th days of their menstrual cycle to minimize any ovulatory or late-luteal influences. Acute effects (day 10) were assessed 1.5 h after capsules and sodas were ingested and chronic effects (day 20) by testing before any morning treatments were consumed.

On acute test days (**Table 2**), fasting subjects had blood drawn and were given a breakfast that was the same on day 10 of each treatment period. Subjects then had brief physical examinations, reported any adverse symptoms, and left with a lunch that was also the same on each test day. Subjects consumed the treatment (capsules and soda) at 1000 and ate lunch at 1130. They returned to the CRC at 1430 for mood assessment with the Profile of Mood States (POMS; 23). Blood was drawn and the treatment substance was taken again at 1500. Subjects returned at 1620 for repeat mood assessment and blood sampling, which were followed by neuropsychologic testing and repeat blood sampling.

Meals were standardized on test days and breakfast contained 11 g protein, 6 g fat, and 75 g carbohydrate. Lunch provided 34 g protein, 16 g fat, and 107 g carbohydrate for men and 26 g protein, 9 g fat, and 84 g carbohydrate for women. Given that proteins are estimated to contain  $\approx 5\%$  phenylalanine, the standard breakfast would have provided  $\approx 90$  mg phenylalanine for a 60-kg male or the equivalent of 1.5 mg/kg. When compared with the active treatments (HIAP and LOAP) and the amount consumed by a hypothetical subject of the same weight (1575 mg for HIAP, 525 mg for LOAP) before cognitive testing, the diet provided inconsequential amounts of phenylalanine relative to the treatments, which represented substantial challenge doses.

On chronic test days (**Table 2**), subjects arrived for blood sampling and breakfast followed by mood assessment and neuropsychologic testing. After this, subjects had their blood drawn again, had a physical examination, and reported any adverse symptoms. The treatment was taken at 1000 and an EEG was obtained later at the BI-DMC. Subjects stopped treatment for that period after their EEG, and observed a 10-d washout before the next treatment.

## Dependent measures

### Physical

Physical measures included supine and standing blood pressure, weight, temperature, and heart and respiratory rates. Brief physical and neurologic examinations with strength and reflex testing were also performed.

### Laboratory

Blood was collected for glucose, insulin, and amino acid tests; for toxin screens; and for routine hematology (hemoglobin and hematocrit, and red blood cell, white blood cell, differential, and platelet counts), and fasting blood chemistry tests (total protein, albumin, calcium, inorganic phosphorus, cholesterol, glucose, urea nitrogen, uric acid, alkaline phosphatase, lactate dehydrogenase, total bilirubin, serum aspartate aminotransferase, alanine aminotransferase, sodium, potassium, chloride, carbon dioxide, and creatinine). Samples were also obtained for urinalysis.

Amino acids (ie, alanine, arginine, aspartate, glutamate, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, tyrosine, and valine) were analyzed on an amino acid analyzer (HPLC System model 334; Beckman Instruments, Palo Alto, CA), except for tryptophan, which was analyzed by fluorometry (24). Glucose was determined with a kit (Worthington Flozyme Glucose; Cooper Biomedical, Freehold, NJ) based on the coupled enzyme method (25). Insulin concentration was obtained from radioimmunoassay by using a kit (Incstar, Stillwater, MN). Toxin screens were carried out commercially (Met-Path, Boston). Urine screens for drugs of abuse (ie, amphetamines,

**TABLE 2**

Schedule of treatments and procedures on the acute (day 10) and chronic (day 20) testing days<sup>1</sup>

Time	BD	TX	NE	PE	B	TS	L	PO	NT
0800	XO	O	XO	XO					
0815					XO			O	
0830									O
0955	O								
1000						XO	X		
1445								X	
1455	X								
1500						X			
1620								X	
1625	X	X							
1630									X
1730	X								

<sup>1</sup>X, day 10; O, day 20. BD, blood draw; TX, toxin screen; NE, neurologic examination; PE, physical examination; B, prepared breakfast; TS, treatment substance taken; L, prepared lunch; PO, Profile of Mood States (23); NT, neuropsychologic testing.

mines, barbiturates, benzodiazepines, cocaine, marijuana, methaqualone, opiates, and phencyclidine) were performed by the homogeneous enzyme multiplied immunotechnique method (EMIT; Syva, Palo Alto, CA). A serum screen for alcohol was done by gas chromatography.

## Adverse experiences

Adverse symptoms were evaluated at each visit and subjects could use an emergency messaging system. Time of onset, duration, intensity, and frequency were recorded for any adverse physical, cognitive, or behavioral symptom. Concurrent history was obtained to identify any other potential etiologies. Before breaking the blinding, all adverse symptoms were reviewed and classified as related or unrelated to treatment. For example, fatigue, breathing trouble, and headache with a concurrent history of upper respiratory infection would not have been classified as an adverse experience. While still blinded, investigators also reviewed complaints for symptoms present only during one treatment. This yielded 32 potential treatment-specific symptoms that were grouped into 5 neurobehavioral categories: irritability, emotionality, cognition, sleep, and appetite.

## Neurophysiology

EEGs were performed with a Grass machine (model 8 or 9, 18-channel, scalp electrodes; Grass Instruments Corp, Quincy, MA) by using international 10–20 system montages for electrode placement. Recording was for 45 min with brief hyperventilation and photic stimulation and were read by board-certified electroencephalographers who were blinded to treatment and did not interact with the subjects.

## Neuropsychology

Cognitive measures were selected to screen functioning in the frontal and temporolimbic networks, which are responsible for many aspects of mood, memory, and behavior. The order of administration and the specific tests are summarized in **Table 3**. Detailed descriptions of these tests appear elsewhere (20) and alternate, equivalent forms were used at each testing. Subjects were first administered a word list learning test. Verbal and non-verbal attention span was then assessed. Short-term recall of the



**TABLE 3**

Neuropsychologic functions tested, measures given, and order of administration at each testing session on the acute (day 10) and chronic (day 20) testing days<sup>1</sup>

Function	Test administered
Verbal learning	20-word list, 5 trials, free recall
Verbal attention span	Digit Span, forwards and backwards
Spatial attention span	Corsi Block Test, forwards and backwards
Short-term memory	Free recall of word list
Verbal fluency	Controlled Oral Word Association
Response set alternation	Trailmaking Tests, form A and form B
Response set inhibition	Stroop Test, interference condition
Motor response set alternation	Auditory Reciprocal Motor Programs
Motor response set inhibition	Auditory, Go-No Go
Overall cognitive efficiency	ThinkFast
Long-term memory	Free recall of word list

<sup>1</sup>Tests described in reference 20.

word list was obtained next and then verbal fluency was measured. Response set and motor response set alternation and inhibition were tested and subjects were then given the computer-administered test, a measure of overall cognitive efficiency. Long-term word list recall was obtained last to measure storage of recently acquired verbal information.

### Mood

POMS ratings were for 6 scales: tension, anger, depression, vigor, fatigue, and confusion. To assess substance-dependent effects on mood, subjects completed the POMS on day 10 before their afternoon treatment and then later, before neuropsychologic testing. The POMS on day 20 was completed in the morning before the treatment substance was consumed.

### Statistical analyses

An a priori statistical plan (ClinTrials, Lexington, KY) was developed before the blind was opened with significance set at the  $P \leq 0.05$  significance level. Data were recorded on case report forms and copies were sent to ClinTrials. The neurocognitive tests, POMS factors, amino acids, Phe:LNAA values, and all blood values, including glucose and insulin, were analyzed by a series of univariate, multifactor analyses of variance (ANOVAs).

Preliminary ANOVAs decided whether sex and testing day could be pooled for the treatment ANOVAs, which then compared differences between treatments (aspartame, sucrose, and placebo) for both doses (HIAP and LOAP). Follow-up analyses were performed for any significant effects. The adverse experiences and EEGs were analyzed with the exact form of McNemar's test for correlated proportions (26).

## RESULTS

### Laboratory

Toxin screens and laboratory values confirmed that subjects were compliant with the protocol. Any positive screen results were traced to the metabolites of cold remedies. Amino acid analyses showed significant differences during aspartame treatment. On acute test days, both aspartame groups had significant increases in Phe:LNAA compared with their values when receiving placebo and sucrose (Figure 1). This elevation was sustained

throughout the neuropsychologic testing, with elevated Phe:LNAA at repeat blood drawing as well (Table 4, Figure 1, and Figure 2).

On chronic test days, blood drawn in the fasted state before breakfast showed no chronic elevation in Phe:LNAA with the LOAP treatment (Figure 1). With the HIAP treatment, phenylalanine and Phe:LNAA were slightly but significantly greater on day 20 (Figure 2). This confirmed treatment compliance and showed that a high dose was needed to sustain elevations overnight. After breakfast, this increase disappeared and treatment differences were no longer significant. Phe:LNAA values, therefore, returned to normal in just over 12 h, even when subjects had been consuming  $45 \text{ mg} \cdot \text{kg body wt}^{-1} \cdot \text{d}^{-1}$  for 3 wk.

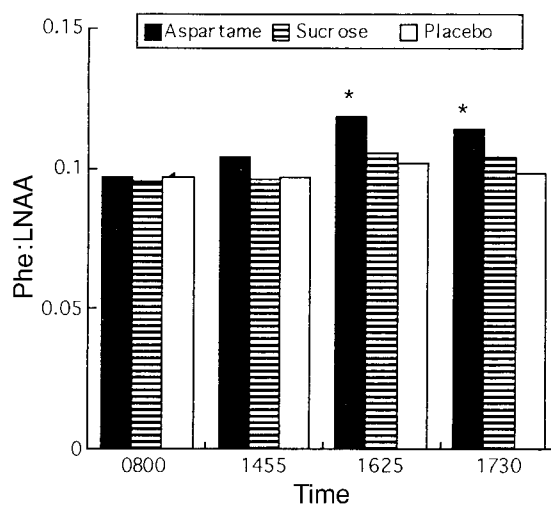
No other laboratory values, including those for all other amino acids, glucose, and insulin, yielded any significant findings due to treatment. The absence of a glucose effect during sucrose treatment was likely due to the timing of blood sampling. The schedule was designed to sample phenylalanine (1.5 h postdose) but was perhaps not ideal for measuring glucose response.

### Adverse experiences

There was no significant treatment effect for adverse experiences. Four symptoms were identified as occurring with sufficient frequency for statistical analysis: headache, fatigue, nausea, and acne. The incidence of each was compared by treatment and no significant difference was found between aspartame, sucrose, or placebo treatments (Table 5). The most frequent complaint was headache, and of 40 reported, 15 occurred with aspartame, 14 with sucrose, and 11 with placebo. This complaint was not dose-related because 11 of the aspartame headaches were reported with the LOAP treatment. For the neurobehavioral categories, 32 experiences were classified as occurring for only 1 treatment, of these, 13 were during administration of placebo, 13 during sucrose, and only 6 during aspartame (Table 5).

### Electroencephalograms

No EEG abnormalities were associated with any treatment.



**FIGURE 1.** Ratios of phenylalanine to large neutral amino acids (Phe:LNAA) for all subjects in the low-aspartame ( $15 \text{ mg} \cdot \text{kg body wt}^{-1} \cdot \text{d}^{-1}$ ) group on the acute testing day (day 10). \*Significantly different from sucrose and placebo,  $P < 0.05$ .

**TABLE 4**

Plasma concentrations of phenylalanine (Phe) and the ratio of phenylalanine to all other large neutral amino acids (Phe:LNAA) on the acute testing days (day 10), before and after neuropsychologic testing<sup>1</sup>

Group and treatment	Blood sampling time			
	1625		1730	
	Phe	Phe:LNAA	Phe	Phe:LNAA
	$\mu\text{mol/L}$		$\mu\text{mol/L}$	
HIAP ( <i>n</i> = 24)				
Aspartame	78.5 ± 12.2 <sup>2</sup> (56.8–104.1)	0.138 ± 0.023 <sup>2</sup> (0.101–0.183)	71.8 ± 8.7 <sup>2</sup> (53.0–87.0)	0.132 ± 0.016 <sup>2</sup> (0.101–0.169)
Placebo	56.2 ± 10.4 (42.0–83.6)	0.097 ± 0.010 (0.075–0.116)	52.8 ± 10.6 (36.0–84.0)	0.095 ± 0.012 (0.066–0.117)
Sucrose	56.3 ± 8.9 (41.4–77.9)	0.103 ± 0.011 (0.084–0.129)	50.4 ± 5.6 (40.9–60.6)	0.096 ± 0.009 (0.079–0.110)
LOAP ( <i>n</i> = 24)				
Aspartame	67.9 ± 10.2 <sup>2</sup> (56.8–106.5)	0.118 ± 0.022 <sup>2</sup> (0.087–0.195)	60.7 ± 10.6 <sup>2</sup> (43.2–95.7)	0.114 ± 0.022 <sup>2</sup> (0.072–0.196)
Placebo	61.0 ± 9.8 (42.8–86.5)	0.105 ± 0.018 (0.075–0.158)	57.2 ± 9.4 (38.1–75.30)	0.104 ± 0.015 (0.079–0.137)
Sucrose	55.2 ± 6.7 (43.2–71.3)	0.102 ± 0.013 (0.080–0.128)	51.6 ± 5.1 (38.9–62.7)	0.098 ± 0.007 (0.085–0.113)

<sup>1</sup> $\bar{x} \pm \text{SD}$ ; range in parentheses.

<sup>2</sup>Significantly different from placebo and sucrose treatments,  $P < 0.05$  (planned comparison).

All EEG findings were judged to be mild, normal variants. Of the 220 EEGs, 24 had such variants, of which 9 occurred during aspartame treatment, 6 with LOAP, and 3 with HIAP. No epileptiform transients were observed and statistical comparison by treatments showed no significant differences.

#### Neuropsychologic measures

No treatment substance altered performance on any cognitive or neuropsychologic measure. The HIAP and LOAP groups did not differ during baseline and there was no main effect by treatment at any acute or chronic testing. Practice effects were observed for backwards spans and verbal list learning. Subjects

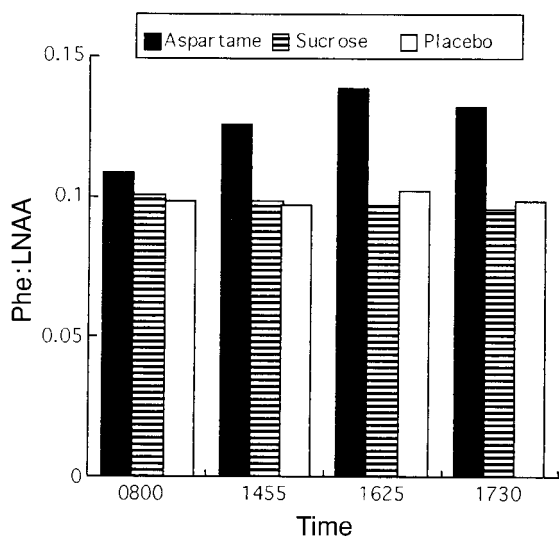
had improved backwards spans ( $P < 0.05$ ), learned more words over 5 trials ( $P < 0.02$ ), and had better mean learning ( $P < 0.0001$ ) as their participation in the study progressed. This was independent of the order of treatments, however, and would be consistent with a practice effect. No order effect by treatment was observed for any task.

#### Mood

POMS scales showed no main effect for treatments, nor were any treatment-by-day or treatment-by-sex interactions observed.

#### DISCUSSION

This study did not confirm our hypothesis. Although increases



**FIGURE 2.** Ratios of phenylalanine to large neutral amino acids (Phe:LNAA) for all subjects in the high-aspartame (45 mg·kg body wt<sup>-1</sup>·d<sup>-1</sup>) group on the acute testing day (day 10). All comparisons of aspartame with sucrose and placebo were significant,  $P < 0.05$ .

**TABLE 5**

Adverse reactions reported by all subjects and classified by investigators before they knew of group assignments<sup>1</sup>

	Treatments				
	All	LOAP	HIAP	Sucrose	Placebo
Number of symptoms reported					
Headache	40	11	4	14	11
Fatigue	10	3	1	4	2
Nausea	9	1	1	3	4
Acne	10	1	2	4	3
Symptoms reported fitting investigator categories					
Irritability	9	0	2	2	5
Cognition	6	1	0	2	3
Emotionality	5	0	0	3	2
Appetite	5	1	1	3	0
Sleep	7	0	1	3	3

<sup>1</sup>*n* = 51, including dropouts if relevant. LOAP, low-dose aspartame (15 mg·kg body wt<sup>-1</sup>·d<sup>-1</sup>); HIAP, high-dose aspartame (45 mg·kg body wt<sup>-1</sup>·d<sup>-1</sup>).

in Phe:LNAA were observed that were 23–39% higher with aspartame than with placebo or sucrose, there was no effect on neurocognitive or neurophysiologic functioning. Consuming a protein-rich meal before aspartame ingestion diminishes elevations in Phe:LNAA (27). Consequently, consumers who might restrict food intake and then drink an aspartame-containing beverage with a carbohydrate snack might experience higher Phe:LNAA values acutely than those observed here. Our subjects may, in fact, have had such concentrations at times, given that balanced meals were only provided on test days. Our sample did not, however, have a higher incidence of adverse experiences with aspartame, even though they far exceeded population estimates of daily consumption. The average daily intake in the 90th percentile in the United States is only  $\approx 3.0$  mg/kg (28). Figure are similar for Canada (5.9 mg/kg; 29), the United Kingdom (1.6 mg/kg; 30), and Germany (2.8 mg/kg; 31). The dose used in our LOAP condition was, therefore, well beyond these 90th percentile estimates and the HIAP treatment provided a dose equivalent to improbable levels of consumption.

Our findings corroborate the results of another double-blind, placebo-controlled, crossover study of aspartame on the activity level, behavior, and cognitive ability of preschool and elementary school children (32). The increases in phenylalanine and Phe:LNAA were similar to those we observed but aspartame did not affect the mood, activity levels, behavior ratings, or cognitive results of these children, a result that replicates earlier findings (11–13).

One study reported that giving a bolus of aspartame (40 mg/kg) to children with primary generalized-absence seizures increased the mean number of seconds per hour spent in spike-wave discharges but the actual number of seizures manifested did not increase (33). Although these findings cannot be interpreted with confidence for methodologic reasons (34), more recent studies of children with epilepsy showed no relation between consumption of aspartame and the frequency of either epileptiform discharges or seizures (35).

Research has also been conducted on children with attention deficit hyperactivity disorder (ADHD; 36). In a double-blind, placebo-controlled, crossover study, children with ADHD consumed a morning bolus of either aspartame (34 mg·kg body  $\text{wt}^{-1}\cdot\text{d}^{-1}$ ) or placebo for 2 wk. Outpatient behavioral ratings were made by their parents and inpatient cognitive and biochemical tests were performed. Phenylalanine concentrations increased significantly with aspartame and were 50–60% higher than concentrations with placebo. Norepinephrine, epinephrine, dopamine, homovanillic acid, and 5-hydroxyindoleacetic acid values, however, did not differ between treatments and there was no effect observed on any behavioral measure.

Some adults have reported seizures as an adverse reaction after consuming aspartame (37). Over several years, and after canvassing >8000 neurologists, 18 such patients were identified. These subjects participated as inpatients in a double-blind, crossover study with aspartame (50 mg·kg body  $\text{wt}^{-1}\cdot\text{d}^{-1}$ ) and placebo with the same diet on both treatment days. Phenylalanine concentrations were 60% higher with aspartame than with placebo but none of these allegedly sensitive patients experienced a clinical seizure, nor were electrographic seizures or abnormalities observed in response to an aspartame dose equivalent to 20 (355 mL, or 12 oz) aspartame-sweetened beverages.


Heterozygotes for phenylketonuria (PKUH) are individuals who might be sensitive to aspartame because they have approxi-

mately one-half the ability that normal homozygotes have to metabolize phenylalanine. PKUH subjects have been tested (38) after taking the same doses as our HIAP and LOAP groups or placebo for 12 wk. Subjects had cognitive tests, EEGs, and biochemistry tests in a randomized, double-blind, placebo-controlled, crossover study. Similar to our finding, phenylalanine and Phe:LNAA values were significantly higher with HIAP treatment than with placebo. There was, however, no effect on the cognitive and electrographic dependent measures, and it was concluded that aspartame is safe, even for this metabolically vulnerable population.

Patients with chronic liver disease, in whom phenylalanine may precipitate a portal systemic encephalopathy, have also been studied (39). They were given a single bolus dose of aspartame (15 mg/kg) after an overnight fast. Phenylalanine concentrations increased significantly and were 65% higher than with placebo. Tyrosine and aspartate concentrations, however, were not significantly altered and there was no difference between groups on a portal systemic encephalopathy index derived from cognitive, neurologic, biochemical, and electrographic measures.

A double-blind, placebo-controlled, parallel group study in healthy subjects showed that there was no effect on biochemical measures or symptom complaints for 6 mo while consuming aspartame doses (75 mg·kg body  $\text{wt}^{-1}\cdot\text{d}^{-1}$ ) equivalent to  $\approx 10$  L aspartame-sweetened beverage daily (40). Even in extreme doses, therefore, any amino acid effects of aspartame consumption appear to be transient. This is consistent with our own finding on day 20 when, after 3 wk of a high aspartame dose, phenylalanine and Phe:LNAA concentrations returned to baseline values once subjects consumed breakfast.

Given all of the above and our own findings, we are skeptical about recent claims that aspartame may be related to self-reported neuropsychologic and neurologic symptoms (41). The report of these claims was retrospective and cognitive testing was only conducted with a portion of the sample under conditions in which neither food nor aspartame intake were controlled. Given the transient effect on phenylalanine concentrations that we observed at doses of aspartame nearly impossible for the average consumer to ingest, it seems highly improbable that normal use could produce neurologic or neuropsychologic deficits.

When adverse experiences are alleged in response to aspartame consumption, we recommend a placebo-controlled, double-blind, challenge test be carried out. Such a test can be done even for a single patient using a repeated-measures, crossover design (42). The dietary, nutritional, and behavioral circumstances under which the alleged experience occurred should also be duplicated. Only in this way can allegations regarding the safety of any food product be evaluated properly before speculation regarding harmful effects begins. The dose of aspartame taken by our HIAP group was nearly 20 times the 90th percentile average daily intake of aspartame and still did not result in adverse behavioral, neuropsychologic, or neurophysiologic effects. Consequently, we conclude that aspartame is safe for the general population. 

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