

NOTICE TO PHYSICIAN

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(Sample) Letter of Medical Necessity

Insurer
(Address)

Re: **(Patient's name)**
Date of Birth:
Policy Number: **(Patient's ID number)**

Dear **(Insurer's contact's name and title)**:

I am writing to request prior authorization to initiate Sucraid® (sacrosidase) Oral Solution for **(Name of patient)**. This letter provides evidence that this enzyme replacement therapy is medically necessary for **(his/her)** care and that it is an accepted treatment for sucrase deficiency caused by congenital sucrase-isomaltase deficiency (CSID). This is a rare genetic disorder that affects a patient's ability to digest certain sugars due to absent or low levels of two digestive enzymes, sucrase and isomaltase. These enzymes are involved in the digestion of sugar and starch. Untreated patients with sucrase deficiency caused by CSID experience gastrointestinal symptoms such as diarrhea, excessive gas, bloating, abdominal cramps, and, in infants and young children, malnutrition.^{1,2}

The following sections provide detailed information about the patient's medical history, a description of the treatment, and the reasons for using Sucraid® in this case.

Patient History and Diagnosis

On **(Date)**, I diagnosed **(Patient name)** with sucrase deficiency caused by CSID. **(Include complete information on diagnosis and methods used in the determination of diagnosis, such as evaluation of the patient's case history, a disaccharidase assay test using a small bowel biopsy taken during an esophagogastroduodenoscopy [EGD] procedure, or a sucrose breath test [hydrogen methane or ¹³C]. Include proof of response to therapy [e.g., describe symptoms improved, quality of life, etc.] Also list previous therapies that have been tried and failed [e.g., nutritional counseling, dietary adjustments] and what factors led to the discontinuation of these therapies.)**

In my clinical judgment, all diagnostic assays have limitations. A disaccharidase assay test using a small bowel biopsy taken during an esophagogastroduodenoscopy (EGD) is no exception. The fact that treatment with Sucraid® alleviated symptoms of this patient suggests this patient benefited from Sucraid®.

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Treatment Description and Rationale

Sucraid® is approved by the U.S. Food and Drug Administration and is indicated for the treatment of sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID), in adult and pediatric patients 5 months of age and older. Please see Attachments 1 and 2.

I have chosen to treat **(Patient's name)** with Sucraid® based on the history previously stated, and because it is the indicated medical treatment for sucrase deficiency caused by CSID. I believe the patient's prognosis without Sucraid® is __. However, with Sucraid®, the prognosis is _____. In summary, Sucraid® is medically necessary in this case and should be covered and/or reimbursed. Please feel free to contact me if you require additional information.

Sincerely,
(Physician's name)

(Do not submit the sample letters verbatim. The sample letter is intended to be a guide only. Letters should be drafted using your own words. Be specific and thorough with patient data, treatment rationale, and expected outcomes. Attach as much supporting documentation as possible and reference it in the body of the letter.)

¹Treem WR. Congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr.* 1995;21(1):1-14.

²Treem WR. Clinical aspects and treatment of congenital sucrase-isomaltase deficiency: *J Pediatr Gastroenterol Nutr.* 2012;55(suppl2):S7-S13. doi:10.1097/01.mpg.0000421401.57633.90

Important Safety Information for Sucraid® (sacrosidase) Oral Solution

Indication

Sucraid® (sacrosidase) Oral Solution is indicated for the treatment of sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID), in adult and pediatric patients 5 months of age and older.

Contraindication

Sucraid® is contraindicated in patients known to be hypersensitive to yeast, yeast products, glycerin (glycerol), or papain.

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Warnings, Precautions, and Additional Important Safety Information

- **Severe Hypersensitivity Reactions**

Severe hypersensitivity reactions, including wheezing, difficulty breathing, rash, pruritis, and swelling of the face, lips, mouth, or tongue have been reported with administration of Sucraid®. Sucraid® contains papain, which is associated with hypersensitivity reactions.

- **Increased Blood Glucose Concentration in Patients With Diabetes Mellitus**

Sucraid® enables the products of sucrose hydrolysis, glucose and fructose, to be absorbed and may increase blood glucose concentrations. Monitor blood glucose concentrations and adjust the diet accordingly for patients with diabetes mellitus.

- **Dietary Starch Restriction**

Sucraid® does not replace isomaltase. Therefore, patients may still experience symptoms of CSID while taking Sucraid®. Consider dietary starch restriction in addition to Sucraid®, especially in patients in whom symptoms are not adequately controlled by Sucraid®.

- Adverse reactions as a result of taking Sucraid® may include worse abdominal pain, vomiting, nausea, diarrhea, constipation, difficulty sleeping, headache, nervousness, and dehydration.

- The effects of Sucraid® have not been evaluated in patients with secondary (acquired) disaccharidase deficiency.

- **DO NOT HEAT SOLUTIONS CONTAINING SUCRAID®.** Do not put Sucraid® in warm or hot fluids. Do not reconstitute or consume Sucraid® with fruit juice since the acidity of the juice may reduce the enzyme activity of Sucraid®. Half of the reconstituted Sucraid® should be taken at the beginning of the meal or snack and the other half during the meal or snack.

- Sucraid® should be refrigerated at 36°F-46°F (2°C-8°C) and should be protected from heat and light; single-use containers can be removed from refrigeration and stored at 59°F-77°F (15°C-25°C) for up to 3 days (72 hours). Refer to Instructions for Use for full information on how to take Sucraid®.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.



QL60103

Prescribing Information

Sucraid® (sacrosidase) Oral Solution:

DESCRIPTION

Sacrosidase is an enzyme with the chemical name of β,D-fructofuranoside fructohydrolase. The enzyme is derived from baker’s yeast (*Saccharomyces cerevisiae*). It has been reported that the primary amino acid structure of this protein consists of 513 amino acids with an apparent molecular weight of 100,000 Da for the glycosylated monomer (range 66,000- 116,000 Da). Reports also suggest that the protein exists in solution as a monomer, dimer, tetramer, and octomer ranging from 100,000 Da to 800,000 Da. It has an isoelectric point (pI) of 4.5.

Sucraid®(sacrosidase) Oral Solution is an oral enzyme replacement therapy.

Sucraid is a pale yellow to colorless, clear solution with a pleasant, sweet taste. Each milliliter (mL) of Sucraid contains 8,500 International Units (I.U.) of the enzyme sacrosidase, the active ingredient.

Sucraid may contain small amounts of papain (see WARNINGS). Papain is a protein-cleaving enzyme that is introduced in the manufacturing process to digest the cell wall of the yeast and may not be completely removed during subsequent process steps. Sucraid contains sacrosidase in a vehicle comprised of glycerin, water, citric acid, and sodium hydroxide to maintain the pH at 4.0 to 4.7. Glycerol (glycerin) in the amount consumed in the recommended doses of Sucraid has no expected toxicity.

This enzyme preparation is fully soluble with water, milk, and infant formula. **DO NOT HEAT SOLUTIONS CONTAINING SUCRAID.** Do not put Sucraid in warm or hot liquids (see DOSAGE AND ADMINISTRATION, Administration Instructions).

CLINICAL PHARMACOLOGY

Congenital sucrase-isomaltase deficiency (CSID) is a chronic, autosomal recessive, inherited, phenotypically heterogeneous disease with very variable enzyme activity. CSID is usually characterized by a complete or almost complete lack of endogenous sucrose activity, a very marked reduction in isomaltase activity, and a moderate decrease in maltase activity.

Sucrase is naturally produced in the brush border of the small intestine, primarily the distal duodenum and jejunum. Sucrase hydrolyzes the disaccharide sucrose into its component monosaccharides, glucose and fructose. Isomaltase breaks down disaccharides from starch into simple sugars. Sucraid does not contain isomaltase.

In the absence of endogenous human sucrase, as in CSID, sucrose is not metabolized. Unhydrolyzed sucrose and starch are not absorbed from the intestine and their presence in the intestinal lumen may lead to osmotic retention of water. This may result in loose stools.

Unabsorbed sucrose in the colon is fermented by bacterial flora to produce increased amounts of hydrogen, methane, and water. As a consequence, excessive gas, bloating, abdominal cramps, diarrhea, nausea, and vomiting may occur.

Chronic malabsorption of disaccharides may result in malnutrition. Undiagnosed/untreated CSID patients often fail to thrive and fall behind in their expected growth and development curves. Previously, the treatment of CSID has required the continual use of a strict sucrose-free diet.

CLINICAL STUDIES

A two-phase (dose response preceded by a breath hydrogen phase) double-blind, multi-site, crossover trial was conducted in 28 pediatric patients (approximately 5 months to 12 years of age) with confirmed CSID. During the dose response phase,the patients were challenged with an ordinary sucrose-containing diet while receiving each of four doses of sacrosidase: full strength (9000 I.U./mL) and three dilutions (1:10 [900 I.U./mL], 1:100 [90 I.U./mL], and 1:1000 [9 I.U./mL]) in random order for a period of 10 days. Patients who weighed no more than 15 kg received 1 mL per meal; those weighing more than 15 kg received 2 mL per meal. The dose did not vary with age or sucrose intake. A dose-response relationship was shown between the two higher and the two lower doses. The two higher doses of sacrosidase were associated with significantly fewer total stools and higher proportions of patients having lower total symptom scores, the primary efficacy end-points. In addition, higher doses of sacrosidase were associated with a significantly greater number of hard and formed stools as well as with fewer watery and soft stools, the secondary efficacy end-points.

Analysis of the overall symptomatic response as a function of age indicated that in CSID pediatric patients up to 3 years of age, 86% became asymptomatic. In pediatric patients over 3 years of age, 77% became asymptomatic. Thus, the therapeutic response did not differ significantly according to pediatric age.

A second study of similar design and execution as the first used 4 different dilutions of sacrosidase: 1:100 (90 I.U./mL),1:1000 (9 I.U./mL),1:10,000 (0.9 I.U./mL), and 1:100,000 (0.09 I.U./mL). There were inconsistent results with regards to the primary efficacy parameters.

In both trials, however, pediatric patients showed a marked decrease in breath hydrogen output when they received sacrosidase in comparison to placebo.

The effects of Sucraid have not been evaluated in patients with secondary (acquired) sucrase deficiency.

INDICATIONS AND USAGE

Sucraid®(sacrosidase) Oral Solution is indicated for the treatment of sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID), in adult and pediatric patients 5 months of age and older.

CONTRAINDICATIONS

Sucraid is contraindicated in patients known to be hypersensitive to yeast, yeast products, glycerin (glycerol), or papain (see WARNINGS).

WARNINGS

Severe Hypersensitivity Reactions

Severe hypersensitivity reactions, including wheezing, rash, and pruritis, have been reported with administration of Sucraid. Sucraid contains papain, which is associated with hypersensitivity reactions (see DESCRIPTION).

A pediatric patient in the clinical trials experienced a hypersensitivity reaction of severe wheezing that required hospitalization. Postmarketing cases of cutaneous hypersensitivity reactions have also been reported.

Instruct patients or caregivers to stop Sucraid and seek medical attention if symptoms suggestive of a hypersensitivity reaction occur. Sucraid is contraindicated in patients who have had a known hypersensitivity reaction (see CONTRAINDICATIONS).

PRECAUTIONS

Increased Blood Glucose Concentrations in Patients with Diabetes Mellitus

Sucraid enables the products of sucrose hydrolysis, glucose and fructose, to be absorbed and may increase blood glucose concentrations. Monitor blood glucose concentrations and adjust the diet accordingly for patients with diabetes mellitus.

Dietary Starch Restriction

Sucraid does not replace isomaltase. Therefore, patients may still experience symptoms of CSID while taking Sucraid. Consider dietary starch restriction in addition to Sucraid, especially in patients in whom symptoms are not adequately controlled by Sucraid.

Information for Patients

See Patient Package Insert and the Instructions for Use.

Drug Interactions

Fruit Juice

The acidity in fruit juice may reduce the enzyme activity in Sucraid. Administration of Sucraid with liquids other than water, milk, or infant formula has not been studied and is not recommended (see DOSAGE AND ADMINISTRATION, Administration Instructions).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals with Sucraid have not been performed to evaluate the carcinogenic potential. Studies to evaluate the effect of Sucraid on fertility or its mutagenic potential have not been performed.

Pregnancy

Teratogenic Effects

Animal reproduction studies have not been conducted with Sucraid. Sucraid is not expected to cause fetal harm when administered to a pregnant woman or to affect reproductive capacity. Sucraid should be given to a pregnant woman only if clearly needed.

Nursing Mothers

The Sucraid enzyme is broken down in the stomach and intestines, and the component amino acids and peptides are then absorbed as nutrients.

Pediatric Use

The safety and effectiveness of Sucraid for the treatment of sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID), have been established in pediatric patients aged 5 months and older. Use of Sucraid for this indication is supported by evidence from adequate and well-controlled studies in pediatric patients (see CLINICAL STUDIES AND ADVERSE REACTIONS).

Geriatric Use

Clinical trials of Sucraid did not include patients 65 years of age and older to determine if they respond differently from younger adult patients.

ADVERSE REACTIONS

The following adverse reactions associated with the use of sacrosidase were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In clinical studies of up to 54 months duration, a total of 52 patients were treated with Sucraid. The reported adverse reactions (number of patients) were as follows: abdominal pain (4), vomiting (3), nausea (2), diarrhea (2), constipation (2), insomnia (1), headache (1), nervousness (1), and dehydration (1).

Hypersensitivity reactions (wheezing, rash, and pruritis) have been reported (see WARNINGS).

DOSAGE AND ADMINISTRATION

Important Administration Information

- Administer Sucraid with each meal or snack.
- Mix Sucraid with cold or room temperature water, milk or infant formula prior to administration. Administration of Sucraid in liquids other than water, milk, or infant formula has not been studied and is not recommended. Do not mix or consume Sucraid with fruit juice.
- Do not warm or heat the water, milk, or infant formula before or after addition of Sucraid.
- Administer half of the dose at the beginning of the meal or snack and the other half of the dose during the meal or snack.

Recommended Dosage

The recommended dosage is:

- *Patients weighing 15 kg and less:* 8,500 International Units (1 mL) administered orally with each meal or snack.
- *Patients weighing more than 15 kg:* 17,000 International Units (2 mL) administered orally with each meal or snack.

Preparation and Administration Instructions for Patients Weighing 15 kg or Less

Multiple-Dose Bottle:

1. Using the measuring scoop provided, add 1 scoop of Sucraid (1 mL) to 60 mL of cold or room temperature water, milk, or infant formula.
2. Stir to mix well.
3. Administer half of the mixed Sucraid solution (30 mL) at the beginning of the meal or snack and the other half of the mixed solution (30 mL) during the meal or snack.
4. Do not save any of the mixed Sucraid solution for later use.
5. Rinse the measuring scoop with water.

Single-Use Container:

1. Empty the entire contents of the single-use container (2 mL) in 120 mL of cold or room temperature water, milk, or infant formula.
2. Stir to mix well.
3. Divide the mixed Sucraid solution into two separate 60 mL portions. The first portion (60 mL) is for immediate use.
 - Administer half of the first portion (30 mL) of the mixed Sucraid solution at the beginning of the meal or snack and the other half of the first portion (30 mL) of the mixed Sucraid solution during the meal or snack.
4. Store the second portion of the mixed Sucraid solution (60 mL) at 2°C to 8°C (36°F to 46°F) for up to 24 hours for administration with the next meal or snack.
 - Discard the mixed Sucraid solution if not used within 24 hours.

Preparation and Administration Instructions for Patients Weighing More than 15 kg

Multiple-Dose Bottle:

1. Using the measuring scoop provided, add 2 scoops of Sucraid (2 mL) to 120 mL of cold or room temperature water, milk, or infant formula.
2. Stir to mix well.
3. Administer half of the mixed Sucraid solution (60 mL) at the beginning of the meal or snack and the other half of the mixed Sucraid solution (60 mL) during the meal or snack.
4. Do not save any of the mixed Sucraid solution for later use.
5. Rinse the measuring scoop with water.

Single-Use Container:

1. Empty the entire contents of the single-use container (2 mL) in 120 mL of cold or room temperature water, milk, or infant formula.
2. Stir to mix well.
3. Administer half of the mixed Sucraid solution (60 mL) at the beginning of the meal or snack and the other half of the mixed solution during the meal or snack (60 mL).
4. Do not save any of the mixed Sucraid solution for later use.

HOW SUPPLIED

118 mL Multiple-Dose Bottle

Sucraid (sacrosidase) Oral Solution is available in 118 mL (4 fluid ounces) multiple-dose translucent plastic bottles, packaged two bottles per carton. Each mL of solution contains 8,500 International Units of sacrosidase. A 1 mL measuring scoop is provided with each bottle. A full measuring scoop is 1 mL.

NDC# 67871-111-04 (2 x 118 mL multiple-dose bottles)

Store under refrigeration at 2°C to 8°C (36°F to 46°F). Discard four weeks after first opening due to the potential for bacterial growth. Protect from heat and light.

2 mL Single-Use Container

Sucraid (sacrosidase) Oral Solution is available in 2 mL, single-use containers that are packaged into a foil pouch. Each 2 mL single-use container contains 17,000 International Units of sacrosidase. Each foil pouch holds a card of 5 containers. Five pouches are then packaged in a box (25 containers). Six boxes are further packaged in a carton (150 containers).

NDC# 67871-111-07 (150 x 2 mL single-use containers)

Store under refrigeration, 2°C to 8°C (36°F to 46°F). Protect from light. Single-use container can be removed from refrigeration and stored at 15°C to 25°C (59°F to 77°F) for up to 3 days (72 hours).

Manufactured by:
QOL Medical, LLC Vero Beach, FL 32963
U.S. License No. 2195

www.sucraid.com
For questions call 1-866-469-3773

Rev <08/24>

Patient Information

SUCRAID® (Su-kreid) (sacrosidase) Oral Solution

What is SUCRAID?

SUCRAID is a prescription medicine for the treatment of people who were born with a lack of (deficiency) sucrase, which is part of congenital sucrose-isomaltase deficiency (CSID). It is not known if SUCRAID is safe and effective in children under 5 months of age.

Do not take or give your child SUCRAID if you or your child:

- are allergic to yeast, yeast products, glycerin (glycerol), or papain. See the end of this Patient Information leaflet for a complete list of ingredients in SUCRAID.
- Before you take or give your child SUCRAID, tell your healthcare provider about all of your medical conditions, including if you or your child:
 - have diabetes. SUCRAID can interact with the food in your diet and may change your blood sugar levels. Your healthcare provider will tell you if your diet or diabetes medicines need to be changed.
 - are pregnant or plan to become pregnant. It is not known if SUCRAID will harm your unborn baby.
 - are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take SUCRAID while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take or give SUCRAID?

- **See the detailed Instructions for Use that come with this Patient Information leaflet for instructions about the right way to take or give SUCRAID.**
- SUCRAID should be taken or given exactly as prescribed by your healthcare provider.Do not change the dose of SUCRAID without talking to your healthcare provider.
- SUCRAID comes in a 118-mL multiple-dose bottle or a 2-mL single-use container.Your healthcare provider will decide which type of SUCRAID is best for you to use.
- The dose of SUCRAID depends on body weight.Your healthcare provider will tell you how much SUCRAID you should take or give your child.
 - The dose for a child 33 pounds (15 kg) or less is 1 mL or 28 drops of SUCRAID in 2 ounces of water, milk, or infant formula.
 - The dose for a child or adult more than 33 pounds (15 kg) is 2 mL or 56 drops of SUCRAID in 4 ounces of water, milk, or infant formula.
- SUCRAID can only be dissolved in cold or room temperature water, milk, or infant formula. **Do not** put SUCRAID in warm or hot liquids.
 - **Do not** mix SUCRAID with fruit juice. **Do not** take or give SUCRAID with fruit juice.
 - **Do not** warm or heat the mixed solution before taking or giving SUCRAID.
- Measure your dose or your child's dose of SUCRAID using the measuring scoop that comes with the SUCRAID bottle.**Do not** use a kitchen teaspoon or other measuring device.
- SUCRAID should be taken or given with each meal or snack. Half of the SUCRAID dose should be taken at the beginning of each meal or snack. Take or give the remaining SUCRAID dose during the meal or snack.
- Rinse the measuring scoop with water after each use.
- SUCRAID does not break down some sugars found in foods that have starch, such as wheat, rice, and potatoes. Your healthcare provider may tell you to avoid eating foods with starch.

What are the possible side effects of SUCRAID?

SUCRAID may cause serious side effects, including:

- **severe allergic reactions.** Severe allergic reactions have happened in some people taking SUCRAID. Tell your healthcare provider right away or go to the nearest emergency room if you have any of the following symptoms:
 - difficulty breathing
 - wheezing
 - rash
 - swelling of the face, lips, mouth, or tongue

Your healthcare provider may need to monitor you or your child carefully when first starting treatment with SUCRAID.

The most common side effects of SUCRAID include:

- stomach (abdominal) pain
- vomiting
- nausea
- diarrhea
- constipation
- problems sleeping
- headache
- nervousness
- dehydration

These are not all of the possible side effects of SUCRAID. **Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

How should I store SUCRAID?

- **SUCRAID 118 mL multiple-dose bottle**
 - Store in the refrigerator between 36°F to 46°F (2°C to 8°C).
 - Throw away after 4 weeks of first opening the multiple-dose bottle.
 - Protect from heat and light.
- **SUCRAID 2-mL single-use container**
 - Store in the refrigerator between 36°F to 46°F (2°C to 8°C)
 - After removing from the refrigerator, the 2-mL single-use container can be stored between 59°F to 77°F (15°C to 25°C) for up to 3 days (72 hours).
 - Protect from heat and light.

• Keep SUCRAID and all medicines out of the reach of children.

General information about the safe and effective use of SUCRAID.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. **Do not** use SUCRAID for a condition for which it was not prescribed. **Do not** give SUCRAID to other people, even if they have the same symptoms that you have. It may harm them.You can ask your pharmacist or healthcare provider for information about SUCRAID that is written for health professionals.

What are the ingredients in SUCRAID?

Active ingredient: sacrosidase

Inactive ingredients: Citric acid, glycerol, sodium hydroxide, and water.

Manufactured by:
QOL Medical, LLC Vero Beach, FL 32963
U.S. License No. 2195
For more information, go to www.Sucraid.com or call 1-866-469-3773.

This Patient Package Insert has been approved by the U.S. Food and Drug Administration

Revised: August 2024

Instructions for Use

SUCRAID® (Su-kreid) (sacrosidase) oral solution:
118 mL Multiple-Dose Bottle

Read this Instructions for Use before you start taking or giving SUCRAID to a child, and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your or your child's medical condition or treatment.



Important information you need to know before taking or giving SUCRAID:

- Your healthcare provider will decide the right dose of SUCRAID for you or your child. **Do not** change the dose of SUCRAID without talking to your healthcare provider.
- The dose of SUCRAID depends on body weight. Your healthcare provider will tell you how much SUCRAID you should take or give your child.
 - The dose for a child 33 pounds (15 kg) or less is 1 mL or 28 drops of SUCRAID in 2 ounces of water, milk, or infant formula.
 - The dose for a child or adult more than 33 pounds (15 kg) is 2 mL or 56 drops of SUCRAID in 4 ounces of water, milk, or infant formula.
- SUCRAID can only be dissolved with cold or room temperature water, milk, or infant formula. **Do not** put SUCRAID in warm or hot liquids. **Do not** dissolve SUCRAID with fruit juice. **Do not** take or give SUCRAID with fruit juice.
- **Do not** warm or heat the mixed solution before taking or giving SUCRAID.
- Measure your dose or your child's dose of SUCRAID using the measuring scoop that comes with the SUCRAID bottle. **Do not** use a kitchen teaspoon or other measuring device.
- SUCRAID should be taken or given with each meal or snack. Half of the SUCRAID dose should be taken or given at the beginning of each meal or snack. Take or give the remaining SUCRAID dose during the meal or snack.
- **Do not** use the SUCRAID multiple-dose bottle if the seal has been damaged. Contact your pharmacist or healthcare provider if you cannot use the SUCRAID multiple-dose bottle.

Supplies needed to take or give SUCRAID:

- SUCRAID 118 mL multiple-dose bottle
- 1 measuring scoop (included in SUCRAID carton)
- 2 to 4 ounces of cold or room temperature water, milk, or infant formula (not included)
- Meal or snack (not included)

How to take or give SUCRAID:

Step 1: Check the expiration date on the SUCRAID bottle. **Do not** use SUCRAID after the expiration date on the bottle has passed.

Step 2: Write down the date the bottle is first opened in the space provided on the bottle label.

Step 3: Each bottle of SUCRAID has a plastic screw cap that covers a dropper dispensing tip. Remove the plastic screw cap by twisting it to the left.

Step 4: Use the measuring scoop that comes in your SUCRAID carton to measure your or your child's prescribed dose. See **Figure 1**. Reseal the bottle after each use by replacing and twisting the plastic screw cap to the right until tight.



Figure 1

Step 5: Mix your or your child's prescribed dose in 2 ounces or 4 ounces of cold or room temperature water, milk, or infant formula as instructed by your healthcare provider. See **Figure 2**.



Figure 2

Step 6: Take or give half of the mixed solution at the beginning of each meal or snack. Take or give the remaining mixed solution during the meal or snack.

Step 7: Rinse the measuring scoop with water after each use.

Throwing away (disposal of) SUCRAID:

- Throw away (discard) the SUCRAID multiple-dose bottle and any remaining medicine in your household trash 4 weeks after first opening.

How should I store SUCRAID?

- Store the SUCRAID multiple-dose bottle in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Protect SUCRAID from heat and light.

Keep SUCRAID and all medicines out of the reach of children.

Manufactured by:
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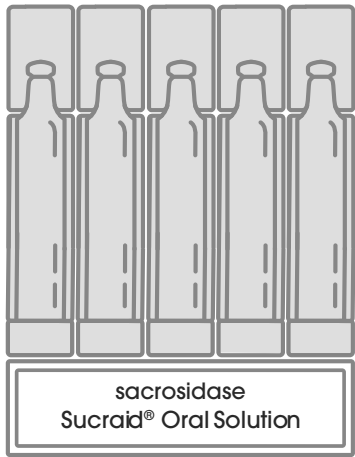
For more information, go to www.sucraid.com or call 1-866-469-3773.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Issued: May 2022

Instructions for Use

Sucraid® (Su-kreid) (sacrosidase) Oral Solution:
2-mL Single-Use Container

Read this Instructions for Use before you start taking or giving Sucraid to a child, and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your or your child's medical condition or treatment.



Important information you need to know before taking or giving Sucraid:

- The 2-mL single-use container is for children and adults.
- Sucraid is supplied in 2-mL single-use containers in a foil pouch. Each foil pouch holds 5 single-use containers. **Each container is one 2 mL Sucraid dose.**
- Your healthcare provider will decide the right dose of Sucraid for you or your child. **Do not** change the dose of Sucraid without talking to your healthcare provider.
- Sucraid can only be dissolved with cold or room temperature water, milk, or infant formula. **Do not** put Sucraid in warm or hot liquids. **Do not** dissolve Sucraid with fruit juice. **Do not** give or take Sucraid with fruit juice.

- **Do not** warm or heat the mixed solution before taking or giving Sucraid.
- Sucraid should be taken or given with each meal or snack. Half of the Sucraid dose should be taken at the beginning of each meal or snack. Take or give the remaining Sucraid dose during the meal or snack.
- **Do not** use the Sucraid single-use container if the seal has been damaged. Contact your pharmacist or healthcare provider if you cannot use the Sucraid single-use container.

Supplies needed to take or give Sucraid:

- 1 Sucraid 2-mL container
- 4 ounces of cold or room temperature water, milk, or infant formula (not included)
- Meal or snack (not included)
- Spoon to mix (not included)

How to take or give Sucraid:

Step 1: Check the expiration date on the Sucraid foil pouch. **Do not** use Sucraid if it is past the expiration date. Remove 1 Sucraid 2-mL container from a foil pouch.

Step 2: Twist the cap to the left to remove it from the container. See **Figure 1**.

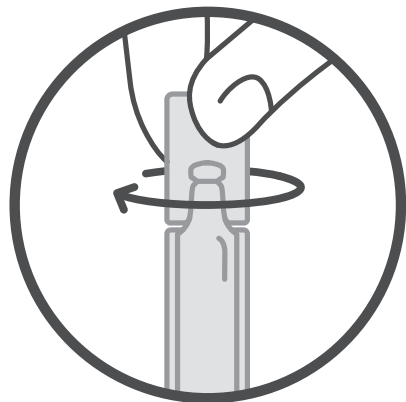


Figure 1

Step 3: Squeeze all the Sucraid solution in the container into 4 ounces of cold or room temperature water, milk, or infant formula. See **Figure 2**.



Figure 2

Step 4: Mix your or your child's prescribed dose in 4 ounces of cold or room temperature water, milk, or infant formula. See **Figure 3**.

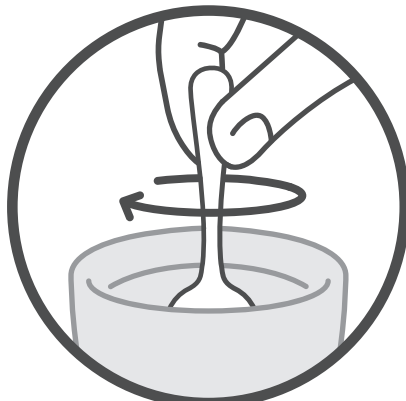


Figure 3

Step 5: For patients weighing more than 33 pounds (15 kilograms):

- The entire 4 ounces of mixed solution will be taken or given during each meal or snack. Take or give half of the mixed solution (2 ounces) at the beginning of the meal or snack and take or give the other half of the mixed solution (2 ounces) during the meal or snack.

For patients weighing 33 pounds (15 kilograms) or less:

- Divide the 4-ounce mixed solution into two separate 2-ounce portions.
- Take or give half of the first portion (1 ounce) at the beginning of the meal or snack and take or give the other half of the first portion (1 ounce) during the meal or snack.
- Store the second portion (2 ounces) in the refrigerator at 36°F to 46°F (2°C to 8°C) for the next meal or snack. Take or give half of the second portion (1 ounce) at the beginning of the next meal or snack and take or give the other half of the second portion (1 ounce) during the meal or snack.
- Throw away the second portion (2 ounces) if you do not use it within 24 hours.

Throwing away (disposal of) Sucraid:

- Throw away expired or empty Sucraid containers in your household trash.

How should I store Sucraid?

- Store the Sucraid single-use container in the refrigerator between 36°F to 46°F (2°C to 8°C).
- The Sucraid single-use container may be stored between 59°F to 77°F (15°C to 25°C) for up to 3 days.
- Protect Sucraid from heat and light.

Keep Sucraid and all medicines out of the reach of children.

Manufactured by:
QOL Medical, LLC Vero Beach, FL 32963
U.S. License No. 2195

For more information, go to www.Sucraid.com or call 1-866-469-3773.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
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Invited Review

Congenital Sucrase-Isomaltase Deficiency

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Sucrase-isomaltase deficiency has received much less attention than lactase deficiency. Although much of the world's population is predisposed to become lactose-intolerant at an early age, the occurrence of sucrase-isomaltase deficiency, either as a result of an inherited condition or secondary to diffuse mucosal injury, is relatively rare. Recently, however, sucrase-isomaltase deficiency has been the focus of increased research activity; important new work has included the elucidation of molecular defects associated with the inherited form of sucrose malabsorption and the recent cloning of the human sucrase-isomaltase gene.

This paper will focus on congenital sucrase-isomaltase deficiency (CSID), including its epidemiology, clinical presentation, and natural history. Normal enzyme structure, synthesis, and processing will be reviewed in order to facilitate understanding of the molecular pathogenesis of CSID. Finally, newer aspects of treatment, including the demonstration of effective enzyme-replacement therapy, will be emphasized. The reader is referred to several excellent reviews for further details (1-3).

SUCRASE-ISOMALTASE: STRUCTURE, BIOSYNTHESIS, AND CONTROL OF ACTIVITY

Role in Digestion (Table 1)

Sucrase-isomaltase (SI) is one of four brush-border disaccharidases. Three of these, including SI, maltase-glucoamylase, and trehalase, are α -glucosidases involved in the digestion of sucrose and starch. After hydrolysis of starch by salivary and pancreatic α -amylases, the resulting products are α

1-4 linked maltose, maltotriose, and malto-oligosaccharides, α 1-6 linked branched dextrins (α -limit dextrins), and glucose. Sucrase hydrolyzes the α 1-4 linked glucose linkages of maltose and maltotriose and the glucose-fructose linkage of sucrose. Isomaltase is an α -glucosidase and cleaves the α 1-6 glucopyranosyl bonds of branched oligosaccharides (α -limit dextrins), the 1-6 linkages of isomaltase, as well as the 1-4 linkages of maltose. The SI complex also hydrolyzes α -glucosides with up to six glucose residues (4). The maltase-glucoamylase complex overlaps with SI activity by hydrolyzing α 1-4 glucose linkages of maltose, maltotriose, starch, glycogen, and other oligosaccharides from their nonreducing ends with maximal affinity for medium-sized polysaccharide chains with 6-10 glucose residues (5). Approximately 80% of the maltase activity is accounted for by SI and only 20% by the maltase-glucoamylase complex. The fourth brush-border disaccharidase, lactase-phlorizin hydrolase, is a β -galactosidase that hydrolyzes the β 1-4 linkage of disaccharide but not of cellulose. SI activity is distributed along the whole length of the small intestine. The highest activity occurs in the jejunum, with 20-30% less activity proximal to the ligament of Treitz and distally in the ileum (6).

Structure

SI is a heterodimer complex composed of two similar but not identical subunits. Each subunit consists of a single glycosylated polypeptide chain with an apparent molecular weight in the 120-160 kDa range. Carbohydrate moieties account for ~15% of the molecular mass (7). Recent cloning of the SI cDNA has shown that the SI complex is synthesized as a single precursor of ~260 kDa starting from the N-terminus of isomaltase with ~1827 amino acid residues (3,8).

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TABLE 1. Role of brush-border enzymes in digestion of disaccharides and starch

Enzyme	Bond cleaved	Substrate	Products
Lactase	β -(1-4) galactosidase (β -glucosidase)	Lactose	Glucose, galactose
Sucrase	α -(1-4) glucosidase	Sucrose, maltose, maltotriose, α -limit dextrins with terminal α 1-4 links	Glucose, fructose malto-oligosaccharide with α 1-6 linkage
Glucoamylase	α -(1-4) glucosidase	Maltose, maltotriose malto-oligosaccharide (glucose polymers with maximal affinity for chains of 6-10 residues)	Glucose, malto-oligosaccharide with terminal α 1-6 linkage
Isomaltase (α -dextrinase)	α -(1-6) glucosidase	Maltose, isomaltose, α -limit dextrins (malto-oligosac- charide with terminal α 1-6 links)	Glucose, malto-oligosac- charides
Trehalase	α - and β -glucosidase (tested on renal trehalase)	Trehalose (found principally in mushrooms)	Glucose

The isomaltase subunit alone interacts with the enterocyte membrane directly via a highly hydrophobic segment at its N-terminal region (Fig. 1). This segment is 20 amino acid residues long and spans the lipid membrane bilayer only once. This domain functions both as a permanent membrane anchor and as a signal peptide that directs targeting to the endoplasmic reticulum (9). It is followed by a 22-residue serine/threonine-rich glycosylated stretch, which presumably forms the stalk on which the globular, catalytic domains are directed into the intestinal lumen (8). The active sites of both enzymes protrude out into the lumen. The sucrase subunit is more peripheral and does not interact with the hydrophobic core of the membrane at all.

After synthesis, glycosylation, and transport to the brush border, prosucrase-isomaltase is rapidly processed by pancreatic proteases, predominantly elastase in the rat and trypsin in humans (10). These proteases cleave the molecule, yielding isomaltase (~125 kDa) and sucrase (~140 kDa). The two subunits remain associated by noncovalent strong ionic interactions. Recent work with rat intestinal membrane vesicles suggests that the postinsertional processing of the prosucrase-isomaltase as well as the structural and functional relationships of the final subunits are much more complex than has been generally assumed. The enzyme, rather than being a simple dimer, may exist in two oligomeric forms consisting of combinations of the subunits strategically interrelated so that the sucrase catalytic site appears to sterically regulate the availability of the isomaltase site (11). A reduction in sucrase activity in rat brush-border membrane vesicles in response to increasing temperature leads to a reciprocal in-

crease in isomaltase activity through recruitment of functional isomaltase catalytic sites.

The glycosylation of SI is similar to other disaccharidase complexes and includes two main steps (Fig. 1); the cotranslational acquisition of glucan units of a high mannose type at the endoplasmic reticulum and the subsequent trimming and complex glycosylation in the Golgi apparatus (12). This results in a mature SI that contains a large proportion of asparagine-linked oligosaccharides made up of sialic acid, galactosamine, N-acetyl galactosamine, and mannose, as well as mucin type O-glycosidic linkage characterized by a bond between an N-acetyl galactosamine residue and a serine or threonine residue on the polypeptide chain (13). The peptide sequence of human SI precursor contains 18 putative N-glycosylation sites (14). Knowledge of the N-glycosylation sites is particularly useful for the study of CSID, where the absence of expression of this enzyme is often associated with a block in its transport and with abnormalities in glycosylation.

Molecular Biology

The gene encoding human SI has been localized to the long arm of chromosome 3 (15,16). A comparison between the human enzyme and SI in the rabbit, rat, and pig shows a high degree of homology of both nucleotide and amino acid sequences in the N-terminal and active site regions (16). An optimal alignment of the two subunits reveals a high degree of homology between the isomaltase and sucrase portions (41% for amino acids and 52% at the DNA level), indicating that SI probably evolved by partial gene duplication (8). In addition, homology

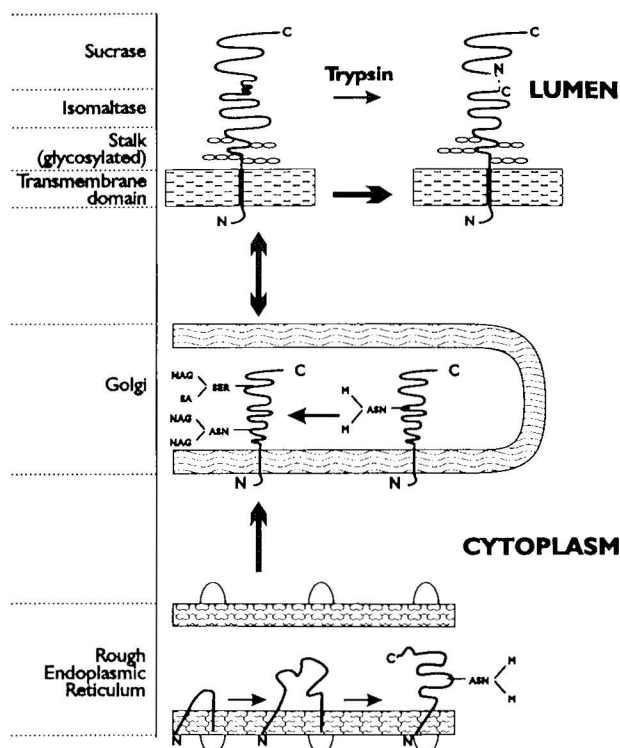


FIG. 1. Cotranslational modification and posttranslational processing of sucrase isomaltase (SI) in the enterocyte organelles and intestinal lumen. SI is synthesized as a long polypeptide chain carrying two similar but not identical active sites (pro-sucrase-isomaltase). The pro-SI is inserted into the rough endoplasmic reticulum (RER) via the same N-terminal hydrophobic region, acting as a targeting protein to the RER, which will later act as the anchor in the brush-border membrane. In the RER, the polypeptide elongates and is glycosylated at asparagine sites (ASN) with mannose (M) residues. The glycoprotein then migrates to the Golgi complex, where mannose residues are trimmed and complex glycosylation with N-acetyl galactosamine (NAG) and sialic acid (SA) residues at ASN and serine (SER) sites takes place. After complex glycosylation, the pro-SI is inserted into the enterocyte membrane, with the sucrase catalytic domain protruding furthest out into the lumen. Pro-SI is then rapidly processed by trypsin, yielding the two subunits of isomaltase and sucrase associated by noncovalent strong ionic interactions.

at the active site indicates that human SI, human lysosomal α -glucosidase, and yeast glucoamylase probably shared an ancestral gene and are only differentiated significantly at the N-terminal regions, accounting for the different biosynthetic pathways and cellular location of these enzymes (17). The SI complex is synthesized by small-intestinal epithelial cells with a noncleavable signal sequence that also contains the membrane anchoring domain. In contrast, the N-terminus of human lysosomal α -glucosidase comprises a signal peptide that is cleaved off, generating a soluble glycoprotein whose final desti-

nation is an intracellular organelle, the lysosome. Southern blotting, sequencing, and mRNA studies indicate that, in comparison with normal small intestine, the structure of the SI gene and its mRNA are unaltered in the two human colon cancer cell lines Caco-2 and HT-29 (14).

Northern blots of RNA extracted from subpopulations of rat and human intestinal epithelial cells that are isolated from villus and crypt compartments show that the cloned gene hybridizes to a 6.5 kb band predominantly in villus RNA (18). RNA probes have localized the greatest accumulation of SI mRNA to the nucleus of cells at the crypt-villus junction. Abundant mRNA is also seen in cells from the lower mid-villus region in both the nucleus and cytoplasm, with a disappearance of nuclear mRNA and a decline in cytoplasmic mRNA from the mid-villus to the tip (19).

Using full-length rabbit and partial human SI cDNA clones as probes, a good correlation has been demonstrated between the expression of SI at the levels of mRNA and protein. Thus, similar to other proteins expressed in enterocytes including liver fatty acid binding protein, cytochrome P450IIB1, and aminopeptidase N, SI is regulated at the level of increasing mRNA abundance as cells migrate from crypt to mid-villus (19). For these reasons, SI is considered a useful marker for enterocyte differentiation. The decrease in sucrase enzymatic activity in villus tip cells has been attributed to enzymatic degradation of the sucrase portion of the dimeric enzyme by luminal pancreatic proteases (20); however, a decrease in the steady-state levels of SI mRNA may also play a role secondary to either a decrease in transcription of the gene or more rapid degradation of cytoplasmic mRNA.

Control of Enzyme Activity (Table 2)

The regulation of oligosaccharidases is a dynamic process since their half-life is only 4–16 h; therefore, maintenance of activity at the brush border requires several cycles of synthesis and degradation during the life cycle of the human intestinal cell. Multiple factors modulate the activity of SI at the level of transcription, translation, glycosylation, and processing by luminal proteases. In addition, factors such as the age of the cell, its degree of differentiation along the villus, and proximal versus distal intestinal location play an important role in determining enzyme activity. Finally, dietary components and circulating hormones may alter the ac-

TABLE 2. *Control of sucrase-isomaltase activity at different levels and sites*

	Increased activity	Decreased activity
Transcription	Crypt-villus junction	Villus tip
Translation	Jejunum	Ileum
Glycosylation	Complex	Simple (high-mannose)
Pancreatic proteases	Pancreatic duct obstruction	↑ Pancreatic enzymes
Diet	High-sucrose, high-carbohydrate diet	Fasting, high-protein, low-carbohydrate diet
Hormones	Thyroxine, corticosteroids	

tivity of brush-border enzymes by varying their synthesis or degradation rate.

Both in rabbits and in humans, SI is most likely primarily controlled at the transcriptional level, since the enzyme activities have a high correlation coefficient with the level of SI mRNA (21). The fact that autoradiographic grains representing SI mRNA are first noted over nuclei in cells at the crypt-villus junction and only seen in the cytoplasm as these cells migrate into the mid-villus region further supports the hypothesis that transcription of the sucrase-isomaltase gene is activated (18). The cellular or extracellular factors that signal the nucleus to initiate SI gene transcription are largely unknown. Over 3000 base pairs of the 5' flanking region of the gene are required for high-level expression. Recently, Traber et al. have shown the enterocyte-specific transcription of the gene in mice and humans is controlled by a 183 base pair promoter located immediately upstream of the transcriptional start site (22,23). This promoter contains at least three nuclear protein-binding sites that appear to bind intestine-specific nuclear protein complexes required for transcriptional activity. These protein complexes have not been fully characterized.

Levels of SI activity may be regulated posttranslationally as well as at the mRNA level. Based on results of differential immunohistochemical staining and immunoprecipitation studies, Beaulieu et al. concluded that SI protein is synthesized in both crypt and villus cells, but that there are differences in posttranslational processing of the protein (24). In the rat, there is a three- to fivefold greater activity of SI in the jejunum versus the ileum. Although no differences are found in SI mRNA abundance between the two sites, the relative rate of de novo

synthesis of all forms of the enzyme is three to fivefold greater in the jejunum than the ileum, and a greater proportion of jejunal SI mRNA is associated with membrane-bound polyribosomes, suggesting greater translational efficiency (25).

These results indicate that along the longitudinal axis of the small intestine, SI expression is regulated by differences in translational mechanisms. In the rabbit, the in vitro biosynthesis of SI correlates well with the steady-state levels of its cognate mRNA all along the small intestine; however, the ratio of sucrase activity to SI mRNA is lower in the jejunum versus the ileum, again suggesting that variations in sucrase activity along the intestine are due both to transcriptional and posttranslational events (26).

Changes in glycosylation may be partially responsible for the posttranslational regulation of SI activity. After synthesis of a carbohydrate-free precursor in ribosomes bound to the membrane of endoplasmic reticulum, SI is conjugated to N-linked polymannose chains to form high-mannose glycoproteins. The high-mannose precursor is then transported from the rough endoplasmic reticulum to the Golgi complex, where the addition of complex O-linked oligosaccharide chain takes place, yielding the mature "complex" precursor. The high-mannose form has a substantially lower specific activity than the complex glycosylated form (27). High-mannose glycosylation seems to be essential for proper and timely polypeptide folding of the enzyme, allowing it to escape the endoplasmic reticulum. Fructose rapidly induces a block in the expression of SI and other brush-border membrane glycoproteins. The underlying mechanism involves abnormal high-mannose glycosylation and misfolding of the nascent polypeptide chains, thereby delaying exit from the endoplasmic reticulum and leading to degradation by rapid proteolytic breakdown (28,29). Changes in glucose metabolism may also inhibit the biosynthesis of SI both through a decrease in mRNA levels and an inhibitory effect on the conversion of the high-mannose to the complex glycosylated form. Glucose itself, monensin (when used in concentrations that induce increased glucose consumption), and forskolin through increased glycogenolysis via activation of adenylate cyclase all impair glycosylation of the enzyme (30,31).

After complex glycosylation in the Golgi body and transport to the microvillus membrane in vesicles, insertion and processing of SI to subunits pro-

ceeds via a complex series of cleavage steps mediated by pancreatic trypsin (32). The major cleavage site in humans is located between an arginine and isoleucine residue, yielding the sucrase subunit with isoleucine at its N-terminus. This is a trypsin-specific site that is not attacked by either elastase or chymotrypsin. Pancreatic proteases also participate in the luminal degradation of mature SI and appear to be at least partially responsible for the loss of sucrase activity in mature villus tip cells and in ileal enterocytes. Studies in animal models of pancreatic duct obstruction or bypass have demonstrated a decreased rate of degradation in duct-ligated animals, leading to increased SI activity and a disappearance of the usual proximal to distal gradient of sucrase activity in the small bowel (33–35).

Dietary factors and endogenous hormones are also important regulators of SI activity. SI is an inducible brush-border enzyme; both enzyme activities are increased by feeding a high-sucrose or high-carbohydrate diet and decreased by fasting (36). In rats, the mRNA levels of SI increase rapidly after sucrose force-feeding, and these changes correlate with the corresponding increase in enzyme synthesis, enzyme activity, and amounts of immunoreactive enzyme (37). This rapid increase in mRNA accumulation suggests that sucrose feeding induces an increase in transcription of the gene. Rats fed a high-protein, low-carbohydrate diet develop decreased sucrase activity. This effect appears to be at least partially a consequence of increased degradation of sucrase because it is correlated with marked increases in luminal trypsin activity and accumulation of isomaltase monomer, considered a degradation product of the enzyme (35).

Both thyroxine and glucocorticoids induce the precocious appearance of SI in the rat small intestine, mediated primarily by increases in the abundance of its mRNA (38,39). In humans, the SI complex is expressed in small intestine throughout gestation and in an identical form in the fetal colon between 12 and 30 weeks gestation. Before 30 weeks gestation, the enzyme is present only as the single polypeptide prosucrase-isomaltase; whereas after that time, two subunits are also present (40). Mature active SI is also expressed in adenocarcinoma of the colon and in the human colon carcinoma cell lines, Caco-2 and HT-29 (41). These cell lines have been particularly useful in studying enterocyte differentiation and the factors that regulate gene expression of human disaccharidases.

CONGENITAL SUCRASE-ISOMALTASE DEFICIENCY

Molecular Defect

There is abundant phenotypic variation in patients with CSID. All CSID patients lack sucrase, but some have only traces of isomaltase activity, others have reduced but significant isomaltase activity, and still others almost normal activity. The presence of residual isomaltase activity in many patients suggests that CSID is not the consequence of complete absence of SI gene expression. It appears that this phenotypic variation may be mirrored in genotypic heterogeneity. Although specific genetic mutations have not been identified as yet, different molecular defects documented in patients with CSID indicate abnormalities of intracellular processing (glycosylation and folding), intracellular transport, and homing and insertion of the enzyme into the brush-border membrane (Table 3).

It is well known that cellular mutations leading to amino acid substitutions may influence the processing and intracellular transport of glycoproteins (42,43). These point mutations may substantially affect the folding of peptide chains, leading to improper glycosylation. Normal glycosylation of disaccharidases is necessary for the sorting of the enzymes to the brush-border membrane. Tunicamycin, an antibiotic that inhibits N-linked high-mannose glycosylation of proteins, greatly reduces the expression of disaccharidases in brush-border membranes of pig small intestine, leading to rapid intracellular degradation of newly synthesized enzyme (44). Monensin, which allows high-mannose glycosylation but interferes with complex glycosylation of disaccharides in the Golgi body, affects the further transport of the enzyme to the microvillus membrane.

As many as five different transport incompetent or functionally altered enzymes have been discovered in patients with CSID (45) (Table 3). The first molecular phenotype was described by Hauri et al. in 1985 in a 5-year-old girl with no sucrase but low residual intestinal isomaltase activity (46). Immunoelectron microscopy with monoclonal antibodies that reacted specifically with various forms of the prosucrase-isomaltase in biopsy samples from healthy subjects revealed that the enzyme was confined predominantly to the microvillus membrane of enterocytes and there was minimal labeling of the Golgi apparatus. In contrast, in the patient, immunoreactive SI was found almost exclusively in the

TABLE 3. Molecular defects in patients with CSID

	Molecular phenotype				
	I	II	III	IV	V
Location	Golgi	RER	Brush border	Brush border	RER, basolateral membrane
Form	High-mannose precursor	High-mannose and complex precursors	Mature enzyme (catalytically altered sucrase subunit)	Complex precursor (intracellular)	High-mannose precursor
Intracellular degradation products	Present	Present	Absent	Present (sucrase subunit)	?
Microvillus membrane	Absent	Absent	Present (both subunits)	Present (isomaltase subunit only)	Absent
Sucrase activity	0	0	0	0	0
Isomaltase activity	Low	0	Normal	Normal	0

RER, rough endoplasmic reticulum.

Adapted from Sterchi EE, Lentze MJ, Nail HY. Molecular aspects of disaccharidase deficiencies. *Baillieres Clin Gastroenterol* 1990;4:79-96; and from Fransen AM, Hauri HP, Ginsel LA. Naturally occurring mutations in intestinal sucrase-isomaltase provide evidence for the existence of an intracellular sorting signal in the isomaltase subunit. *J Cell Biol* 1991;115:45-57.

Golgi cisternae and associated vesicular structures, with no specific labeling in the microvillus membrane. Immunoprecipitation experiments revealed that the enzyme localized to the Golgi appeared to be the high-mannose form plus lower-molecular-weight degradation products. Subsequently, a second patient was reported with abundant synthesis of a high-mannose SI with arrest of further intracellular processing and failure of a mature glycoprotein form to reach the brush-border membrane (47).

There are several other human diseases associated with disordered intracellular processing of glycoproteins. The intrahepatic accumulation of abnormal glycoprotein in the piZZ phenotype of α -1-antitrypsin deficiency is related to a single amino acid substitution with subsequent failure to transport the high-mannose secretory product through the endoplasmic reticulum (48).

Further study at the subcellular and protein level of patients with CSID has revealed that the maturation and intracellular transport of the enzyme are blocked at different stages along with biosynthesis pathway (45). In a second molecular phenotype, a high-mannose form of the enzyme is incompletely trimmed and blocked not in the Golgi but in the endoplasmic reticulum. A third phenotype appears to be the result of a mutation affecting only the catalytic site of sucrase; the mature enzyme is found inserted into the brush-border membrane and isomaltase activity is relatively preserved (49). Study of a fourth phenotype reveals variants of pro-sucrase-isomaltase precursors that are converted

from the high-mannose form to the mature complex glycosylated form at a slow rate. The enzyme undergoes intracellular cleavage to two subunits and the sucrase subunit is degraded, whereas the isomaltase subunit is normally transported to the brush border (50). In this patient, isomaltase activity was normal. Finally, a mutant phenotype has been recently described where the mannose-rich polypeptide precursor of the enzyme is normally synthesized but remains in the endoplasmic reticulum, does not undergo terminal glycosylation in the Golgi, and is missorted to the basolateral membrane rather than homing to its normal location in the brush-border membrane (50).

These last two naturally occurring mutations provide evidence that structural features in the isomaltase region of pro-sucrase-isomaltase act as an intracellular sorting signal, allowing for transport from the trans-Golgi network to the brush-border membrane (51). The nature of these structural features and of the intracellular elements that recognize them is not yet known.

There have been several cases of CSID in which no immunoreactive forms of sucrase-isomaltase were observed via immunoprecipitation or electron microscopy either on the brush border or intracellularly (45). These cases may represent a defect in transcriptional regulation of sucrase-isomaltase expression. Alternatively, the enzyme may be synthesized but improperly folded and hence not recognized by the specific monoclonal antibodies used to detect the protein.

Incidence

Congenital sucrase-isomaltase deficiency (CSID) is considered a rare autosomal recessively inherited disease, but it is likely that the prevalence has been underestimated (Table 4). Given the wide phenotypic variation and the probability that a variety of genetic mutations cause CSID of varying severity, it is likely that numerous patients suffering from chronic diarrhea remain undiagnosed. Previous studies have attempted to ascertain the number of heterozygote carriers in the general population based on measurements of sucrase enzyme activity in small-intestinal biopsy specimens. Heterozygotes are defined as those with a level of sucrase activity below the lower limit for the normal population, with ratios of sucrase:lactase activity of <0.9 and with normal small-bowel morphology. Using these criteria, Peterson and Herber estimated the incidence of heterozygotes to be 8.9% of the general population in the United States (52). Welsh et al. found a much lower incidence of $\sim 2\%$ heterozygotes in the Caucasian population (one in 2500 homozygotes according to the Hardy-Weinberg equation) and no case that satisfied these criteria among 53 African Americans tested (53). In Denmark, only one case of CSID was uncovered in over 2000 patients biopsied because of abdominal pain and diarrhea (54). The incidence appears to be much higher in Greenland, Alaskan, and Canadian Eskimos (54–56). In Greenlanders with diarrhea, the incidence of sucrose malabsorption is 10.5% (47). In the general population of Greenland, $\sim 5\%$ of those tested showed very low sucrase activity in small-bowel biopsies, and 12.5% had activity below the lower limit of the control population (2).

Numerous cases have been described of CSID among siblings and parents. Kerry and Townley biopsied parents of four children with CSID and found most of them to have sucrase activities below the lowest values in a control group. Seven of the eight parents had a sucrase:lactase ratio below 0.8 (57). From these data, it seems reasonable to as-

sume that CSID is transmitted via autosomal recessive inheritance.

The previous data on heterozygotes suggests that CSID may be more prevalent than previously believed. A small number of patients with intermittent or persistent diarrhea have been diagnosed in adult life (2,58). Because they have no family history and no history of growth failure or malabsorption, these patients have been assumed to suffer from irritable bowel syndrome.

Pathogenesis

Malabsorption of dietary disaccharides and starch in the proximal small intestine gives rise to an osmotic load that stimulates peristalsis in the ileum and colon. In response to the osmotic pressure difference between blood and lumen, water flows into the permeable jejunum and sodium moves into the lumen down its concentration gradient. The end-result is a large volume of intraluminal isotonic fluid with a normal sodium concentration held within the lumen because of the osmotic pressure generated by the malabsorbed carbohydrate solute. When the capacity of colonic bacteria to ferment malabsorbed carbohydrate and the ability of the colonocyte to absorb fluid and the resulting short-chain fatty acids is overwhelmed, diarrhea ensues.

Unabsorbed carbohydrates present in the distal small intestine have effects on distant gastrointestinal functions and the absorption of other nutrients as well (59). They inhibit gastric emptying and accelerate small-intestinal transit because of a decrease in water and sodium absorption. Accelerated duodenal and small-bowel transit may also contribute to the malabsorption of starch, fat, or even monosaccharides. Malabsorption of oligo- and monosaccharides may lead to disruption of the normal postprandial surge of hormones such as insulin, C-peptide, and gastric inhibitory peptide (60).

CSID is not invariably associated with severe diarrhea. Whether sugar or starch malabsorption produces symptoms depends not only on the residual enzyme activity, but also on additional factors such as the quantity of ingested carbohydrate, the rate of gastric emptying, the effect on small-bowel transit, the metabolic activity of colonic bacteria, and the absorptive capacity of the colon. For many of these parameters, the infant is at a disadvantage compared to the adult; this undoubtedly contributes to the increased severity of symptoms seen in many

TABLE 4. Prevalence of CSID in various populations

Group	Percentage
Greenland Eskimos	2–10%
Native Alaskans	3.0%
Canadian native peoples	3.6–7.1%
Danes	$<0.1\%$
North Americans	$\leq 0.2\%$

Data compiled from references (2), (52–57).

infants with CSID. In infants, the length of the small intestine is shorter and the reserve capacity of the colon to absorb excess luminal fluid is reduced compared to adults. Some infants may be consuming a high-carbohydrate diet in the form of juices, baby food fruits and vegetables, and cereals. In young infants with carbohydrate malabsorption, small-intestinal and colonic transit is likely to be more rapid, allowing less time for alternative paths of carbohydrate digestion, including the salvage of malabsorbed carbohydrate by colonic bacterial fermentation.

Compensatory mechanisms for starch digestion limit the diarrheagenic effects of starch malabsorption in patients with CSID. Isomaltase activity is often low but not necessarily absent in these patients. Most starch consumed by young patients has a low content of α -1-6 glucosyl bonds, and the residual isomaltase may be sufficient to hydrolyze these linkages. Glucoamylase activity is normal or increased and is still sufficient to ensure the adequate digestion of the α -1:4 bonds of amylopectin. In addition, the capacity of colonic bacteria to ferment starch is usually well developed in infants by 6 months of age (61,62).

Clinical Presentation

The clinical presentation of CSID is variable; in part, it depends on the introduction of sucrose into the diet. Breast-fed babies or infants consuming lactose-containing formulas will not manifest symptoms until they ingest juices, solid foods, or medications sweetened by sucrose. Baby cereals usually cause less severe symptoms because of the compensatory mechanisms for starch digestion.

Table 5 summarizes the presenting symptoms in 23 patients with CSID. There is an even sex distribution but an overwhelming predilection for Caucasians to be affected, with only one Hispanic patient

and no African Americans diagnosed. In only two instances is there a family history, with two affected sisters and a father and son among the group studied. Chronic watery diarrhea and failure to thrive are common findings in infants and toddlers (63). Other nonspecific findings in this age group include abdominal distention, gassiness, colic, irritability, excoriated buttocks, diaper rash, and (at times) vomiting. Half the patients were diagnosed after the age of 5 years with long histories of chronic diarrhea and abdominal pain.

A minority of severely affected patients require hospitalization for diarrhea and dehydration, malnutrition, muscle wasting, and weakness (64). Often, the correct diagnosis is delayed while other causes of severe chronic diarrhea are entertained (65). These infants may be presumed to have cow's milk or soy protein allergy and often are subject to multiple formula changes. An improvement in symptoms while ingesting a casein-hydrolysate formula may be interpreted as support for this mistaken diagnosis when in truth it reflects the switch in carbohydrate to glucose polymers, which are more dependent on glucoamylase activity for intraluminal digestion. Other diagnoses often considered are cystic fibrosis, celiac disease, severe viral gastroenteritis, or other causes of intractable diarrhea. Support for these possibilities may come from the mild steatorrhea documented in some patients (2). This finding is thought to be due to rapid intestinal transit or chronic malnutrition with partial villus atrophy. Transient hypoglycemia, acidosis, dehydration, and lethargy may lead to consideration of inborn errors of metabolism.

A delay in the diagnosis may also be related to empiric institution of a low-sucrose diet by the parents. Some children attain relatively normal growth and manifest chronic symptoms of intermittent diarrhea, bloating, and abdominal cramps (Table 5). As toddlers, they may be considered to have chronic, nonspecific diarrhea of childhood (66) and are often not diagnosed until the age of 5 years. In older children, symptoms of crampy abdominal pain, gas, and intermittent diarrhea suggest irritable bowel syndrome. Institution of a diet for these conditions including the avoidance of fruit juices, soft drinks, and fructose- and sorbitol-containing beverages and fruits may actually ameliorate symptoms by simultaneously reducing the sucrose load in the diet.

In some societies, dietary habits may mask symptoms. Up until recently, Greenland Eskimos con-

TABLE 5. Presenting symptoms in 23 patients with CSID

Symptoms	Frequency	Mean age at diagnosis (yr)
Chronic diarrhea and failure to thrive	7/23	2.0 $\pm$ 1.1
Chronic diarrhea with normal growth	9/23	5.6 $\pm$ 3.5
Irritable bowel syndrome, abdominal pain	7/23	15.4 $\pm$ 7.3

sumed low-carbohydrate, high-protein, high-fat diets. Only recently has the sugar content of their diet reached European levels (2,54,64). Of 20 Greenland Eskimos diagnosed by McNair et al. with CSID in 1972, seven were adults who denied any gastrointestinal symptoms, presumably as a result of their low-sucrose diet (67). In spite of the various ages and symptoms at presentation of patients with CSID shown in Table 5, there was no difference in the intestinal levels of sucrase-isomaltase or maltase activity measured from small-bowel biopsies in any of these groups.

CSID has been diagnosed in adult patients (58,68,69). Many adults with CSID give a history of feeding difficulties during their infancy and intermittent symptoms since childhood (58,63). Occasionally, the symptoms appear as late as the time of puberty (69). In these patients, the underlying enzyme deficiency can be unmasked by an enteric infection. The symptoms that persist in adult life may be limited to some increase in bowel frequency and to abdominal distention and flatulence, especially at the end of the day, although episodic watery diarrhea associated with large sucrose intake still occurs. In a few patients, diarrhea has alternated with constipation, causing further confusion with irritable bowel syndrome. Some investigators have noted a tendency for spontaneous improvement of symptoms with age; in particular, the starch tolerance seems to improve (1). Possible explanations for these observations include self-regulation of the diet to limit sucrose ingestion and an adaptive increase in colonic salvage of carbohydrate through the stimulatory effects of chronic carbohydrate malabsorption on the fermentative activity of colonic flora.

Diagnostic Evaluation

Several diagnostic tests are available; each has its advantages and pitfalls. An excess of reducing substances ($>0.5\%$) may be demonstrated in liquid stool from a patient with CSID provided the fecal sucrose is hydrolyzed by boiling with 0.1 N HCL. The pH of the stools in a patient with CSID classically should fall between 5.0 and 6.0. Both of these tests have a high degree of false-negative results (70). The presence of sucrose in fecal effluent can also be sensitively detected by paper chromatography.

Prior to the advent of hydrogen breath tests, oral sucrose tolerance tests were the mainstay of the

noninvasive diagnosis of CSID. In children, a rise in blood glucose of >20 mg/dl after a 2.0 g/kg sucrose load is considered an indication of sucrose malabsorption. However, there is a high incidence of false-positive tests (flat sucrose tolerance curve) due to delayed gastric emptying, which can only be verified by intraduodenal instillation of the sucrose load (71).

Sucrose Breath Tests

Sucrose breath hydrogen tests have been extensively validated in children with sucrose malabsorption and normal controls (72). In normal sucrose-tolerant subjects given a 1.0–2.0 g/kg oral sucrose load (≤ 50 g), the change in breath hydrogen excretion over baseline is <10 parts per million. Two previous studies of children with CSID have shown an elevation of breath hydrogen >20 parts per million over baseline between 90 and 180 min after the ingestion of sucrose (72,73).

False negatives can occur with this test (74). Of 23 patients studied, we have documented that our two youngest patients with CSID (both 10 months of age) and one 10-year-old patient failed to show elevated breath hydrogen excretion over a 3-h period when given oral sucrose (2 g/kg sucrose up to 50 g). These patients appear to be non-hydrogen producers; this hypothesis can be confirmed by conducting a breath hydrogen test with a nonabsorbable carbohydrate substrate such as lactulose.

The prevalence of non-hydrogen producers has been estimated to be 2–20% of the general population (75–78). However, recent data have suggested that this figure is an overestimation and that most subjects will produce small amounts of hydrogen in response to malabsorbed carbohydrate if the test is extended beyond 3 h (79). A delay in gastric emptying of a concentrated sucrose load might prolong the transit of malabsorbed sucrose to the cecum in some patients with CSID. Another potential confounder is the acid milieu that may exist in the colon of patients with chronic sucrose and starch malabsorption. Reduction of colonic intraluminal pH secondary to chronic lactulose ingestion has been shown to significantly reduce the intracolonic production of hydrogen (80). A chronically low pH in the colon of patients with CSID may mask the expected rise in colonic hydrogen production and breath hydrogen excretion.

These potential pitfalls suggest that care must be taken in the interpretation of sucrose breath hydro-

gen tests in patients with potential CSID. First, it is important to monitor the symptoms and stool pattern of such patients for 24 h after the breath test is done. Patients who experience significant diarrhea and other symptoms in spite of "negative" sucrose breath hydrogen tests should be screened by other methods. Second, obtaining breath hydrogen determinations for up to 4 h after the ingestion of sucrose may enhance the sensitivity of the test. Third, insistence on a change in breath hydrogen excretion of >20 parts per million over baseline may exclude some patients with CSID, especially if the sucrose load ingested is <1 g/kg. Finally, an unrestricted diet prior to administration of the sucrose breath test may mask a positive test by lowering the intracolonic pH and limiting hydrogen production.

Differential Urinary Disaccharides

Following ingestion, a small fraction of intact disaccharide diffuses unmediated across the intestinal mucosa. The exact quantity is determined by absorptive area, permeability, rate of intestinal transit, and factors controlling intraluminal concentration, such as dilution and rate of hydrolysis. Because most absorbed disaccharides are completely and rapidly excreted into urine, the fraction of an ingested dose excreted in the urine is determined by the gastrointestinal factors described, provided renal function is normal. When lactulose, which resists mucosal hydrolysis, is ingested together with a hydrolyzable test disaccharide such as sucrose, correction for variables other than hydrolysis is obtained and the sucrose:lactulose ratio specifically indicates the corresponding mucosal sucrase activity. Active hydrolysis of sucrose or isomaltose results in calculated ratios >0.3, whereas the absence of SI produces ratios of these disaccharides to lactulose approaching one (81,82). In practice, this test of differential urinary disaccharide excretion consists of administering simultaneous lactulose, lactose, isomaltose, and sucrose after an overnight fast and then collecting urine for 10 h. After recording the urinary volume, an aliquot is analyzed by quantitative paper or thin-layer chromatography for the sugars tested.

Using this method, Maxton et al. have demonstrated excellent agreement between differential urinary disaccharide excretion and small-intestinal disaccharide determinations in patients with CSID (81,82). The addition of rhamnose to the test sugars allows the calculations of a urinary lactulose:rham-

nose ratio, which has been shown to be a useful index of intestinal mucosal permeability (83). CSID is associated with normal mucosa and normal permeability. It can therefore be distinguished from disaccharidase deficiency secondary to diffuse small-intestinal disease, in which the lactulose:rhamnose permeability would be expected to be increased. This test appears to offer a noninvasive method of assessing the activity of multiple intestinal disaccharidases and mucosal permeability simultaneously.

Intestinal Disaccharidases

Measurement of intestinal disaccharidases has remained the gold standard for the diagnosis of CSID. A small-bowel biopsy obtained either with a capsule placed in the proximal jejunum or with the endoscope in the second or third portion of the duodenum will provide material not only for enzyme activity determinations but for histological examination as well. At least two biopsy specimens taken via a standard upper endoscope and three biopsy specimens taken with the pediatric upper endoscope should be obtained for disaccharidase determinations. The mucosa is usually normal histologically, but some patients with severe malnutrition may show mild partial villous atrophy.

In spite of the various ages and symptoms at presentation of the patients summarized in Table 5, sucrase activity is either completely or almost completely absent in 15 of 20 patients tested, isomaltase activity is markedly reduced in 14 of 20 tested, and maltase activity is reduced by 60–90% in 18 of 20 tested. Glucoamylase activity is usually normal, accounting for the residual measured maltase activity (5). In some cases, a reduction of the measured amount of glucoamylase activity has been observed (84). Lactase and alkaline phosphatase levels should be normal.

It is important to ascertain the location of small-bowel biopsy specimens when interpreting intestinal disaccharidase levels. Simultaneous biopsies of the proximal jejunum and the second portion of the duodenum in the patients with histologically normal mucosa and normal disaccharidases have shown a 30–40% reduction in lactase, sucrase, and maltase activity in the duodenum compared to the jejunum (85,86). This finding does not appear to be the result of a sampling error since it is in agreement with disaccharidase determinations in intestinal resection specimens (53,87). Most endoscopic small-

bowel biopsy specimens are obtained from the duodenum; however, much of the published normative data for intestinal disaccharidases comes from tissue obtained from the jejunum with a Crosby capsule (88,89).

Sucrase-isomaltase deficiency is defined as the reduction of enzyme activities to levels lower than at least two standard deviations below the mean for biopsy specimens from normal patients with normal small-bowel histology. Combining the actual measured values of sucrase, isomaltase (palatinase), maltase, and lactase activities with the sucrase:lactase ratio can increase the diagnostic accuracy of the test for CSID. Provided the patient does not have primary lactase deficiency or secondary disaccharidase deficiency from partial or total villous atrophy, the normal sucrase:lactase ratio in adults is 1.9 ± 0.2 (mean $\pm$ SEM) when the biopsy specimen is obtained from the duodenum and 1.6 ± 0.2 when it is taken from the proximal jejunum (85). This ratio should decrease in children <3 years of age since among young children with normal small-bowel histology, lactase levels are generally increased compared to older children whereas sucrase activity remains constant (88). However, the ratio should never be <1.0 unless there is isolated decreased sucrase-isomaltase activity; it should actually increase in primary lactase deficiency or diffuse small-bowel injury and secondary disaccharidase deficiency, where lactase levels are usually more severely depressed than SI activity.

Treatment

Currently, the treatment of CSID consists of life-long adherence to a strict sucrose-free diet. It is seldom necessary to make the diet starch-free as well except in infants, or in older children in whom the institution of a sucrose-free diet does not lead to prompt disappearance of symptoms. In this case, the starch content of the diet must be reduced with special attention to foods having a high amylopectin content, such as wheat and potatoes (2). Compliance with this diet is difficult, and there appears to be a high incidence of chronic gastrointestinal complaints, decreased weight for height, and decreased weight for age in patients with CSID followed after diagnosis (63,64,90). Neither sucrose nor fructose, both of which are known to stimulate sucrase and maltase activity when ingested by normal adults, have been shown to induce enzyme activity in pa-

tients with CSID. There is no evidence that deficient SI activity increases with age.

Enzyme substitution therapy has recently been applied to patients with CSID. A study of eight children with CSID showed that a small amount of lyophilized baker's yeast (*Saccharomyces cerevisiae*) eliminated or lessened symptoms of diarrhea, cramps, or bloating, and also lowered breath hydrogen when administered with an oral sucrose load (91). However, baker's yeast is not palatable in this form and is poorly accepted, especially by young children. As a by-product of the manufacture of belt-dried baker's yeast, a liquid preparation containing high concentrations of yeast-derived invertase (sucrase) is obtained. Invertase is a β -fructofuranosidase and cleaves only sucrose having no effect on maltooligosaccharides. In vitro, it is extremely potent, stable with refrigeration, and tasteless when mixed with water (92). It is also relatively resistant to changes in pH even at levels approximating the intragastric environment. Degradation by pepsin appears to be prevented by buffering intragastric pH and taking the enzyme with food to provide other potential protein substrates for pepsin activity (92).

Recently, 14 patients with CSID were treated with liquid yeast sucrase. Breath hydrogen excretion was significantly reduced in response to a sucrose load, and symptoms of diarrhea, abdominal pain, and gas were prevented or ameliorated in patients consuming a sucrose-containing diet. Improvement in symptoms correlated well with increasing concentrations of the enzyme supplement (92). These results suggest that liquid yeast sucrase may allow the consumption of a more normal diet by children with CSID and decrease the high incidence of chronic gastrointestinal complaints. Secondary sucrase deficiency caused by celiac disease, severe viral or parasitic gastrointestinal infections, the acquired immunodeficiency syndrome, or the short-bowel syndrome may also be amenable to treatment with liquid yeast sucrase.

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hydrolyze sucrose, maltose, short 1–4 linked glucose oligomers, branched (1–6 linked) α -limit dextrins, and starch (1). Exposure to these nutrients provokes osmotic diarrhea with pain, bloating, and abdominal distention; rapid small bowel transit and malabsorption of other nutrients; excessive bacterial fermentation of malabsorbed carbohydrate with colonic gas production and acidification of the stools; and at times, chronic malnutrition and failure to thrive (2). After the sucrase-isomaltase (SI) gene was identified on chromosome 3 (3q25–26) and was cloned in 1992 by Chantret and colleagues, more than 25 mutations in the gene responsible for the synthesis of SI have been discovered (3–6). These mutations result in a variety of defects in the folding of the synthesized propeptide chain; the initial high mannose and then complex glycosylation; the sequential export from the endoplasmic reticulum to the Golgi apparatus, and eventually to the apical membrane; the anchoring of the N-terminal aspect of the isomaltase subunit in the enterocyte microvillus membrane; and the normal architecture of the sucrase and isomaltase catalytic sites, which are independent of each other and can be affected separately, leading to isolated deficiencies (5,6). The intracellular phenotypic heterogeneity is reflected in a range of enzymatic capability ranging from completely absent sucrase activity to low but present residual activity and from completely absent isomaltase activity to normal activity. Because SI is responsible for approximately 60% to 80% of the maltase activity in the brush border of the enterocyte, maltase activity is also significantly reduced in almost all cases.

In addition to the degree of enzyme deficiency, the appearance of overt clinical manifestations of CSID is partially determined by the amount of sugar and starch being consumed. Approximately 60% of the total calories consumed in the average diet in the United States originate from carbohydrates, with 30% of carbohydrate calories deriving from sucrose (7). The typical adult consumes about 150 lb of sugar per year and 65 lb of sucrose. The influence of the dietary consumption of sucrose is best illustrated by the natural history of CSID in Greenland, where approximately 5% to 10% of Greenland Eskimos are affected (8). Before the introduction of a Western diet in the middle part of the last century provoked by the settlement of Greenland by northern Europeans from Denmark and other European countries, CSID was unknown among the indigenous population, who consumed a fish-and-marine mammal-based diet, relatively high in fat and protein and low in carbohydrates and sucrose. A marked increase in diarrhea and other gastrointestinal symptoms in the indigenous population led to studies in the 1970s that delineated the prevalence of CSID. The early introduction of sucrose and starch in the form of baby juices, baby food fruits and certain vegetables, and sucrose- and maltodextrin-containing infant formulas also plays a role in the timing of clinical manifestations of CSID.

Other hormonal and dietary factors and micronutrients also influence small intestinal sucrase activity. Unlike lactase activity

Clinical Aspects and Treatment of Congenital Sucrase-Isomaltase Deficiency

William R. Treem

Congenital sucrase-isomaltase deficiency (CSID) was first described by Weijers and colleagues in 1960 and has subsequently been defined as an inherited deficiency in the ability to

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that is unresponsive to lactose consumption, sucrase activity is inducible by a high-sucrose, high-carbohydrate diet and reduced by a high-protein, low-carbohydrate diet (9). Both thyroxine and corticosteroids induce the expression of SI on the brush border of the enterocyte (10). In animal models, dietary-induced iron deficiency results in decreased small-bowel disaccharidase activity, with lactase affected more than SI (11). This appears to be the result of decreased gene expression caused by overexpression of PDX-1, a repressor of the lactase and sucrase promoter regions. PDX-1 overexpression can be reversed with restoration of a normal iron-containing diet and replenishment of iron stores. Naturally occurring phytochemicals in the diet (eg, cinnamon extract, onions, garlic, certain spices, mushrooms, chamomile tea) can act as inhibitors of amylase and intestinal α -glucosidases, thus influencing luminal sucrase activity (12). In patients with CSID and mutations allowing some residual SI activity, these hormonal and dietary factors may influence the onset and severity of symptoms.

PREVALENCE OF CSID

The actual prevalence of CSID is still a matter of debate. Substantial progress in cloning disease-causing mutations has opened the possibility of conducting large-scale population-based screening. In a recent study by Scott and colleagues, all 48 exons of the 100-kb SI gene on chromosome 3 were sequenced in 31 biopsy-proven patients with CSID and 55 different mutations were identified, with at least 1 of the 4 most common mutations found on 32 (59%) of the affected alleles (4). If one assumes the Hardy-Weinberg equilibrium for mutations in the population, then there is an 83% probability that an individual with severe clinical manifestations of CSID will have at least 1 of these 4 mutations. The results of this study raise the possibility in the near future of a genetic screening test both for population prevalence studies and to aid in the diagnosis of new cases. With the availability of DNA harvesting from buccal mucosa, the feasibility of genetic testing in young infants and children increases substantially. Studies are in progress to determine whether genetic testing also can be done on intestinal epithelial biopsy specimens opening the possibility of simultaneously determining disaccharidase levels and genetic mutations for CSID.

Clinical studies of relatively homogenous selected populations have yielded high rates of CSID, ranging from 5% to 10% in Greenland Eskimos, 3% to 7% in Canadian native peoples, and about 3% in Alaskans of native ancestry (13,14); however, estimates of the prevalence of CSID in other North American and European populations generally range from 1 in 500 to 1 in 2000 among non-Hispanic whites, with a lower prevalence in African Americans and whites of Hispanic descent. These studies evolved from older studies of intestinal disaccharidase levels in adult patients undergoing endoscopy for gastrointestinal symptoms (15,16). The estimates have shown low levels of sucrase activity >1 standard deviation (SD) below the mean in mucosal biopsy specimens from 2% to 9% of patients, even in the absence of overt mucosal injury. If one assumes that some of these patients represent heterozygotes for CSID, then the prevalence quoted above seems plausible; however, the diagnosis of CSID is rarely made even in infants and young children, suggesting the possibility that the phenotype of CSID may be much broader and more variable than previously thought and that a large proportion of affected adult and pediatric patients are not being tested and diagnosed.

This hypothesis receives support from the analysis of recently released whole exome sequence data (Exome Variant Server, <http://evs.gs.washington.edu/EVS>). Belmont and colleagues at the Children's Nutrition Research Center at the Baylor College of

Medicine reviewed the SI gene sequence data in a population of approximately 3500 North American white adults ascertained as controls or with atherosclerosis and no known bias for gastrointestinal disease. These data showed 271 rare missense variants with an aggregate allelic frequency of 0.03864. Based on this allele frequency, and assuming that the alleles segregate independently, Hardy-Weinberg proportions were used to estimate the frequency of homozygotes and compound heterozygotes for rare alleles. Although it is not known whether all of these variants result in decreased enzyme activity, the large number of variants could be consistent, with an estimated frequency of 1:670 affected patients and 7% carriers in this population (personal communication, Dr John Belmont, February 28, 2012; public data at the Exome Variant Server).

There are several pieces of clinical evidence that support the view that CSID is more prevalent than previously believed. Studies of disaccharidase levels from intestinal biopsy specimens sent to 2 pediatric reference laboratories have shown surprisingly frequent results for a pattern suggesting CSID. In 2 studies of almost 1000 biopsies each, sucrase deficiency was defined as >1 SD below the mean activity level in 1 study and $<10\%$ of the mean in another (17,18). As defined, sucrase deficiency was found in 11% and 13% of biopsy specimens in the 2 studies. Included were specimens with isolated sucrase or SI deficiency only (1.0% and 1.1%, respectively), SI and maltase-glucoamylase (MGAM) deficiency only (3.0% and 2.4%, respectively), and pandisaccharidase deficiency (5.8% in both studies). Pandisaccharidase deficiency was more likely accounted for by acquired diffuse intestinal villous injury. Although correlation with histology was not provided, the surprisingly high numbers of isolated SI and combined SI-MGAM deficiencies without lactase deficiency suggest that specific genetically determined enzyme deficiencies may be playing a role.

Although small intestinal disaccharidases are most often investigated in the clinical setting of diarrhea in infants and young children, the role of disaccharidase deficiencies and specifically SI deficiency in other gastrointestinal syndromes also has been entertained. Small series of patients with CSID have revealed a subgroup of adolescents and even adults who present with dyspepsia, gas, and/or irritable bowel syndrome (IBS) rather than the classic presentation of watery diarrhea, failure to thrive, diaper rash, irritability, and acidic stools in infancy (2,19,20). Karnsakul and colleagues studied 44 children and adolescents with dyspepsia, only 4 of whom had intermittent diarrhea (21). Patients underwent endoscopy with small bowel biopsies and disaccharidases and one-third had low sucrase activity (>1 SD from the mean), including 4 of 44 with isolated low sucrase activity, and 11 of 44 with sucrase and pandisaccharidase deficiency, but no significant villous atrophy. In addition, in preliminary follow-up studies of families with index cases of CSID uncovered in a child, patients with a long-term diagnosis of IBS were subsequently identified as having CSID (22).

After the sequencing of all of the exons of the CSID gene, most patients with CSID studied by Scott and colleagues have been found to be homozygous or compound heterozygotes for disease-causing mutations (4). Kerry and Townley showed that the parents of 4 children with CSID had intestinal sucrase activity below the lower limits of normal and a sucrase:lactase ratio <0.8 , both consistent with the heterozygous state and supporting an autosomal recessive pattern of inheritance (23); however, 3 patients in Scott and colleagues' study who presented with classical symptoms and biopsy-proven absent sucrase activity with absent or low isomaltase activity, and 2 others with milder decreases in both enzymes, appeared to be heterozygote carriers with a mutation on 1 allele and a wild-type gene on the other. These small studies lend credence to the hypothesis that CSID is more prevalent than previously

thought; manifests with milder phenotypes that may even omit diarrhea as a prominent symptom; and may be transmitted in ways other than strict autosomal recessive inheritance. The combination of the “heterozygous” state with other genetic and/or dietary and nutritional interactions may provoke gastrointestinal symptoms in certain patients.

PRESENTATION AND NATURAL HISTORY OF CSID

The classical presentation of CSID is severe watery diarrhea, failure to gain weight, irritability, and diaper rash in a 9- to 18-month-old infant who has been exposed to sucrose and starch in the form of baby juices, baby food fruits, teething biscuits, crackers, and other starches. Factors that contribute to the predilection for a presentation during infancy include the shorter length of the colon and a decreased capacity for colonic reabsorption of fluid and electrolytes, more rapid small intestinal transit, a high carbohydrate diet, and the ontogeny of amylase activity that does not reach “adult” levels until the second year of life (24); however, clinical studies during the last 20 years and a retrospective review of 65 patients with CSID have revealed a variety of presentations that defy the conventional view (5,22,25,26). Table 1 describes the symptoms at presentation in these 65 patients. Although most have presented with the classic symptoms, a significant minority have only been diagnosed between 2 to 8 years old after normal growth and a previous diagnosis of chronic nonspecific diarrhea of childhood (“toddler’s diarrhea”), or even later during adolescence or young adulthood carrying a diagnosis of diarrhea-predominant IBS. Up to one-third have had vomiting as a prominent symptom, suggesting again that dyspepsia, gas, bloating, and even reflux-like symptoms may predominate in some patients. Other anecdotal reports have mentioned hypercalcemia and nephrocalcinosis in infants with CSID, and even renal calculi in 2 adults with CSID (27,28).

In a follow-up study of 65 patients with CSID who responded to a questionnaire after being identified by a record of prescriptions for enzyme replacement therapy, 53 of 65 reported the onset of symptoms before 1 year of age, 7 between 1 and 10 years old, and 5 after 10 years of age (22); however, the age at which a diagnosis was made was shifted to the right, with only 17 of 65 diagnosed in the first year, 30 between 1 and 5 years, 10 between 5 and 10 years, and 8 after 10 years of age. The potential reasons for this delay in diagnosis include a mistaken diagnosis of protein intolerance in infancy with multiple formula changes and the elimination of glucose oligomers (maltodextrin) that are partially hydrolyzed by sucrase in favor of glucose monomers in amino acid-based formulas (29). A diagnosis of food allergy often also leads to the elimination of juices and baby foods that may have a high sucrose load, further masking the true underlying cause of diarrhea in patients with CSID. Later in childhood, a diagnosis of chronic

nonspecific diarrhea often will result in a lower carbohydrate, higher fat diet, and the elimination of all juices with improvement in symptoms of patients with CSID (30). Older children and adolescents with CSID and diarrhea-predominant IBS may learn which foods trigger their symptoms and avoid those foods, thus masking their true diagnosis. In addition, chronic carbohydrate malabsorption may act as a prebiotic stimulus to colonic bacterial growth, creating a significant increase in the capacity to ferment and salvage malabsorbed carbohydrate, and stimulate colonic short-chain fatty acid synthesis and sodium and fluid reabsorption by the colonocyte (31). Colonic bacterial flora “adaptation” may thus contribute to a decrease in diarrhea symptoms over time in some patients with CSID.

DIAGNOSIS OF CSID

At present, the gold standard for the diagnosis of CSID remains small intestinal biopsy specimens assayed for lactase, sucrase, isomaltase (palatinase), and maltase activity. In general, the criteria applied to make the diagnosis of CSID include normal small bowel morphology in the presence of absent or markedly reduced sucrase activity, isomaltase activity varying from 0 to full activity, reduced maltase activity, and normal lactase activity, or in the setting of reduced lactase, a sucrase:lactase ratio of <1.0. Table 2 summarizes the disaccharidase activities in 36 patients with CSID; all were included in 2 pivotal clinical trials included as part of the new drug application (NDA) for sacrosidase submitted to the Food and Drug Administration (FDA; NDA 20-772/S-011, 1998). Sucrase activity was absent in 24 of 36 (66%) patients, and in all but 3, activity was less than the third percentile of 977 values in “controls,” which consisted of unselected small bowel biopsies from children with diarrhea and other gastrointestinal symptoms (18). All sucrase activity values in patients with CSID were <10th percentile of controls. Almost two-thirds (23/35) had absent palatinase (isomaltase) activity, and all but 2 were <10th percentile, with 1 of those in the normal range and 1 with elevated activity. Maltase activity was variable. No patient had absent activity, but the mean equaled 41.5 U/g protein and the majority (25/36, 69%) exhibited reductions >2 standard deviations from the mean in controls. All but 2 patients demonstrated <10% of control activity. Two patients exhibited normal activity. There was no clear correlation between absent or residual sucrase activity with the spectrum of decreased maltase activity. Because the brush border enzyme MGAM is responsible for at least 20% of maltase activity, those patients with low maltase activity may be examples of combined deficiencies of SI and MGAM (32,33). Elevated lactase enzyme activity levels were found in 3 of our patients and have been found in a small minority of patients with CSID in most studies to date.

Recent studies of the SI gene in symptomatic patients with intestinal disaccharidase deficiency have identified compound

TABLE 1. Presenting symptoms in 65 patients with CSID (22)

Symptom	No. patients (%)
Diarrhea	62 (95)
Bloating/gas	55 (85)
Abdominal pain	43 (66)
Irritability	43 (66)
Diaper rash	40 (62)
Failure to thrive	39 (60)
Nausea/vomiting	22 (34)
Irritable bowel syndrome	12 (18)

TABLE 2. Intestinal biopsy disaccharidase activities in 36 patients with CSID (U/g protein) (42,43)

	Sucrase (n = 36)	Isomaltase (palatinase) (n = 35)	Maltase (n = 36)	Lactase (n = 36)
Mean	2.3	1.9	41.5	30.5
Standard deviation	4.4	5.8	34.7	19.2
Median	0	0	29.2	27.6
Minimum	0	0	10.9	5.2
Maximum	15.4	33.3	166.7	101.5

heterozygotes with less severely reduced sucrase and isomaltase and even what appears to be true heterozygotes with 1 normal allele and what appears to be a more severe mutation on the other allele (4–6,34). One patient in the cohort studies by Scott et al appeared to have normal wild-type genes on both alleles with moderately reduced sucrase activity and symptoms provoked by sucrose consumption, which suggested acquired sucrase deficiency even in the presence of normal small intestinal morphology (4). Other causes of false-positive results come from biopsies taken in the proximal duodenum, where disaccharidase levels are often only approximately two-thirds of the levels found in the proximal jejunum (35). In addition, mishandling of biopsy specimens resulting in inadequate rapidity of freezing and premature thawing can result in a diffuse reduction in disaccharidase activity. Studies of replicate intestinal biopsy disaccharidase assays have demonstrated a coefficient of variation of 27%, stressing the variability of the assay (18). This variation emphasizes the role of clinical judgment in making the diagnosis of CSID from mucosal disaccharidase assay values.

Other less invasive methods of diagnosis include the sucrose breath hydrogen study and differential urinary disaccharides (36,37). Although relatively easy to accomplish, the sucrose breath hydrogen study is compromised by significant contamination from both false-positives (secondary sucrase deficiency from villous injury, dumping syndrome, and bacterial overgrowth) and false-negatives (nonhydrogen producers, antibiotic interference, delayed gastric emptying). Also, this test can provoke severe symptoms as a result of the 2-g/kg oral sucrose load given to patients with CSID. The differential urinary disaccharide test examines the ratio of urinary sucrose:lactulose, which should approach 1.0 in patients with CSID; however for accurate results, this test relies on obtaining an accurate 10-hour urine collection that is difficult in many infants and young children and the presence of normal intestinal permeability.

Figure 1 summarizes data from studies of the utility of a ^{13}C -sucrose breath test to diagnose CSID (38). This test requires the administration of a small dose of uniformly labeled ^{13}C -sucrose mixed in unlabeled maltodextrin in water as a carrier and the subsequent collection of $^{13}\text{CO}_2$ -enriched breath samples every 15 minutes for 2 hours. The separate administration of ^{13}C -glucose mixed in maltodextrin and collection of $^{13}\text{CO}_2$ allows ^{13}C -sucrose hydrolysis and digestion to be expressed as a coefficient of glucose oxidation (CGO). As Figure 1 shows, the mean percent CGO of ^{13}C -sucrose in 10 patients with CSID is $25\% \pm 21\%$ compared with $146\% \pm 45\%$ in 10 age-matched controls. A cutoff of 79% CGO yields 100% sensitivity and specificity for CSID. Although the test

requires 2 breath tests and infrared spectrophotometry, it has several advantages: it is noninvasive, has excellent sensitivity and specificity, and avoids provocation of gastrointestinal symptoms because of an excessive sucrose load.

TREATMENT OF CSID

Previous follow-up studies of children with CSID treated with sucrose- and starch- restricted diets have demonstrated that only 10% of patients remain consistently asymptomatic, and 60% to 75% still experience diarrhea, gas, and/or abdominal pain, with a lower proportion (20%) complaining of nausea. Only approximately half of these children are compliant with the prescribed diet (39,40). Harms and colleagues described the amelioration of both hydrogen production and gastrointestinal symptoms in 8 children with CSID treated with Baker's yeast (*Saccharomyces cerevisiae*) cakes before a sucrose breath hydrogen test (41). *S. cerevisiae* contains a β -fructofuranoside fructohydrolase with sucrase but not maltase or isomaltase activity. By using specific growing conditions to promote increased enzyme activity and belt drying to preserve this activity, the food industry has for many years been using this enzyme to convert sugarcane (sucrose) to molasses and keep the centers of cream-filled candies liquid. Preclinical studies on a liquid preparation derived from the *S. cerevisiae* (sacrosidase) grown under these conditions showed that 1 mL of this preparation contained approximately 8500 U of sucrose-hydrolyzing activity (8500 μmol glucose formed per minute per milliliter) (42). Sacrosidase was free of lactase, isomaltase, or maltase activity; rich in mannose glycosylation; maintained stable activity with refrigeration; and did not lose significant activity with a pH down to 1.0. Incubation of the enzyme with pepsin at or near the pH optimal for pepsin activity (1.5), however, produced a rapid loss of activity. Preincubation of the pepsin with bovine serum albumin provided a decoy for the pepsin and allowed preservation of sacrosidase activity even at a pH of 1.5.

Figure 2 shows the results of sucrose breath hydrogen studies on the first child with CSID treated with sacrosidase under an orphan drug grant from the FDA. Two breath tests with 2 and 4 g/kg sucrose loads produced a marked rise in breath hydrogen and gastrointestinal symptoms; however, breath tests accompanied by sacrosidase treatment prevented the rise in breath hydrogen and the symptoms. Subsequent pivotal trials in >40 subjects between the ages of 5 months and 29 years were conducted, with the diagnosis of CSID based on chronic watery diarrhea with an acid pH, a tissue

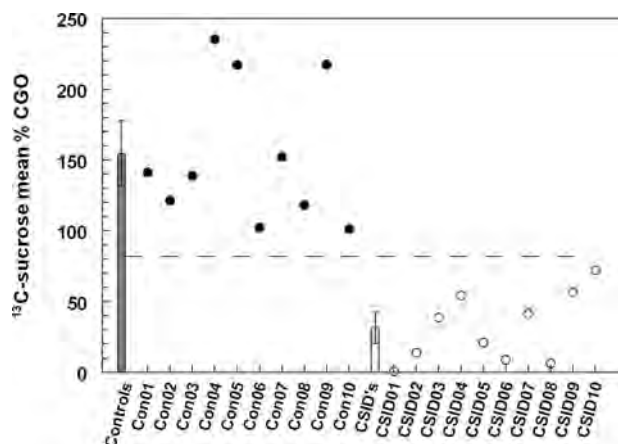


FIGURE 1. Data summary from studies of the utility of a ^{13}C -sucrose breath test to diagnose CSID.

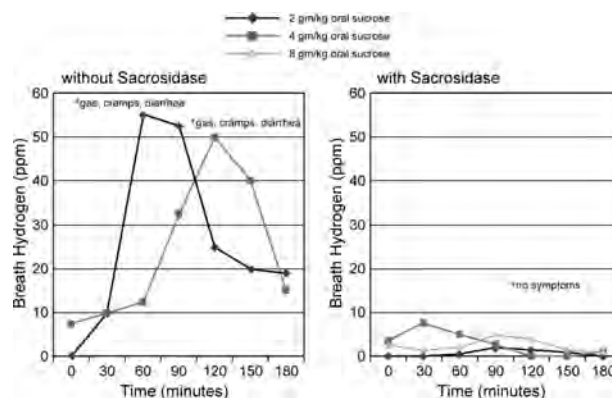


FIGURE 2. Results of sucrose breath hydrogen studies on the first child with CSID treated with sacrosidase under an orphan drug grant from the Food and Drug Administration.

sucrase activity level of <10% of the mean of controls, a normal lactase level, and a normal lactose breath hydrogen test (42,43). These multicenter, double-blind, randomized studies used 3 increasing dilutions of sacrosidase and an undiluted form in 4 arms given to each subject in random order during a 10-day period in which time the subjects consumed a normal sucrose-containing (approximately $1.75\text{--}2.5\text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) and starch-containing ($5.2\text{--}5.8\text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) diet. Two breath hydrogen studies (with and without sacrosidase) were performed in the first study and 3 (with and without sacrosidase and with sacrosidase plus cow's milk acting as a pepsin decoy) in the second pivotal study.

The results of these studies can be summarized as follows. All dilutions of sacrosidase reduced symptoms of sucrose

malabsorption provoked by both the breath tests and the period of unrestricted diet; the undiluted preparation most significantly reduced watery stools, gas, cramps, and bloating. Full-strength (undiluted) sacrosidase normalized these symptoms and the stool frequency in comparison with the baseline period of a sucrose-free, starch-restricted diet and no sacrosidase treatment. Full-strength sacrosidase resulted in 81% of patients, consuming an unrestricted diet, remaining asymptomatic, compared with 78% untreated during the baseline, diet-restricted period. Excessive breath hydrogen production was blocked by the double-blind administration of sacrosidase compared with placebo and was further reduced by consuming milk before sucrose ingestion (Fig. 3A). A study of the ^{13}C -sucrose breath test with and without sacrosidase administration

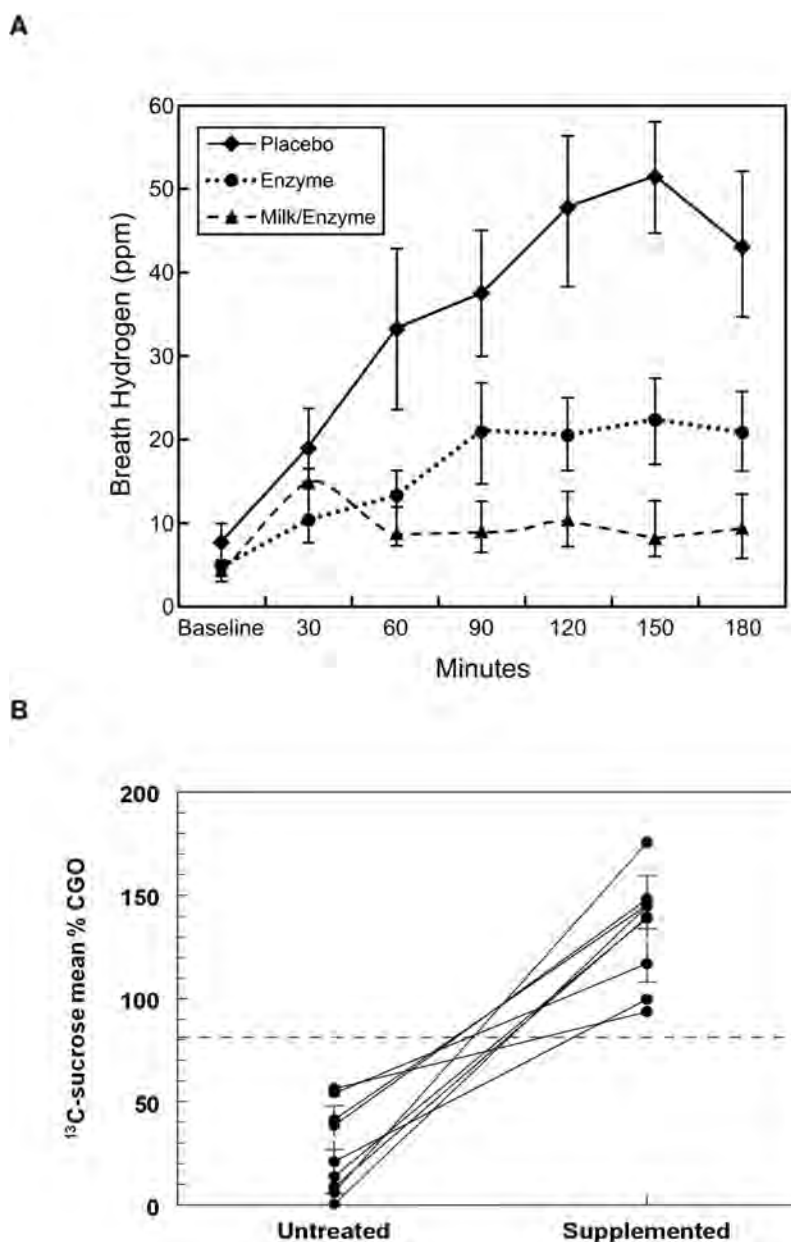


FIGURE 3. A, Excessive breath hydrogen production blocked by the double-blind administration of sacrosidase compared with placebo and was further reduced by consuming milk before sucrose ingestion. B, A study of the ^{13}C -sucrose breath test with and without sacrosidase administration confirmed these results and shows that all of the subjects had normalized CGO with therapy.

TABLE 3. Persistence of symptoms in 65 patients with CSID treated with Sucraid (22)

Symptom frequency	Diarrhea, %	Bloating/gas, %	Nausea/vomiting, %	Abdominal pain, %
0 times per week	46	43	96	91
1 time per week	28	18	4	9
2–3 times per week	12	13	0	0
>3 times per week	14	26	0	0

confirmed these results and shows that all of the subjects had normalized CGO with therapy (Fig. 3B) (37). Adverse events were limited to unrelated episodes of vomiting, pallor, and dehydration, each in a single subject, and a possibly related event of wheezing in a young child with known asthma, who was later found to have a positive skin test for sacrosidase (43). This incident led to the recommendation on the label to perform skin tests on patients with asthma before sacrosidase is administered. No other patients have been described with this adverse effect. These studies resulted in the submission of an NDA to the FDA and approval of Sucraid (sacrosidase) as treatment for CSID in 1998. Treatment was covered by Medicaid, after which private insurance coverage was approved. Recommendations for dosing on the label suggest using 1 mL with meals or snacks for patients <15 kg and 2 mL with meals or snacks for those >15 kg. Doses are to be split, with half the dose given at the onset of a meal and the other half midway through, when the intragastric environment is buffered to a higher pH and pepsin may be partially decoyed by other proteins.

A preliminary postmarketing surveillance study was conducted involving 229 patients with CSID who received prescriptions for Sucraid (sacrosidase) between 2004 and 2009. Results are summarized in a published abstract and in the proceedings of this symposium (22). Sixty-nine of 229 questionnaires were returned from 60 of 69 patients in 27 states in the United States and from 9 patients in 4 other countries. Included were 39 male patients and 66 of 69 patients younger than 18 years old. Sixty-five patients continued taking Sucraid; 2 had abandoned it because of lack of efficacy and 2 because of its cost. The median duration of therapy was 3 years and one-third had been treated continuously for >5 years. Nine of 65 (14%) patients were exceeding the maximum recommended dose per meal (2 mL) to try to control symptoms. Either a normal diet or a mild sucrose- and starch-restricted diet was consumed by 41 of 65 (65%) patients, but in 27%, strict sucrose restriction with either mild or strict starch restriction was necessary to maintain acceptable suppression of symptoms, even while taking Sucraid. Table 3 summarizes symptoms while patients are being treated with Sucraid. The majority (59/65, 92%) had <3 bowel movements per day, and 74% experienced either no diarrhea or diarrhea once per week, 12% had diarrhea 2 to 3 times per week, and 14% had diarrhea >3 times per week. In 74%, bloating occurred <3 times per week. Abdominal pain and nausea/vomiting were not seen in any patients >1 time per week and were completely absent in >90% of patients. The most common adverse events reported included constipation in 6 of 65, headaches in 5 of 65, and sleep disturbances in 8 of 65. None of these events resulted in discontinuing Sucraid.

CONCLUSIONS

Both clinical studies and molecular/genetic investigations suggest that CSID is a more common disease than previously believed and that genetically modified small intestinal SI digestion accounts for a broad spectrum of clinical phenotypes, including some potentially hidden in large cohorts of patients with IBS, chronic nonspecific diarrhea, and perhaps even dyspepsia (44).

The advent of noninvasive breath tests with excellent sensitivity and specificity and genetic tests of relatively common mutations in the CSID gene hold out the promise of more accurate population prevalence studies and diagnosis of less classic cases, even in adults who are believed to have lifelong functional bowel disorders. The recent approval of an enzyme replacement therapy has allowed liberalization of the previously mandatory sucrose restrictive diet and restored a more normal lifestyle, particularly to infants and young children exposed to a high carbohydrate diet (45). Further modifications of this therapy with the possible additions of enzymes geared to supplement higher maltase and glycoamylase activity may be in the offing to help patients cope with the continued problem of starch malabsorption. Research has demonstrated that additional amylase activity amplifies the effect of SI and MGAM on starch digestion and offers another potential addition to enzyme replacement therapy (18,46).

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Congenital Sucrase-Isomaltase Deficiency: Heterogeneity of Inheritance, Trafficking, and Function of an Intestinal Enzyme Complex

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Brush border membranes are the largest exposed surfaces in tissues. They constitute the interface between the “milieu extérieur” and the “milieu intérieur” of the body in a variety of organs such as the gastrointestinal tract and bile canaliculi, where hydrolytic, absorptive, and secretory processes take place. The intestinal mucosa is the exclusive site for nutrient metabolism and subsequent uptake of the generated products, such as monosaccharides and amino acids. The hydrolysis and absorption of micronutrients are achieved by the concerted action of hydrolases and transporters that are predominantly located in the brush border membranes (BBMs) (1).

The hydrolases are divided into 2 major families, the peptidases and the disaccharidases (2). The peptidases, such as aminopeptidases N (CD13), A, and W, carboxypeptidases P and M, dipeptidylpeptidase IV, or α -glutamyl transpeptidase, are expressed in many tissues, including the intestine and the kidney (3,4). The

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