Lack of effect of sucralose on glucose homeostasis in subjects with type 2 diabetes

V. LEE GROTZ, PhD; ROBERT R. HENRY, MD; JANET B. McGILL, MD; MELVIN J. PRINCE, MD; HARRY SHAMOON, MD; J. RICHARD TROUT, PhD; F. XAVIER PI-SUNYER, MD

ABSTRACT

Objective To investigate the effect of 3-months’ daily administration of high doses of sucralose, a non-nutritive sweetener, on glycemic control in subjects with type 2 diabetes.

Design A multicenter, double-blind, placebo-controlled, randomized study, consisting of a 6-week screening phase, a 13-week test phase, and a 4-week follow-up phase.

Subjects/setting Subjects with type 2 diabetes (age range 31 to 70 years) entered the test phase of this study; 128 subjects completed the study. The subjects were recruited from 5 medical centers across the United States and were, on average, obese.

Intervention Subjects were randomly assigned to receive either placebo (cellulose) capsules (n=69) or 667 mg encapsulated sucralose (n=67) daily for the 13-week test phase. All subjects blindly received placebo capsules during the last 4 weeks of the screening phase and for the entire 4-week follow-up phase.

Main outcome measures Glycated hemoglobin (HbA1c), fasting plasma glucose, and fasting serum C-peptide were measured approximately every 2 weeks to evaluate blood glucose homeostasis. Data were analyzed by analysis of variance using repeated measures.

Results There were no significant differences between the sucralose and placebo groups in HbA1c, fasting plasma glucose, or fasting serum C-peptide changes from baseline. There were no clinically meaningful differences between the groups in any safety measure.

Conclusions This study demonstrated that, similar to cellulose, sucralose consumption for 3 months at doses of 7.5 mg/kg/day, which is approximately three times the estimated maximum intake, had no effect on glucose homeostasis in individuals with type 2 diabetes. Additionally, this study showed that sucralose was as well-tolerated by the study subjects as was the placebo. J Am Diet Assoc. 2003;103:1607-1612.
moieties, nor is it a source of energy (3,4), despite its ability to sweeten. More than 50 countries permit the use of sucralose as a sweetener for foods. In Canada and Australia, sucralose has been in use since the early 1990s. In the United States sucralose has been available since 1998 (5) and, in 1999, the FDA permitted it to be used as a general-purpose sweetener (6).

Extensive testing in normal, nondiabetic laboratory animals and humans has shown that sucralose does not affect blood glucose or insulin concentration (7), however, studies in subjects with diabetes have been limited to an acute study with individuals with type 1 and type 2 diabetes (8) and a small, nonpublished, pilot study in type 2 diabetics with equivocal results. Consumption of sucralose is expected in those with diabetes, who often use non-nutritive sweeteners to reduce their intake of refined sugars (9). Moreover, mean sucralose consumption may be more in this population, relative to the general population, based on current uses of other high-intensity sweeteners (9,10). The present study evaluated the effects of 3-months' daily consumption of high doses of sucralose in subjects with type 2 diabetes.

SUBJECTS AND METHODS

Experimental Design
The study had a double-blind, randomized, parallel-group design and was conducted in five US medical centers. Subjects were eligible for the study if they had type 2 diabetes for at least 1 year; were 31 to 70 years of age; managed their diabetes with either insulin or an oral hypoglycemic agent, but not both; had relatively stable diabetes and a percent HbA1c value of 10 or less; were familiar with capillary blood glucose monitoring and standard diet guidelines for diabetes management; and were in general good health. Eligibility was also confirmed by medical history, including concomitant medications; physical examination, including vital signs and electrocardiogram; and hematological, clinical chemistry, and urinalysis laboratory screens. The protocol was approved by the local institutional review boards, and all subjects enrolled gave their informed consent for participation in the study.

The study was divided into three phases: a 6-week screening phase, a 13-week test phase, and a 4-week follow-up phase. During the screening phase, subject eligibility, baseline glucose homeostasis and general health assessments were determined. On entering the screening phase, all subjects were asked to follow a diet of approximately 14% protein, 30% to 36% fat, and 48% to 55% carbohydrate and to monitor their blood glucose concentration at least three times per day, two days per week, for the duration of the study. Subjects' blood glucose records were checked throughout the study to help ensure compliance to protocol guidelines. Two weeks after entering the screening phase, all subjects were given placebo capsules (cellulose) to take two times (at breakfast and dinner) per day for the remaining 4 weeks of the screening phase. The identity of these capsules was known to the investigators, but not to the study subjects. This 4-week placebo-blind run-in period was designed to help distance from the actual test phase of the study any nontreatment effects that might occur with test phase initiation, such as possible changes in dietary behaviors. Baseline blood glucose homeostasis measures were taken at the end of the 4-week placebo run-in, which included measurement of HbA1c, fasting plasma glucose, fasting serum C-peptide, and diabetes therapeutic regimen (insulin or oral hypoglycemic dosage levels).

At the conclusion of the screening phase and 4-week placebo run-in, subjects were randomized to treatment groups, the identity of which was unknown to either the study subjects or the investigators. Subjects received two capsules per day of either placebo or sucralose (McNeil Specialty Products Company, New Brunswick, NJ), to be taken at breakfast and dinner time for the next 13 weeks. The total daily sucralose dose was 667 mg. Test material compliance was checked by pill count and by qualitative measurement of sucralose in urine samples collected once every 2 weeks beginning 2 weeks before the test phase. During the test phase, subjects were seen at least once every 2 weeks for HbA1c, fasting plasma glucose, and fasting serum C-peptide assessments. Additionally, any adverse events or changes in medications, including antidiabetic ones, were recorded.

During the 4-week follow-up phase of the study (conducted immediately after the test phase), subjects were switched back to the 2-capsule-per-day placebo-blind regimen, as in the screening phase. Subjects were not informed when the actual test phase of the study concluded. This was to help ensure compliance with protocol nutritional and blood glucose monitoring guidelines and to minimize other behavioral changes that might result with knowledge of the actual test-phase cessation date. Blood glucose homeostasis evaluations and documentation of adverse events and changes in medication were performed every other week. At the conclusion of the follow-up phase, subjects also underwent a physical examination and hematology, blood chemistry, and urinalysis assessments.

The primary measure used to evaluate blood glucose homeostasis over the course of the study was HbA1c. Secondary measures were fasting plasma glucose, fasting serum C-peptide, and diabetes therapeutic regimen (insulin or oral hypoglycemic regimen). Blood samples taken for glucose homeostasis assessments were analyzed by a single central laboratory (Diabetes Diagnostic Laboratory, University of Missouri-Columbia). Samples for HbA1c analysis were stored at 4°C and measured by HPLC using the Diamat ion-exchange system (BioRad Laboratories, Hercules, CA). Samples were reanalyzed using the standardized Primus HPLC affinity chromatography system (Primus Corporation, Kansas City, MO), if original analyses indicated possible sample degradation. This was done rarely (<0.2% of samples), and results were standardized to be comparable to the Diamat assay. Plasma and serum samples collected for fasting serum C-peptide and fasting plasma glucose analyses, respectively, were stored frozen until analyses. Fasting serum C-peptide was analyzed by radioimmunoassay (Diagnostic Product Corporation, Los Angeles, CA) and glucose was analyzed by the glucose oxidase method (Cobas Mira Analyzer, Roche Diagnostic Systems, Inc, Somerville, NJ). All other assays were performed according to each center's usual procedures.

Statistical Analysis

Power The number of subjects was based on achieving at least 90% power to detect a 0.6 treatment group difference in percent HbA1c change from baseline. Post-study analysis showed that the study provided more than 99.99% power to detect this difference, and more than 90% to detect a difference of 0.3.

Analyses The evaluation of effects on glucose homeostasis and on safety parameters was based on those subjects who received at least one dose of sucralose or placebo during the
test phase ("intent-to-treat" analysis). Analysis of variance using repeated measures, with treatment group, type of diabetes therapy, study center and visit as factors, was used to assess treatment differences in change from baseline in HbA1c, fasting plasma glucose, and fasting serum C-peptide during the test phase of the study. A χ² test was used to assess changes in diabetes medication dosages by comparing the proportions of subjects who had an increase (first reported change), decrease (first reported change), or no change compared with baseline. Parameters used to evaluate safety were adverse events; hematology, blood chemistry, and urinalysis laboratory parameters; vital signs; and physical and ECG examination data. Fisher exact test was used to determine treatment group differences for all but vital signs, which were evaluated using a t test. Statistical significance was declared if the 2-sided P value was ≤ 0.05.

RESULTS

Demographics

A total of 136 subjects entered the test phase of the study. Of these, 67 were randomized to receive sucralose and 69 to receive placebo. Eight subjects (4 each in the sucralose and placebo groups) discontinued after randomization to the test phase, none as a consequence of an adverse event. Therefore, 128 subjects completed the study. Subjects in both treatment groups were similar with respect to sex, age, race, body weight, height, duration and onset of diabetes, and type of diabetes medication taken (Table 1). As expected, subjects, on average, were obese; mean (±standard deviation) baseline BMI for the sucralose and placebo groups was 32 ± 0.7 and 32 ± 0.9, respectively. Approximately one half of the subjects of both treatment groups took oral hypoglycemic agent(s), which included biguanides and various sulfonylureas that, in type and dose, were similarly distributed among the treatment groups. The remaining subjects in each treatment group took insulin for their dia-

---

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Subject demography and diabetes background</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistic</td>
<td>Placebo (n = 69)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58.0 ± 1.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>94.0 ± 2.67</td>
</tr>
<tr>
<td>Men</td>
<td>46</td>
</tr>
<tr>
<td>Women</td>
<td>23</td>
</tr>
<tr>
<td>White</td>
<td>57</td>
</tr>
<tr>
<td>Black</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes treatment</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>33</td>
</tr>
<tr>
<td>OHA*</td>
<td>36</td>
</tr>
</tbody>
</table>

*OHA, oral hypoglycemic agent(s).

---

There did not seem to be any meaningful differences between the sucralose and placebo groups in concomitant medications.

Treatment Compliance

More than 96% of subjects in both groups were considered compliant based on capsule counts and the results of the qualitative assays for sucralose in collected urine samples. Based on individual body weight and the daily sucralose dosage (666.7 mg) administered, the calculated daily sucralose intake was 7.5 ± 0.2 mg/kg.

Glycated Hemoglobin

The course of HbA1c levels is shown in the Figure. There were no statistically significant differences between the two (sucralose and placebo) groups in HbA1c at baseline, at any visit (P = 0.23 to 0.93), or in the estimated change over time (overall estimated change from baseline through the completion of the test phase) (P = 0.57). In both treatment groups, there was a general downward trend in mean HbA1c levels. Compared with baseline, mean HbA1c levels for the sucralose group were significantly decreased after 2, 8, 10, 12, and 13 weeks of treatment as well as 2 and 4 weeks after treatment cessation. The overall HbA1c change for the sucralose group was also significantly decreased compared to its mean baseline level (P = 0.01). For the placebo group, the difference from baseline in mean HbA1c was statistically significant only at Week 4 of the treatment phase, and the overall change was not statistically different (P = 0.10). Additional statistical analyses evaluated the HbA1c changes from baseline among insulin users and among those taking oral hypoglycemic agents. Similar to the all-subjects analyses, there were no significant differences between the two treatment groups in baseline HbA1c levels or in HbA1c overall change from baseline.

Secondary Measures of Glycemic Control

Fasting plasma glucose Fasting plasma glucose concentrations for the two treatment groups were not statistically significantly different at baseline (Table 2), and there were no significant differences between the two groups in the estimated change from baseline over the course of the study (overall change; P = 0.89) or the change from baseline at any test (treatment) phase visit. Four weeks after treatment cessation, there was a statistically significant difference between the treatment groups in change from baseline, reflecting a −0.64 mmol/L and a +0.40 mmol/L change for the sucralose and placebo groups, respectively (P = 0.02). The lower mean fasting plasma glucose concentration for the sucralose group was also statistically significantly different relative to its own baseline concentration (P = 0.03). There were no other statistically significant within-group fasting plasma glucose changes from baseline noted during the study for either treatment group. The P values for the sucralose and placebo group overall changes from baseline were 0.51 and 0.74, respectively.

Fasting serum C-peptide There was no statistically significant difference between the treatment groups in baseline fasting serum C-peptide concentration. Additionally, there were no between-group (P = 0.29) or within-group (P = 0.51 and 0.33 for the sucralose and placebo groups, respectively) statistically significant differences in fasting serum C-peptide changes from...
FIG. Mean change from baseline in HbA1c (%) values for placebo-treated and sucralose-treated subjects. The between-treatment difference in the estimated HbA1c change over time (overall change) was not statistically significant (P = .57).

Table 2
Summary of fasting glucose and C-peptide data

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th>Sucralose</th>
<th></th>
<th>Between treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SE</td>
<td>n</td>
<td>Mean ± SE</td>
<td>Difference</td>
</tr>
<tr>
<td><strong>Fasting glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P value</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline**</td>
<td>69</td>
<td>9.4 ± 0.35</td>
<td>67</td>
<td>9.7 ± 0.31</td>
<td>0.27</td>
</tr>
<tr>
<td>Overall change</td>
<td>68</td>
<td>−0.080 ± 0.24</td>
<td>65</td>
<td>−0.14 ± 0.21</td>
<td>−0.063</td>
</tr>
<tr>
<td><strong>Fasting C-peptide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>69</td>
<td>1040 ± 80</td>
<td>67</td>
<td>950 ± 70</td>
<td>−90</td>
</tr>
<tr>
<td>Overall change</td>
<td>68</td>
<td>−30 ± 30</td>
<td>65</td>
<td>20 ± 20</td>
<td>50</td>
</tr>
</tbody>
</table>

*To convert mmol/L fasting glucose to mg/dL, multiply mmol/L by 18.0148. To convert mg/dL fasting glucose to mmol/L, multiply mg/dL by 0.05551. Fasting glucose of 9.00 mmol/L = 162 mg/dL.

**Baseline is the average of values obtained at Weeks −2 and 0. Overall change is the mean of the change from baseline to each of the test phase post-baseline time points. Between-treatment difference is the difference between treatment groups in change from baseline. Treatment group differences were tested by analysis of variance using repeated measures, with treatment group, type of diabetes therapy, study center, and visit included in the model and subject treated as random effect.
baseline (overall change, or change at any test or post-test time point) (Table 2).

**Diabetes medications** Changes in diabetes therapeutic regimen, another secondary measure of glucose homeostasis, showed no significant differences in the proportion of subjects who maintained, increased, or decreased their insulin or oral hypoglycemic dose regimen at any time during the study.

**Safety** There were no significant differences between the treatment groups in the type, number, or severity of adverse events reported. No subjects discontinued from the study because of an adverse event, and no adverse events were documented as being probably or definitely related to treatment with sucralose. There were no clinically meaningful differences between the two groups in changes in concomitant medications. There were no clinically meaningful changes in any other safety measure.

**DISCUSSION** This 3-month, randomized, double-blind study in subjects with type 2 diabetes showed no effects of sucralose, at intakes of 667 mg/day, on any measure of glucose control, including HbA1c, fasting plasma glucose, and serum C-peptide, or diabetes therapeutic regimen. Similarly, there were no trends that might suggest an adverse effect on blood glucose control. Conversely, there was a trend for decreased HbA1c levels over the course of the study in sucralose-treated subjects. This trend, however, was not clinically meaningful and the absolute change was small. The overall change in percent HbA1c from baseline to week 13 was $-0.17 \pm 0.07$. This change was similar to the statistically nonsignificant change seen in the placebo group: $-0.11 \pm 0.66$. The slight decrease in HbA1c levels seen in this study is most likely a Hawthorne effect, i.e., a study effect unrelated to the test material, such as an effect of increased attention to glycemic control. Adverse event data showed that subjects tolerated the high dose of sucralose used in this study as well as they tolerated the cellulose placebo. There were no significant differences between the sucralose and placebo groups in the number, type, or severity of reported adverse events. There were also no clinically meaningful between-group differences in concomitant medications. In other safety assessments conducted 4 weeks after treatment cessation, there were no between-group changes that were considered clinically meaningful.

The absence of an effect on long-term glycemic control in this study is consistent with the results of high-dose acute and long-term studies conducted in nonhuman, nondiabetic laboratory species (7). These show no meaningful effect of sucralose on blood glucose homeostasis and include one notable acute study, in which neither insulin nor glucose concentrations were affected in rats administered sucralose intravenously at doses equivalent to $>3$ g/kg orally — approximately 1,300 times the estimated daily intake (EDI) for humans at the 90th percentile (11). The current study results are also consistent with results from studies in nondiabetic human subjects (7,12,13), one of which was specifically designed to assess the possible effect of repeated (12-weeks’) sucralose administration on glycemic control and/or insulin sensitivity (12). They are also consistent with the results of a single-dose study in type 1 and type 2 subjects (8). Although subjects in the current study were considered on average to be obese and used insulin or oral hypoglycemic agents to manage their diabetes, the totality of the results from human studies conducted to assess glycemic control, coupled with the fact that sucralose is not broken down in the body, would lead us to conclude that non-obese subjects or subjects whose diabetes is managed only by diet would respond similarly to sucralose administration. Finally, in countries where sucralose has been available for almost 10 years, no health risks have been found to result from sucralose use, including among individuals with diabetes.

In countries where sucralose has been available for almost 10 years, no health risks have been found to result from sucralose use, including among individuals with diabetes.

The high dose of sucralose tested in this study was made possible by encapsulating the material. Delivering an encapsulated dose also blinded the subjects to the sweet taste of sucralose, thereby removing taste as a potentially confounding factor. The amount of sucralose consumed by subjects in this study was considered significant, because levels administered were approximately 3 times the maximum EDI for sucralose (2.4 mg/kg/day), based on sweetener usage patterns by high-level consumers and conservative assumptions about the use of sucralose in foods and beverages (11). These assumptions were that sucralose would replace all sweeteners (nutritive or non-nutritive) added to foods for which there was not already a well-developed diet market (such as breads, cakes, pies, puddings, confections, condiments) and also replace all the “diet” sweeteners (e.g., aspartame, saccharin) in products with a developed “diet” market. Thus, the daily dose of sucralose consumed in the present study, on average, 7.5 ± 0.2 mg/kg/day, is well in excess of what could be expected to be consumed on a daily basis by any individual.

**APPLICATIONS**

- Sucralose is more stable to heat and acid than peptide-based sweeteners like aspartame (14), and retains its sweetness during ordinary cooking, baking (15), and pasteurization (16). Sensory studies also show that sucralose does not have the bitter aftertaste associated with saccharin and acesulfame potassium (17) and, instead, has a taste profile similar to sugar (1). Thus, sucralose may make possible an expanded number of palatable, lower-kilocalorie, lower-sugar foods and beverages.

- These foods may help some individuals decrease their intake of added sugars, which may be important for persons with, or at risk of, diabetes. A number of studies suggest that foods high in added sugar may increase the risk of obesity (18-25), a known risk factor for diabetes (26). Additionally, a recent 10-week study in overweight subjects with ad libitum food intake showed significant increases in body weight, energy intake, fat mass and blood pressure when the diet included foods and beverages high in added sugar vs when the diet included similar foods and beverages sweetened with non-nutritive sweeteners.
In sum, sucralose-sweetened foods and beverages may be useful tools in the dietary management of individuals with, or at risk of, diabetes, a disease that has increased significantly with the recent epidemic increase in obesity (30,31).

References


The authors thank the contributions of Hsiao-Mei Wiedmeyer, MS, for the discussion of the HbA1c methodology, and Ashley Roberts, PhD, and Ellen Lodato, MS, for their assistance with this investigation.

This study was supported by McNeil Specialty Products Company and Tate & Lyle Specialty Sweeteners.

The average American also consumes more than 20 teaspoons of added sugar (328 kcal) daily (28), and added sugars contribute 12% to 20% of our daily energy intake (29). Thus, foods sweetened with non-nutritive sweeteners may help some individuals cut back meaningfully on both energy and carbohydrate intake, a common goal in medical nutrition therapy strategies for individuals with diabetes. This may be especially important for those whose diabetes or diabetes risk management does not include antidiabetes drugs.