Glycemic Effect of a Single High Oral Dose of the Novel Sweetener Sucralose in Patients With Diabetes

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OBJECTIVE — To examine the effect of a single high oral dose of the novel noncaloric sweetener sucralose on short-term glucose homeostasis in patients with IDDM or NIDDM.

RESEARCH DESIGN AND METHODS — A total of 13 IDDM and 13 NIDDM patients with glycosylated hemoglobin levels <10% completed this double-blind cross-over study. After an overnight fast, patients were administered opaque capsules containing either 1,000 mg sucralose or cellulose placebo, followed by a standardized 360-kcal liquid breakfast. Plasma glucose and serum C-peptide levels were measured over the next 4 h.

RESULTS — Regardless of the type of diabetes, areas under the curves for changes of plasma glucose and serum C-peptide levels after sucralose administration were not significantly different from those after placebo. During test meals with sucralose, one episode of symptomatic hypoglycemia occurred in each of three IDDM patients, but these episodes were not considered the result of sucralose administration.

CONCLUSIONS — The present results support the conclusion that sucralose consumption does not adversely affect short-term blood glucose control in patients with diabetes.

Sucralose (1,6-dichloro-1,6-dideoxy-β-d-fructofuranosyl-4-chloro-4-deoxy-α-d-galactopyranoside) is a novel noncaloric high-intensity sweetener that is exceptionally stable in foods and beverages as well as in baking (1–4). The consumption of sucralose is expected to be high among individuals with diabetes, who often use noncaloric sweeteners to reduce their intake of refined sugars (5). Sucralose is synthesized from sucrose but appears to be metabolically inert (2,6). Extensive testing has shown that sucralose does not affect blood glucose or insulin levels in normal laboratory animals or human volunteers (2). The present study examined the effect of a single high oral dose of sucralose on short-term glycemic control after a liquid breakfast in patients with IDDM or NIDDM.

RESEARCH DESIGN AND METHODS

— The protocol of this randomized double-blind cross-over study included a 2–6 week screening phase, a test phase, and a follow-up evaluation. Physical examinations, clinical chemistry and hematology evaluations, and urinalysis were performed at intervals during the study. The study population included men and women aged <65 years with a diagnosis of diabetes (7) for at least 1 year and an initial GHb level <10% (normal range 5.5–8.2%). Adequate glycemic control was demonstrated by fasting capillary glucose readings <9.7 mmol/l at three clinic visits before dosing. Patients with IDDM were >18 years of age and had a C-peptide level <0.3 nmol/l 15 min after an injection of (1 mg) glucagon; NIDDM patients were >40 years of age and had a glucagon-stimulated C-peptide level >0.6 nmol/l.

Eligible patients underwent two meal tests that were scheduled approximately 1 week apart. Venous blood was sampled 40 and 5 min before test substance administration to determine fasting levels of plasma glucose and serum C-peptide. The patient received his or her usual insulin or sulfonylurea dose 30 min before consuming the test substance, which consisted of 1,000 mg sucralose or cellulose placebo that was contained in three opaque capsules. Immediately after receiving the test substance, patients consumed a standardized 360-kcal liquid breakfast (8 oz Ensure Plus; Ross Products Division, Abbott Laboratories, Columbus, OH). Additional blood samples were collected at 30, 60, 90, 120, 180, and 240 min after completion of the breakfast. Approximately 1 week after the second test visit, patients returned for a follow-up evaluation.

Data are expressed as mean ± SD. For meal test plasma glucose and serum C-peptide data, areas under the curves for changes from baseline (measured 5 min before test substance administration) were estimated by the trapezoid method and were compared by analysis of variance on factors of treatment, diabetes type, and treatment sequence.

RESULTS

— As a group, the 13 IDDM patients who completed the trial were significantly younger (37.8 ± 2.6 years) than the 13 NIDDM patients (54.3 ± 1.7 years, $P < 0.001$). The IDDM and NIDDM groups each consisted of ~60% men and ~40% women. The patients in the IDDM group were Caucasian, while the NIDDM group included four blacks, one Asian, and one Hispanic. Mean body weight was significantly lower in the IDDM group compared with the NIDDM group (72.5 ± 3.6 vs. 95.0 ± 7.3 kg, $P < 0.01$), as was mean BMI (23.7 ± 0.9 vs. 32.0 ± 1.9 kg/m², $P < 0.001$). Duration of diabetes was significantly longer in the IDDM group (15.5 ± 2.6 years) than in

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Table 1—*Areas under the curve for changes in plasma glucose and serum C-peptide levels after the consumption of sucralose or placebo and a liquid breakfast*

		Glucose (mmol/l)		C-peptide (nmol/l)	
	n	Placebo	Sucralose	Placebo	Sucralose
IDDM	13	11.9 ± 3.3	10.3 ± 3.6	0.03 ± 0.03	0.15 ± 0.07
NIDDM	13	5.2 ± 1.9	5.7 ± 1.7	1.65 ± 0.15	1.86 ± 0.22

Data are means ± SD.

the NIDDM group (6.1 ± 1.4 years, $P < 0.01$). Nine NIDDM patients were treated with sulfonylureas, two with diet alone, and two with insulin. The IDDM group had significantly higher GHb levels (9.4 ± 0.3 vs. 8.7 ± 0.2%, $P < 0.05$) and significantly lower glucagon-stimulated C-peptide levels (0.24 ± 0.01 vs. 0.97 ± 0.08 nmol/l, $P < 0.001$) than the NIDDM group.

Neither plasma glucose nor serum C-peptide areas under the curve varied significantly as a function of treatment or test sequence ($P > 0.05$; Table 1). This lack of effect was independent of diabetes type. Although the areas under the curve of IDDM and NIDDM patients for glucose were not significantly different, the area under the curve for C-peptide was smaller in IDDM patients than in NIDDM patients ($P < 0.001$).

In the 27 patients who entered the test phase, three adverse experiences were recorded. These involved one episode of symptomatic hypoglycemia in three IDDM patients. Two of the episodes were considered moderate in severity and one was considered severe. Each episode occurred following sucralose administration on the first test visit. Symptoms abated after the tests were terminated and the patients were allowed to eat. The patient who experienced the severe episode was discontinued from the trial.

Over the course of the trial, no meaningful changes in physical examination findings, clinical laboratory parameters, intercurrent illnesses, or concomitant medications, including insulin or sulfonylureas, were observed.

CONCLUSIONS— The average dose of sucralose administered in the present study amounted to 13.8 and 10.5 mg/kg in IDDM and NIDDM patients, respectively. This single test dose was chosen to exceed the estimated daily intake of the sweetener at the 90th percentile (2.3 mg/kg) and to approach the acceptable daily intake level (15 mg/kg) (8). Despite the high sucralose dose tested, the areas under the curve for changes of plasma glucose and serum C-peptide after sucralose consumption were not significantly different from those observed after placebo. There were only three adverse experiences, each involving an episode of symptomatic hypoglycemia in an IDDM patient.

Although the three episodes of hypoglycemia were temporally related to sucralose administration, these events were not considered the consequence of sucralose consumption for several reasons. First, hypoglycemia is known to be fairly common among patients, such as the study subjects, who were, as required by the protocol, maintaining good glycemic control (9). Second, the protocol did not specify a minimum fasting plasma glucose level, and the caloric content of the test breakfast was not large (360 kcal). Two of the three patients who experienced hypoglycemia had very low fasting plasma glucose levels after insulin administration (2.5 and 1.8 mmol/l at the –5-min baseline). One of these patients later repeated the sucralose test meal without experiencing hypoglycemia. Lastly, if hypoglycemia is defined strictly by a plasma glucose level (<3.6 mmol/l), the number of patients who became hypoglycemic during the sucralose test meals (three IDDM patients) was not greater than the number of patients who had similar glucose values during the placebo tests (three IDDM and two NIDDM patients). These low plasma glucose levels during the placebo test meals were not recorded as adverse events since symptoms were not reported.

In the present study, the changes in plasma glucose and serum C-peptide levels observed in patients with IDDM or NIDDM after a single high dose of the novel sweetener sucralose were not significantly different from those observed after placebo. These results support the conclusion that sucralose consumption does not adversely affect short-term blood glucose control in individuals with diabetes.

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