Adverse Reactions to Aspartame: Double-Blind Challenge in Patients from a Vulnerable Population

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This study was designed to ascertain whether individuals with mood disorders are particularly vulnerable to adverse effects of aspartame. Although the protocol required the recruitment of 40 patients with unipolar depression and a similar number of individuals without a psychiatric history, the project was halted by the Institutional Review Board after a total of 13 individuals had completed the study because of the severity of reactions within the group of patients with a history of depression.

In a crossover design, subjects received aspartame 30 mg/kg/day or placebo for 7 days. Despite the small n, *there was a significant difference between aspartame and placebo in number and severity of symptoms for patients with a history of depression, whereas for individuals without such a history there was not. We conclude that individuals with mood disorders are particularly sensitive to this artificial sweetener and its use in this population should be discouraged.*

Key Words: Aspartame, depression, double-blind study, adverse reactions

Introduction

Since its introduction as an artificial sweetener in July 1983, the dipeptide aspartame (L-aspartyl L-phenylalanine methyl ester) has had an ever-increasing market and been subject to persistent controversy. The Food and Drug Administration (FDA) and multiple clinical studies (Council on Scientific Affairs 1985; Bradstock et al 1986; Garriga et al 1991; Stegink et al 1990; Leone et al 1989) attest to its safety, yet reports of adverse reactions abound. (Drake 1986; Walton 1986; Blundell et al1986; Wurtman 1985; Johns 1986; Camfield et al 1992). It has been reported that two-thirds of such reactions involve neurologic or behavioral symptoms, particularly headaches (MMWR 1984). Reports of adverse reactions are generally anecdotal, and double-blind studies have most often failed to replicate these reactions. Two such widely quoted studies (Leone et al 1989; Schiffman et al 1987) have been criticized both on methodological grounds, (Lipton et al 1988; Steinmetzer and Kunkle 1988) and because they were supported by grants from the Nutrasweet Company, Deerfield, Illinois (Watts 1991).

It has been demonstrated that aspartame can significantly increase rat brain phenylalanine levels (Wurtman 1983), and that aspartame-carbohydrate combinations can raise brain tyrosine levels and suppress the usual increase in tryptophan that follows a carbohydrate-rich meal (Stegink et al 1979). An increase in norepinephrine precursors, coupled with a simultaneous decrease in serotonin precursors, could potentially have a significant impact on central nervous system catecholamine/indoleamine balance. The primary author's clinical experience that patients

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with affective disorder appear particularly prone to adverse reactions to aspartame seems consistent with this data. Patients with clinical syndromes in which a disturbance in monoamines is implicated could be especially vulnerable to adverse consequences to aspartame-induced changes in precursor availability. To date, double-blind studies have not addressed the question of whether patients with mood disorders are especially vulnerable to adverse reactions to aspartame. This question forms the basis of the present study.

Subjects

The project design called for the recruitment of 40 patients with a history of treatment for recurrent major depression, currently doing well with a Brief Psychiatric Rating Scale (RPRS) rating of no greater than 6 at the time of the study. Subjects were recruited by word of mouth, and by a posting and distribution of the study protocol and informed-consent statements among patients, attending physicians, administrative and nursing staff, and medical students at the Western Reserve Care System. All patients were to be over the age of 18, not pregnant, capable of providing informed consent, and free of any history of diabetes, phenylketonuria (PKU), or hypoglycemia. A similar pool of individuals without any psychiatric history, some of whom reported adverse reactions to aspartame and some who did not, was also recruited. After eight patients with a psychiatric history and five individuals without such a history had completed the study, the Western Reserve Care System Institutional Review Board (IRB) halted the project because of the severity of some of the adverse reactions (see Results).

The group of eight patients, ranging in age from 24–60, was comprised of five women and three men. Each had been treated for a recurrent major depression—six on an outpatient basis only and two also receiving inpatient care. Five were receiving an antidepressant at the time of the study: three individuals were on Prozac (Dista Products Co., Div. of Eli Lilly & Co., Indianapolis, IN), 20 mg per day; one was on protriptyline, 40 mg per day; and one on amitriptyline, 250 mg per day.

The nonpatient volunteers—three men and two women—ranged in age from 24–56. Three individuals in this group believed that they were prone to adverse reactions to aspartame (primarily headaches); two knew of no such problems. All are employed at the hospital where the research was conducted.

Study Design

The clinical trial lasted 20 days, with patients and nonpatient volunteers acting as their own controls. After selection, participants were instructed to discontinue all aspartame intake. A 3-day "washout" period followed, after which the trial was initiated. This trial was divided into two 7-day segments, with a second 3-day "washout" interposed. Participants were randomly assigned to receive either aspartame or placebo during the initial 7-day phase, then "crossed over" to receive during the second week whichever was not given during the first.

NutraSweet Company denied the request from the authors to purchase aspartame. Therefore, analytically certified USP grade aspartame was purchased form Schweizerhall, Inc., Piscataway, NJ. Aspartame capsules (300 mg) and placebos of identical appearance containing confectioners sugar were prepared by the hospital pharmacy. The identity code was maintained by the hospital research office, but broken at the request of the chairman of the IRB when the project was interrupted. Subjects received a daily dose of aspartame as close as possible to 30 mg/kg of body weight. For a 70-kg individual this was seven capsules per day during both phases of the trial. Depending on individual dosage, capsules were given on a BID or TID regimen. Approximate equivalence in cans of diet soda would be 10–12 per day.

Each participant monitored his own symptoms using a checklist, one of which was provided for each week of the study. Listed symptoms were: headache, nervousness, dizziness, trouble remembering, binge eating, lower back pain, nausea or upset stomach, feeling blue or depressed, insomnia, uncontrollable temper outburst, and other (to be specified by the subject). For each symptom the participant had to assign the following point value on a daily basis: 0 = not present; 1 = mild (symptom occurs but does not disrupt activities); 2 = moderate (symptom occurs but can be controlled whether by medication or other means; 3 = severe (symptom occurs and disrupts daily activities).

Statistical analyses were performed using Student's *t*-test, paired *t*-test, and Fisher's Exact Test.

Results

The symptoms reported are summarized in Table 1. The severity of some of the reactions is noteworthy; three study participants spontaneously reported that they felt they had been "poisoned." One of the three to use this term felt that her symptoms were so severe that she had to discontinue the capsules—after 3 days of her second week [aspartame]. One patient, a 42-year-old PhD psychologist with a history of recurrent major depression, reported pain in his left eye, followed by retinal detachment requiring emergency surgery. On the day of his surgery (day 4 of his second [placebo] week) he discontinued his capsules and symptoms reporting. Although this event occurred during the placebo week, 6 days after the aspartame had been discontinued, another individual—one of the three to use the term "poisoned"—experienced a conjunctival

Table 1. Summary of Data from Symptom Checklist[a]

	Patients with history of depression		Nondepressed volunteers	
	Placebo	Aspartame	Placebo	Aspartame
Headache	63% (5)	88% (7)	80% (4)	20% (1)
Nervousness	25% (2)	63% (5)	0%	0%
Dizziness	13% (1)	25% (2)	40% (2)	0%
Trouble remembering	0%	63% (5)	0%	20% (1)
Binge eating	13% (1)	13% (1)	0%	0%
Lower back pain	25% (2)	25% (2)	20% (1)	0%
Nausea	25% (2)	100% (8)	40% (2)	20% (1)
Depression	38% (3)	75% (6)	40% (2)	0%
Insomnia	38% (3)	50% (4)	20% (1)	20% (1)
Temper	0%	25% (2)	20% (1)	0%
Other				
More energy	0%	25% (2)	20% (1)	20% (1)
Fatigue	0%	25% (2)	0%	20% (1)
Malaise	0%	38% (3)	0%	20% (1)
Weight loss	13% (1)	0%	0%	0%
Pain in eye	13% (1)	0%	0%	0%
Negative thoughts	0%	13% (1)	0%	0%
Bad taste in mouth	0%	13% (1)	0%	0%
Swollen lips	0%	13% (1)	0%	0%
Facial numbness	0%	13% (1)	0%	0%
Conjunctival hemorrhage	0%	13% (1)	0%	0%
Weight gain	0%	13% (1)	0%	0%
Irritability	0%	25% (2)	0%	0%
Less sleep	0%	0%	20% (1)	0%
Diarrhea	0%	0%	20% (1)	20% (1)
Nightmares	0%	0%	0%	40% (2)
More sleep	0%	0%	0%	20% (1)

[a]Any symptom for which there is a point value of 1 (mild) or greater on at least one of the 7 days.

hemorrhage for the first time in her life during the aspartame week. These events led the Chairman of the IRB to halt the project. At this time 11 individuals had taken all the prescribed capsules and reported symptoms for the entire 14 days of the study. The two individuals mentioned as withdrawing from the study had each taken capsules and reported symptoms for a total of 10 days. Their two 3-day periods of symptom reporting were included in the data. Despite the small number in the study (13), there were several significant findings.

The total point values for reported symptoms and number of reported symptoms are summarized in Table 2. For patients with a history of major depression the difference between the total point values for aspartame and placebo is significant ($p < 0.01$), whereas for the volunteers without such a history it is not. There is a similar significant difference for the number of reported symptoms for the patient group ($p < 0.01$) and no difference for the nondepressed volunteers.

Mean total point values for the three patients with histories of depression not receiving antidepressants at the time of the study compared to those who were are represented in Table 3. There is no significant difference between those who were receiving medication and those who were not.

Although the incidence of headaches within the patient group between the placebo week and aspartame week was not significant, the difference in incidence of headaches between those with a history of depression and those without while receiving aspartame was significant ($p < 0.05$).

Discussion

The lack of validation of the extensive anecdotal reports of adverse reactions to aspartame by double-blind studies may reflect the fact that, to date, such studies have not been performed on what we feel is an especially vulnerable population—individuals with mood disorders. In this study even people who believed that they had problems with aspartame (three of the nondepressed volunteers) did not demonstrate significant differences from placebo, whereas patients with a history of depression and no awareness of aspartame intolerance did demonstrate significant adverse reactions.

Although there are some long-term studies, (Leone et al 1989) 1- or 2-day challenges, such as those of Schiffman

Table 2. Total Point Values and Number of Reported Symptoms[a]

	Patients with history of depression (n = 8)		Nondepressed volunteers (n = 5)	
	Placebo	Aspartame	Placebo	Aspartame
Mean total point value for symptoms (all symptoms across 7 day period)	9.8	40.3	14.4	12.8
SD	13.02	23.47	10.01	8.73
Mean number of reported symptoms	5.8	22.5	10.0	8.0
SD	6.56	12.34	6.63	6.12

[a]Two of the patients had a 3-day rather than 7-day second "week." For one this was during aspartame, for the other, during placebo. Student's *t*-test used for significance levels reported in results.

Table 3. Comparison of Total Symptom Points[a]

	Patients on medication (*n* = 5)		Patients not on medication (*n* = 3)	
	Placebo	Aspartame	Placebo	Aspartame
Mean	14	38.8	2.8	42.7
SD	15.28	29.59	3.01	12.74

Student's *t*-test used for significance levels reported in results.

et al (1987), may not be long enough for difficulties to emerge. In this study, patients most often began to report significant symptoms after day 2 or 3. A 1- or 2-day challenge also does not replicate common patterns of daily consumption.

The fact that two patients developed significant eye problems entered into the decision to halt the study. Although for statistical purposes the eye pain, and subsequent retinal detachment, were recorded as adverse events occurring during the placebo week, there was concern that the process may have been initiated by the preceding week's aspartame trial. There are precedents for concern: Fernstrom et al (1991) demonstrated very large increments in rate retinal phenylalanine concentration after aspartame administration, and in 1988 Roberts reported that in a group of 505 aspartame reactors eye pain or visual changes represented 35% of all complaints (Wurtman 1988). On the basis of this study, one certainly cannot make any definitive statement about aspartame and the eye. We do suggest, however, that further studies be undertaken.

Despite the fact that adverse events led to a very small *n*, a significant pattern of reactions to aspartame emerged in patients with a history of major depression. It would appear that individuals with mood disorders are particularly sensitive to this artificial sweetener; its use in this population should be discouraged.

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