


DIAZOXIDE RESPONSIVE CONGENITAL HYPERINSULINISM


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Congenital Hyperinsulinism refers to a variety of congenital disorders in which hypoglycemia is caused by an excess in insulin secretion.

These conditions are usually present at birth and most become apparent in early infancy.

They can present as transient or persistent; mild or severe. Management depends on each child's presentation.



The beta cells in the pancreas make too much insulin which lowers the blood glucose level. Normal glucose levels are between 70 – 120 mg/dL.

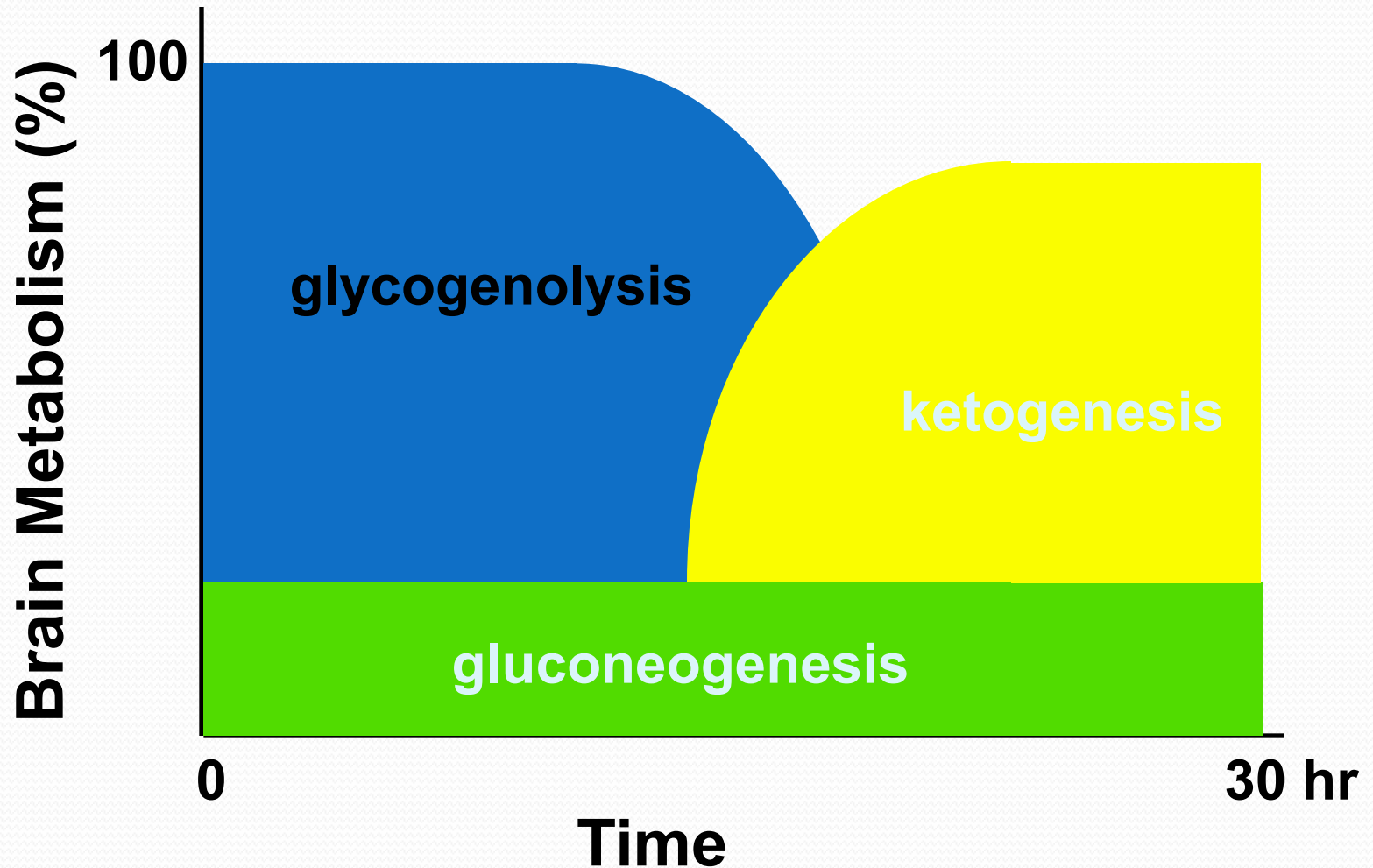
Signs and symptoms of hypoglycemia

- Pale skin, cold clammy skin or inappropriate sweating.
- Irritability or unusual behavior
- Difficult to arouse or lethargic
- Intense hunger
- Rapid heart rate
- Seizures

Normal Carbohydrate Metabolism

1. Glucose-principal fuel source for energy and cell function
2. Glycolysis- initial process in glucose catabolism
3. Glycogenolysis- process where glycogen is converted to glucose in the liver to be used for energy
4. Gluconeogenesis- transformation of amino acids, pyruvate and lactate into glucose or glycogen for fuel
5. Ketogenesis- breakdown of fat into ketones which are used as fuel for the brain

Fasting Systems in Children



Fasting Test Procedure

- Pt needs blood-drawing IV
- Document the following on the flowsheet:
 - Start time of last feeding/meal
 - Any changes in IV dextrose or meds
 - Final prefeed glucose
 - All the tubes should be obtained prior to the beginning of the study

Hypoglycemia Tests

- Diagnostic Fast
- Safety Fast
- Cure Fast
- Oral Protein Tolerance Test
- Glucagon Stimulation Test

Name: _____ I- diagnostic fast

DOB: 06-02-10

Children's Hospital of Philadelphia

Fasting Study Worksheet

Weight= kg Height cm Adm. Date

Fast started at 900 h on 11-20-10, ended at 1952 h on 11-20-10

Fasting Time= 0 hours off IVD

Glucagon Response= +40 pt rise

Urine ketones nd

Time	HR	Glucose mg/dl	Lab Glucose	Precision BOHB(m	Lactate mM	FFA mM	Ketones		Insulin uIU/ml	C-pep ng/ml	IGFB uM	Fr Ca uM	Tot C uM	Ac Carn	CO ng/r	GH mM	NH3 mM	Corti ug/dl	Urine Ketones	Comments
							AcAc mM	B-OH mM												
900	120	88																		fluids ↓ to .5 rate
1000	132	67		0																mom feeding
1100	100	83/78		0																1 hr post feed
1200	120	80		0.1																
1300	108	63/67		0																
1400	125	55/54	54	0																
1430		67/66	60	0																
1530	108	60/60	52	0.1																
1630		60/63	54	0.1																
1730	118	54/55	51	0.2																
1815		60/64	54	0.2																
1830		49/54		0.2																
2000		48/43	45		1	0.75		0.27	<2	0.332		35	36.4	1.4	27	7.4	14	4.2		Glucagon stim
2010		82																		x10
2025		88																		x20
2033		71																		x30
2040		76																		x40

Draw Extra Red Top Tube (4cc) with final Critical Blood Draw

Spin Separate and Freeze for CTRC x4-3338.

Centrifuge Settings: 10 mins on 2000 rpms at temp 4C

Transcribed by

Urine Organic Acids= normal

Acylcarnitine Profile= normal

Interpretation:

The Critical Sample

- Basic Metabolic Panel
 - BG 70-100 mg/dL
 - CO₂ -20-26 mmol/L
- Ammonia nl 35-65 ug/L
- Lactate (light green)-0.5-2.2
- FFA-0.15-0.71 mmol/L
- BOHB-0-0.6 mmol/L
- Insulin-nl <2 uU/mL
- C-peptide-nl 0-3 ng/mL
- IGFBP1-nl 30-1000 ng/mL
- GH-nl >8-10 ng/mL
- Cortisol – nl >18
- Urine Organic Acids
- Acylcarnitine profile
- Carnitine (free and total)

Diagnostic Fast

- Evaluate patients with history of hypoglycemia
- Rule out endocrine or metabolic cause of patient's hypoglycemia
 - Ketotic hypoglycemia
 - HI
 - FAO
 - CDG
- Fasting time varies with age (18-72 hours)
- Ending Criteria: BG <50, BOHB 2.5 x 2, Time, or severely symptomatic
- If BG <50, but BOHB 2.5 or higher, no glucagon

Safety Fast

- To ensure that patients can fast safely for extended period of time
 - (8-12 hours) infants
 - (18) HI-diazoxide responsive
- Performed prior to full endocrine evaluation OR when endocrine cause has been identified to establish safety on home regimen
- End for BG <70, BOHB 2.5x2, Time or s/s
- Labs: ACP, UOA

Cure Fast

- Evaluation of HI patients who have had surgery or who were considered transient HI
- Same fasting criteria as the diagnostic fast, but only obtain an HI draw
 - BG, BOHB, insulin, c-peptide, IGFBP₁
- End for BG<50, BOHB 2.5x2, Time, s/s

OPTT

- NPO 4 hours
- 3 hour test: q15 min for first hr, then q30 min
- For HI patients-diagnostic or routine
- Protein load (1.16 gm/kg of resource powder) given to determine if they have protein sensitive HI (both KATP mutations and HI/HA)
- End for BG <50 or severely symptomatic
- Labs: BG, insulin, ammonia (0 and 60 min)
- Check for allergies-milk protein

Glucagon Stimulation Testing

- After BS confirmed <50 and labs drawn, check blood glucose on Nova (Time 0)
- Give glucagon 1 mg IM/IV
- Check blood glucose every 10 minutes for 40 minutes and document on flowsheet
- If BS does not rise by 20 in 20 minutes, contact MD and stop testing
- Positive response is rise in BS by 30 mg/dL in 40 minutes



FASTING TOLERANCE

Your child will be fasted prior to discharge to determine safe fasting tolerance. The time given is a guide to help you determine when your child needs to eat and/or take medication(s).

This time is arbitrarily cut in half when sick and again is a guide to help you manage glucose levels.

Your child will be periodically admitted in the hospital for a safety fasting test to determine parameters for home management.

Normal Fasting Tolerance

- Newborn- 12-18 hours
- Infant- 24 hours
- Child- 36 hours
- Adult- 48-72 hours

HOME MANAGEMENT

Blood glucose monitoring: Check glucose levels as instructed (usually first AM; before feeds and when symptomatic). If obtaining levels less than 70 mg/dL—repeat and if still less than 70 mg/dL – feed your child with a recheck in glucose within 30 minutes. Repeat until glucose is above 70 mg/dL.

If your child can't consume enough food to increase glucose level (sick; vomiting; too weak or having a seizure) give glucagon injection. Recheck glucose level within 20 – 30 minutes and go to your local hospital (glucagon last about 1 hour)



ER MANAGEMENT

Prior to discharge, you will be given an ER letter to take with you to local hospitals.

If unable to maintain glucose levels greater than 70 mg/dL and you need to seek ER management, please take your letter with you for assistance.

SCHOOL MANAGEMENT

You can request a letter to be given to the school nurse outlining management guidelines for your child while in school and/or daycare



FEEDING GUIDELINES

Eat 3 meals and snacks a day--every day.

Your child's body will use insulin better if he/she eats the same amount of food at the same time every day.

Your child's body needs food for energy and growth.

Skipping meals is not healthy. A regular pattern of eating helps keep blood sugars stable.



Some examples of healthy foods containing complex carbohydrates:

Spinach Whole Barley Grapefruit Turnip Greens
Buckwheat Apples Lettuce Buckwheat bread Prunes
Water Cress Oat bran bread Apricots, Dried Zucchini
Oatmeal Pears Asparagus Oat bran cereal Plums
Artichokes Museli Strawberries Okra Wild rice Oranges
Cabbage Brown rice Yams Celery Multi-grain bread
Carrots Cucumbers Pinto beans Potatoes Dill Pickles
Yogurt, low fat Soybeans Radishes Skim milk Lentils
Broccoli Navy beans Garbanzo beans Brussels Sprouts
Cauliflower Kidney beans Eggplant Soy milk Lentils
Onions Whole meal spelt bread Split peas, nuts



Some examples of foods containing simple carbohydrates:

Table sugar, Corn syrup, Fruit juice, Candy, Cake, Bread made with white flour, Pasta made with white flour, Soda, Candy, All baked goods made with white flour and most packaged cereals



MEDICATIONS

DIAZOXIDE – blocks release of insulin in the beta cells of the pancreas.

DIURIL – helps to release the extra fluid retention caused by taking Diazoxide

OCTREOTIDE – decreases the amount of insulin released by the beta cells of the pancreas.

GLUCAGON – a hormone that releases glucose from the liver stores into the bloodstream.

DIAZOXIDE (proglycem)

Therapeutic Category: antihypoglycemic agent

- **Use:** Hypoglycemia related to islet cell adenoma, carcinoma, hyperplasia, adenomatosis, nesidioblastosis, leucine sensitivity or extrapancreatic malignancy.
- **Pregnancy Risk Factor:** C
- **Lactation:** Not recommended



Contraindications:

Hypersensitivity to thiazides or sulfonamide derivatives; aortic coarctation or aneurysm and arteriovenous shunts.



Dosage: 5 – 15 mg/kg/day in 2 divided doses

NOTE: Need 5 days to reach therapeutic level.

Monitoring parameters: Blood pressure, serum glucose, serum uric acid, CBC, diff/plts and comprehensive metabolic panel.

Dosage form: oral suspension 50 mg/mL

Side effects: edema (puffiness) and hypertrichosis (hairy)

Chlorothiazide (Diuril)

- **Therapeutic Category:** Diuretic agent
- **Use:** Management of mild to moderate hypertension, edema associated with congestive heart failure or nephrotic syndrome.
- **Pregnancy Risk Factor:** C
- **Lactation:** not recommended

Chlorothiazide (Diuril)

- **Contraindications:** Cross sensitivity to other thiazides or sulfonamides. Do not use in anuric patients.

Chlorothiazide (Diuril)

- **Dosage:** Use same guidelines as Diazoxide, otherwise, refer to CHOP formulary for range.
- **Monitoring Parameters:** weight, blood pressure, accurate I/O's, basic metabolic panel.
- **Dosage Form:** oral suspension 250 mg/5 mL
- **Side effects:** hypotension (low blood pressure); electrolyte changes (Na/K)

OCTREOTIDE (Sandostatin)

- **Therapeutic Category:** Antisecretory agent
- **Use:** Hyperinsulinism
- **Pregnancy Risk Factor:** B
- **Lactation:** use with caution

OCTREOTIDE (Sandostatin)

- **Dosage:** 5 – 15 mcg/kg/day given SubQ every 6 – 8 hours.
 - Usual management: Given twice daily (am and afternoon) to manage persistent post-op hypoglycemia.
 - Not usually given to neonates due to risk of NEC.
- **Monitoring Parameters:** Comprehensive Metabolic Panel, IGF-1, IGFBP-3, TSH/T₄, abdominal ultrasound.
- **Dosage Form:** 200 mcg/mL
- **Side effects:** tachyphylaxis, abdominal cramps, nausea, diarrhea, gallstones and growth suppression.



GLUCAGON

Therapeutic Category: Antihypoglycemic agent

Use: management of hypoglycemia

Pregnancy Risk Factor: B

Lactation: unknown



GLUCAGON

Dose: 1 mg injectible

Monitoring parameters: glucose and BP

Dosage form: emergency kit

Side effects: hypotension

FOLLOW-UP GUIDELINES

PCP – 1 – 2 weeks after every hospital evaluation and as needed along with usual well child protocol.

Endocrinologist – 2 – 4 weeks after every hospital evaluation and then every 3 – 6 months. Call office with updates as needed.

Inpatient Evaluation – scheduled on each child's individual as needed basis.

Neurodevelopmental Evaluation (Age 12 – 18 months and 5 years of age) – Early Intervention (OT/PT/Speech)

Patient Origins

