49 yo Woman with Hypoglycemia

Sikarin Upala, MD, MS

February 22, 2018

Dr. Upala does not have any relevant financial relationships with any commercial interests

Learning Objectives

- Understand the importance of the critical sample
- Review hypoglycemia in non-DM
- Review cases series of hypoglycemia

HPI

- 49 yo non-diabetic female
- Had episodes of chest pain, fatigue, palpitation, diaphoresis, tingling sensation (happened 10 hours after her last meal with chicken salad and cocktail)
- Loss of consciousness at home
- EMS with BG 36-> given D50x1 amp
- Mental status improved with dextrose
- No history of previous episodes, LOC or seizure
- No history of diabetes, but mother has T2 diabetes (on insulin)
- No autoimmune disease in family

HPI

- At ED, she started to be confused, sweating and agitated. BG was 35 and started on D10W drip, repeat BG was 76
- Reports drinking alcohol occasionally but denies illicit drugs
- Denies any diarrhea, poor appetite, nausea, vomiting, diarrhea, polyuria, polydipsia, exogenous steroids, insulin or DM medication use
- Admitted to ICU

Other History

- Past Medical History
  - Inflammatory polyarthropathy
  - Arthritis
  - Habitual alcohol use
  - HPV
  - Essential hypertension
- Past Surgical history
  - Cesarean section
- Family History
  - T2DM : mother
- Allergy
  - No Known Allergies
- Social History
  - Smoking 1ppd for 40 years
  - Alcohol 3 beers a day
  - Denies illicit drugs
  - Works as a social worker
- Medication
  - Humira subq every 14 days
  - Hydrocodone-acetaminophen (NORCO) 5-325 mg PO tab

Review of Systems

- Constitutional: **+Fatigue .** No fevers, night sweats, appetite change, unexpected weight change
- HEENT: No photophobia, blurred vision, pain, hearing loss, difficulty swallowing, thirst, hoarseness
- Resp: No cough, dyspnea, increased WOB
- CV: **+ CP, diaphoretic, palpitation,** No DOE, orthopnea, PND, palpitations, LE edema
- GI: No abdominal pain, nausea, vomiting, diarrhea, constipation
- GU: No dysuria, urgency, polyuria, hematuria
- MSK: **+ Myalgias, joint pain, back pain**
- Neuro: +Syncope, No numbness, paresthesias, headaches, tremors, memory problems, seizures
- Heme: No adenopathy or easy bruising/bleeding
- Endo: **+ Hypoglycemia**. No heat or cold intolerance, dry skin, dry hair, hair loss
- Derm: No rashes, ulcers, abdominal striae, hirsutism, acne
- Psych: No mood changes, sleep disturbance, anxiety, depression

Physical Exam

(when I saw her, with normal BG)

- Vitals: BP 144/95 | Pulse 76 | Temp 36.8 °C (98.2 °F) | Resp 15 | Ht 157.5 cm (5' 2") | Wt 59 kg (130 lb) | SpO2 100% | BMI 23.78 kg/m2

- General: No apparent distress. Appears stated age
- HEENT: No pharyngeal erythema. PERRL, EOMI
- Neck: No neck tenderness. No thyromegaly or thyroid nodules appreciated
- Cardiovascular: regular rate and rhythm. No peripheral edema
- Pulmonary/Chest: clear to auscultation bilaterally
- Gastrointestinal: soft, non-tender, non-distended. No rebound or guarding
- Musculoskeletal: normal range of motion of joints
- Neurological: Alert & oriented, no focal deficits
- Lymph: No cervical, supraclavicular, lymphadenopathy
- Skin: No apparent bald spots. No acanthosis nigricans. **No illicit drug mark**
- Psychiatric: normal mood, thought content, appropriate

Lab

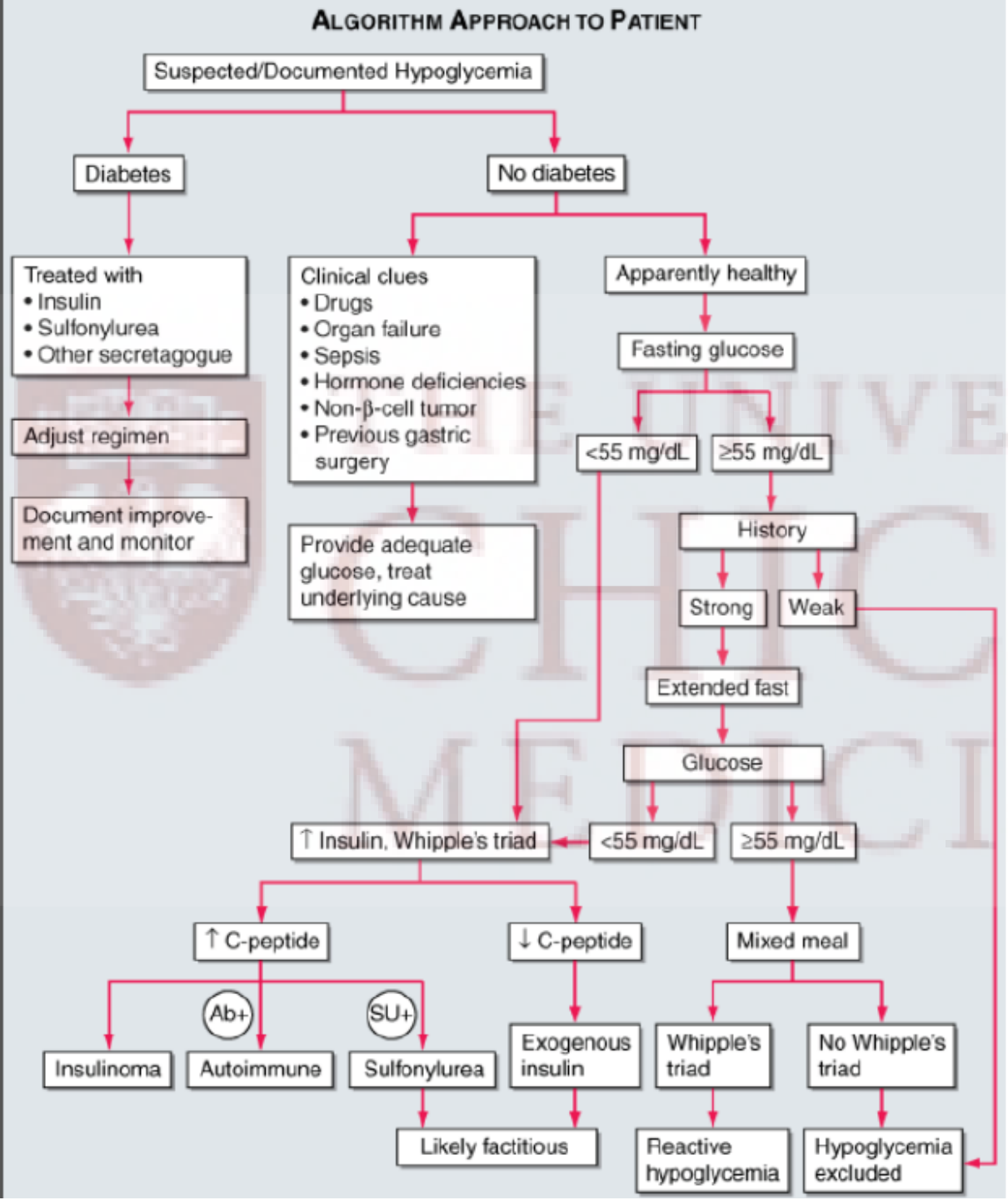
- BG 35, Insulin 7.3 (2.6-24.9), Proinsulin 78 (3-20), C-peptide 0.63 (0.3-2.35), Cortisol 17.5
- A1c 4.9, Lactate 1.6, Beta OH butyrate 5.8 (<0.3)
- Positive alcohol and cocaine
- Na 139, K 3.8, Cl 102, HCO3 10, BUN 6, Cr 0.6
- Ca 9, Alb 4.3
- CBC: Hct 36.4/WBC 6.7/Platelet 251
- AST 53,ALT 14, Alkphos 90, TB 0.3
- Negative tylenol, salicylate

Differential Diagnosis of Hypoglycemia

- Well appearance
  - Endogenous hyperinsulinism
    - Insulinoma
    - Functional B-cell disorder (nesidioblastosis, post RYBG)
    - Insulin antibody-mediated
    - Insulin secretagogue
  - Accidental/surreptitious
- Ill or medicated
  - Drugs-insulin, insulin secretagogues, ETOH
  - Critical illness-hepatic/renal/cardiac failure, sepsis
  - Hormone deficiency-cortisol, glucagon
  - Non islet cell tumor

Critical Sample

- Distinguish hypoglycemia caused by endogenous (or exogenous) insulin use from other mechanisms
- Plasma glucose, insulin c-peptide, proinsulin, B-hydroxybutyrate, cortisol, insulin antibodies, sulfonylurea screen



Critical diagnostic findings when glucose < 55 mg/dL

- Insulin 3 U/mL (18 pmol/L)
- Cpepdide 0.6 ng/mL
- Proinsulin 5 pmol/L

Harrison's Internal Medicine

Critical sample

- BG 35
- Insulin 7.3 (2.6-24.9)
- Proinsulin 78 (3-20)
- C-peptide 0.63 (0.3-2.35)
- Cortisol 17.5
- A1c 4.9
- Lactate 1.6
- Beta OH butyrate 5.8 (<0.3)
- Sulfonylurea screen: + Glyburide

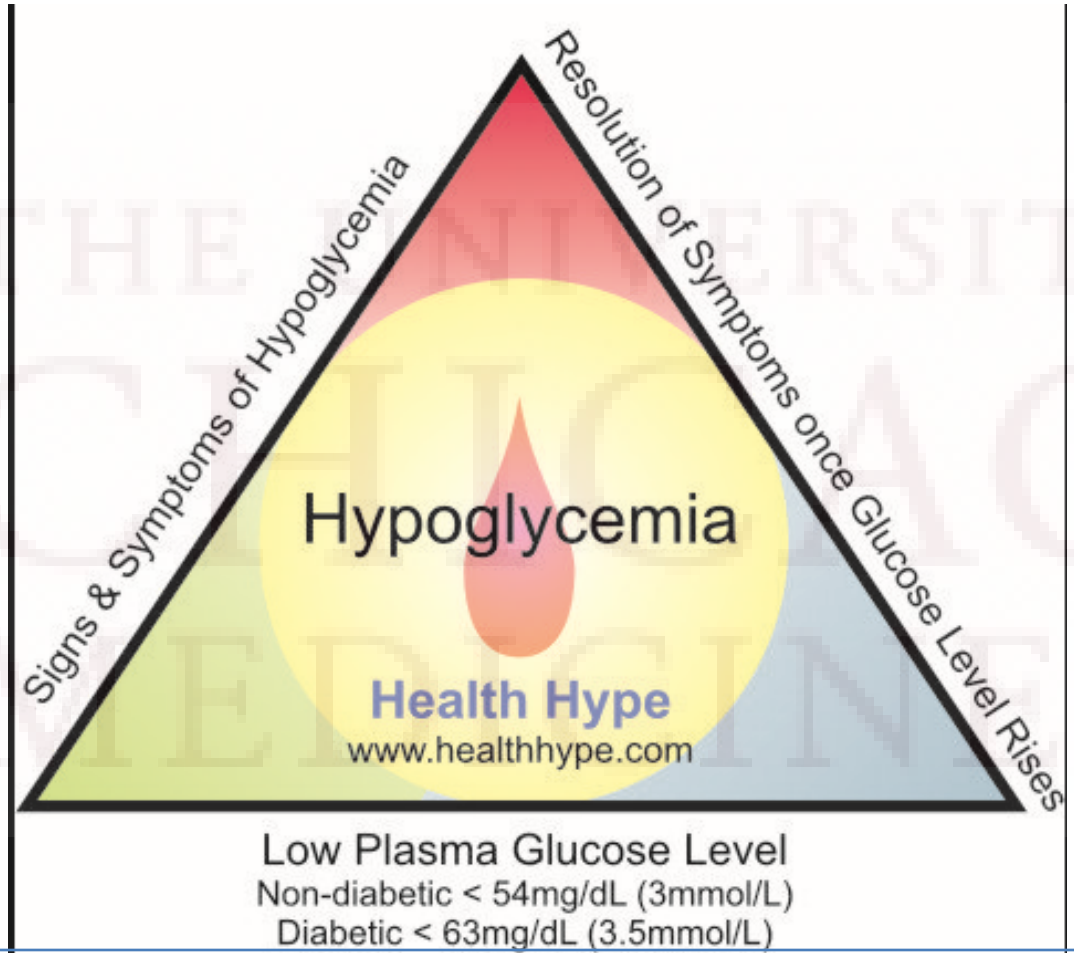
Hypoglycemia: Interpretation of laboratory tests

Symptoms, signs, or both	Glucose (mg/dL)/ (mmol/L)	Insulin (microU/mL)/ (pmol/L)	C-peptide (nmol/L)/ (ng/mL)	Proinsulin (pmol/L)	Beta-hydroxybutyrate (mmol/L)	Glucose increase after glucagon (mg/dL)/ (mmol/L)	Circulating oral hypoglycemic agent	Antibody to insulin	Diagnostic interpretation
No	<55/3	<3/20.8	<0.2/0.6	<5	>2.7	<25/1.4	No	No	Normal
Yes	<55	>>3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
Yes	<55	>>3	>>0.2¶	>>5¶	≤2.7	>25	No	Pos	Insulin autoimmune
Yes	<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGFΔ
Yes	<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin (or IGF) -mediated

Neg: negative; Pos: positive; NIPHS: noninsulinoma pancreatogenous hypoglycemia syndrome; PGBH: post-gastric bypass hypoglycemia; IGF: insulin-like growth factor.
* Patterns of findings during fasting or after a mixed meal in normal individuals with no symptoms or signs despite relatively low plasma glucose concentrations (ie, Whipple's triad not documented) and in individuals with hyperinsulinemic (or IGF-mediated) hypoglycemia or hypoglycemia caused by other mechanisms.
¶ Free C-peptide and proinsulin concentrations are low.
Δ Increased pro-IGF-2, free IGF-2, IGF-2/IGF-1 ratio.

Cryer PE. J Clin Endocrinol Metab 2009

Whipple's triad



Sulfonylurea

- The first reported case of factitious hypoglycemia : chlorpropamide by a non-dm patient
- Hypoglycemia in an older person : mix-up in medication
- All these agents peak up to 8 h and may last >24 h and hypoglycemia is seen many hours after the dose.

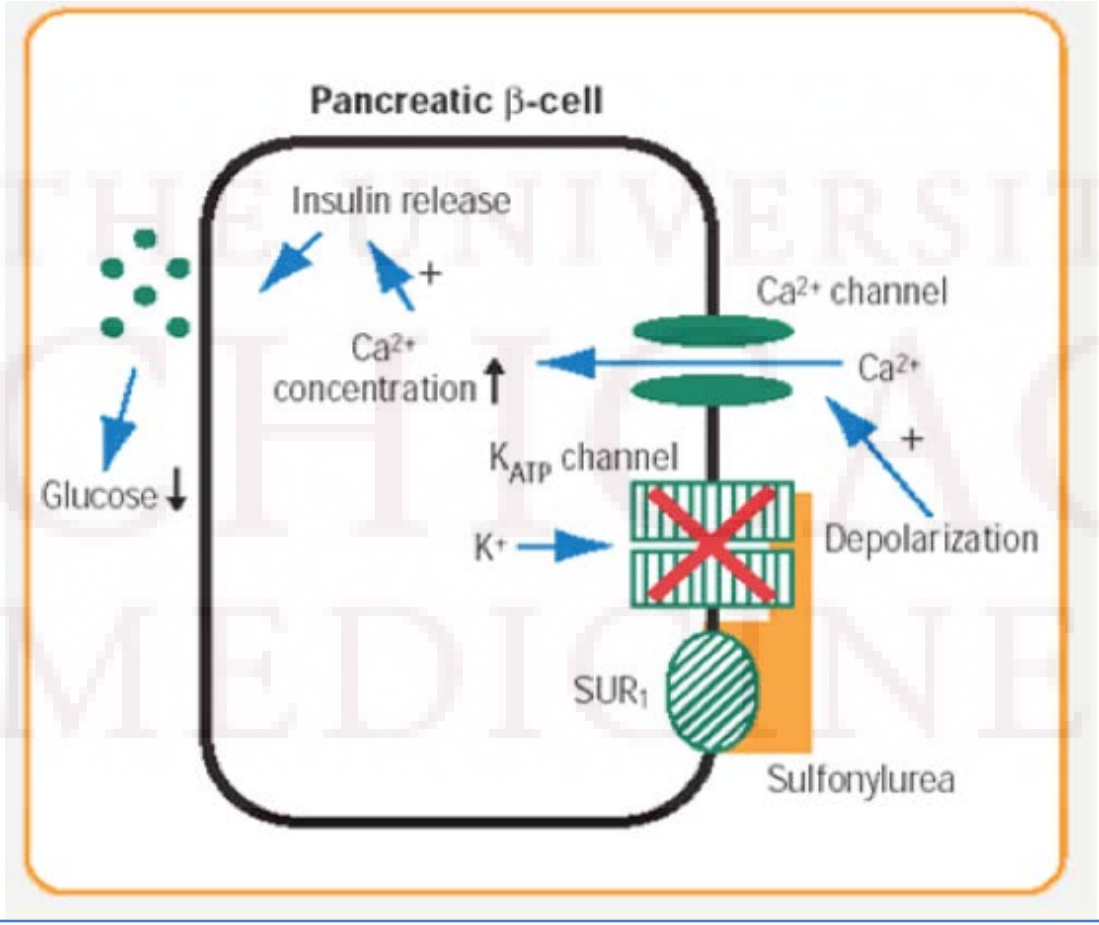
Table 5.1 Characteristics of sulfonylureas and meglitinides

Generic name	Total daily dose range (mg)	Frequency of administration	Half-life (h)	Duration of action (h)	Metabolism
First generation					
Tolbutamide	500–2000	3 times daily	4.5–6.5	6–12	Mainly hepatic, <20% excreted unchanged in urine
Chlorpropamide	125–500	Once daily	36	60	Mainly renal, ~20% hepatic
Tolazamide	100–1000	Twice daily	7	12–24	Renal, hepatic
Second generation					
Glibenclamide (glyburide)	1.25–20*	2 or 3 times daily	Biphasic (4 and 10 h)	12–24	Hepatic (=100%); metabolites excreted in bile (50%) and urine (50%)
Glipizide	2.5–40	Twice daily	2–4	12–24	Hepatic; <10% excreted unchanged in urine
Glipizide extended release	2.5–20	Once daily	>12	24	Hepatic; <10% excreted unchanged in urine
Gliclazide	40–320	Twice daily	10–12	12–16	Hepatic; <5% excreted unchanged in urine
Gliclazide modified release (MR)	30–120	Once daily	12–20	24	Hepatic; <5% excreted unchanged in urine
Third generation					
Glimepiride	1–8 *	Once daily	5–8	16–24	Hepatic; inactive metabolites excreted in urine (60%) and feces (40%)
Meglitinides					
Repaglinide	0.5–16	3–4 times daily	1	2–6	Hepatic
Nateglinide	60–540	3 times daily	0.5–1.9	2–6	Hepatic; excreted in urine

*In Europe the maximum recommended daily dose of glibenclamide (glyburide) is 15 mg and of glimepiride 6 mg.

Guettier JM. Endocrinol Metab Clin North Am. 2006

Mechanism of action



Sulfonylurea

- Herbal products contaminated with sulfonylureas
- According to WHO estimates up to 1% of drugs in the industrialized world are counterfeit. Globally it is an even bigger problem - up to 10% of drugs worldwide are thought to be counterfeit

Kao SL. N Engl J Med. 2009

Power 1 Walnut

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Mon, Mar 15, 2010
The Straits Times

Print-friendly Email a friend

Warning: Those street sex drugs can kill

By Carolyn Quek

BEWARE the dodgy sex drugs that can be bought in the back lanes of red-light areas here.

- 150 nondiabetic patients
- 10 died (men aged 35 to 84)

Kao SL. N Engl J Med. 2009

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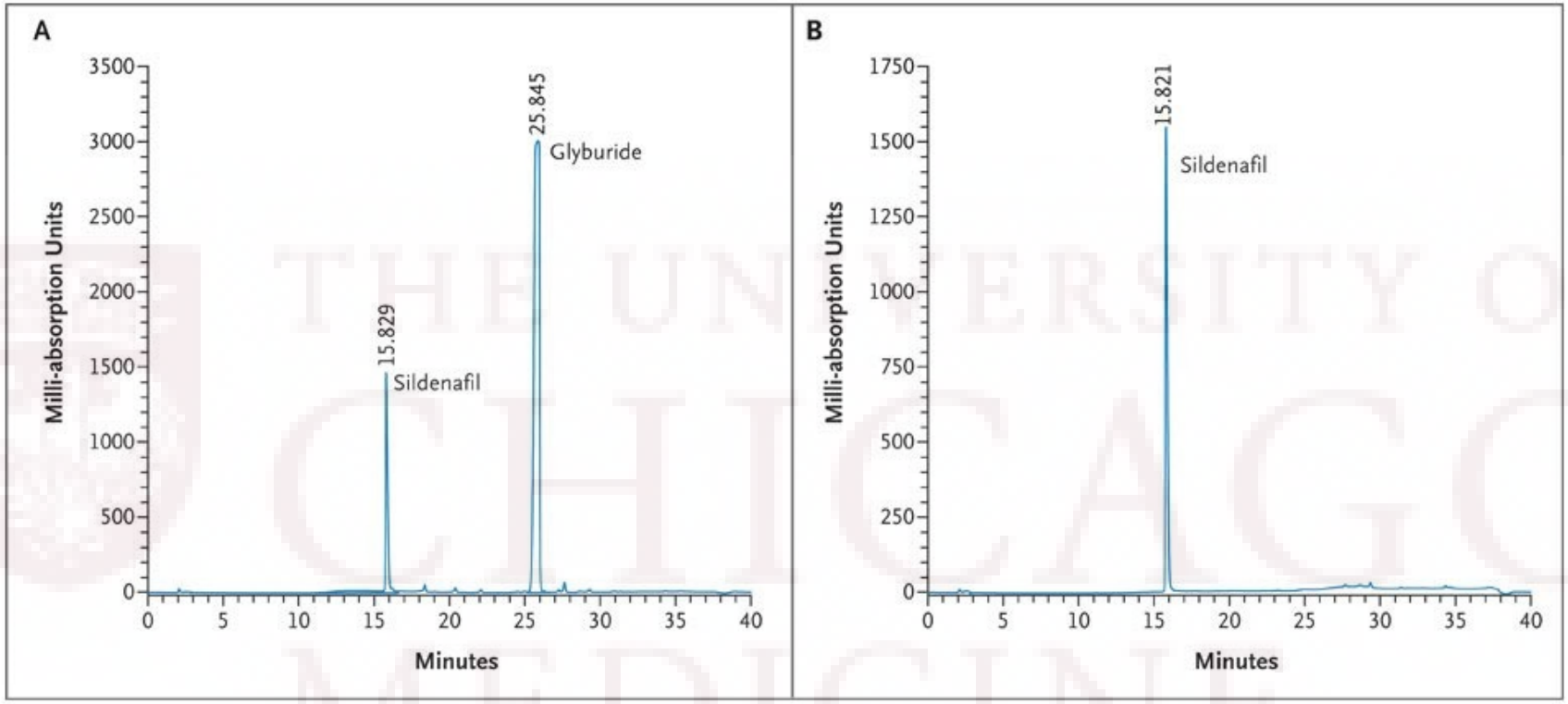

- Contamination of Sexual-Enhancement Drugs. High-performance liquid chromatograms of samples of a drug manufactured in January 2008 (Panel A) and before January 2008 (Panel B)
- contaminated with glyburide from 13 to 100 mg per tablet

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Kao SL. N Engl J Med. 2009

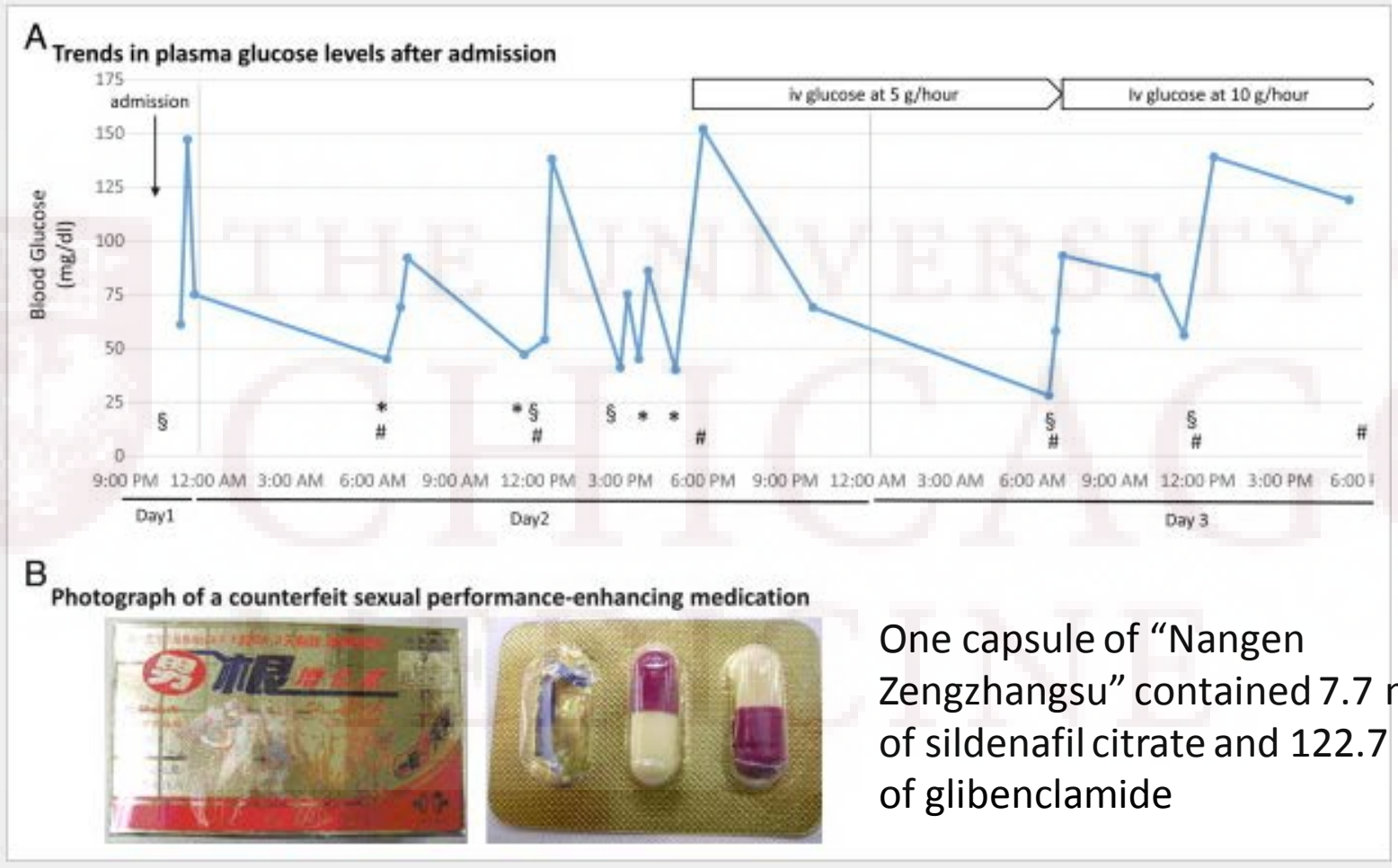
Santi Bovine Penis Erecting Capsule

Zhong Hua Niu Nian

Real Man pills

Africa Black Ant

Nangen Zengzhangsu



One capsule of "Nangen Zengzhangsu" contained 7.7 mg of sildenafil citrate and 122.7 mg of glibenclamide

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Kuramoto N. Diabetes Res Clin Pract. 2015

TABLE 1. Clinical summary of 68 patients

Clinical summary	No. of patients
No. of admissions	
1	60
2	7
3	1
Clinical presentation*	
Coma	39
Convulsion	2
Confusion	18
Right orbit fracture	1
Cerebral oedema	2
Pneumonia	1
Lightheadedness	7
Sweating	6
Drowsiness	11
Others†	5
Outcome	
Fully recovered	63
Vegetative state	1
Cognitive impairment	1
Died	3
Erectile dysfunction product taken	
Nangen Zengzhangsu "男根增長素"‡	12
Jiu Bian Wang "九鞭王"‡	5
Lu Quan "鹿泉"‡	2
San Bian Wan "三鞭丸"‡	1
One yellow capsule known as "fake Viagra"	1
Unnamed red-yellow capsule‡	9
Unnamed brick red rhomboid tablet‡	8
Unnamed blue rhomboid tablet‡§	1
Unnamed red-black capsule	1
Herbal aphrodisiac wine	1
Could not be clarified due to in coma	2
Denied	25

* Data based on the presentation for each admission. Some patients presented more than once, not necessarily with the same symptom

† Others include decerebrate posture, status epilepticus, transient left-sided weakness, slurred speech, and head injury

‡ Erectile dysfunction product available for analysis

§ Taking any erectile dysfunction product at the second admission was denied by a patient

TABLE 2. Non-prescription erectile dysfunction products collected from 14 patients

Product name	Appearance	Patient serial No.	Source	Drug amount (mg)	
				Sildenafil	Glibenclamide
Nangen Zengzhangsu "男根增長素"	Red-yellow capsule	34	China pharmacy	8.6	145
		34	China pharmacy	8.7	136
San Bian Wan "三鞭丸"	Brick red rhomboid tablet	32	China pharmacy	127	0
		32	China pharmacy	118	0
Unnamed product without packaging	Red-yellow capsule	16	Not disclosed	8.2	143
		12	Local pharmacy	7.7	133
		24	Friend	9.1	158
		24	Friend	7.9	138
		42	Friend	8.2	121
Jiu Bian Wang "九鞭王"	Brick red rhomboid tablet	33	Friend	144	0
		33	Friend	66	67
		36	Friend	64	64
		38	Peddler	63	62
Unnamed product without packaging	Brick red rhomboid tablet	47	China pharmacy	78	78
		47	China pharmacy	88	80
		47	China pharmacy	142	0
		47	China pharmacy	160	0
Unnamed product with packaging	Blue rhomboid tablet				
Lu Quan "鹿泉"	Red-yellow capsule				

144 patients, 3 died,
1 vegetative state,
1 cognitive impairment

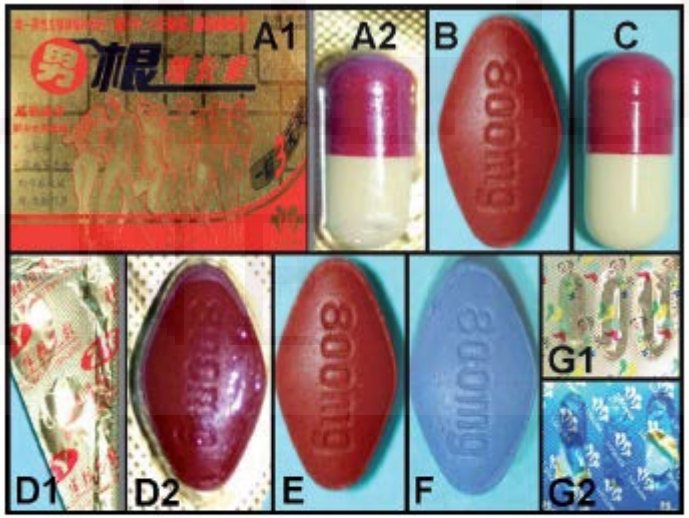

FIG. Seven non-prescription erectile dysfunction products retained by the patients
A1 and A2: the package and a red-yellow capsule of Nangen Zengzhangsu "男根增長素"; B: a brick red rhomboid tablet of San Bian Wan "三鞭丸"; C: a red-yellow capsule of an unnamed product without packaging; D1 and D2: the package and a brick red rhomboid tablet of Jiu Bian Wang "九鞭王"; E: a brick red rhomboid tablet of an unnamed product without packaging; F: a blue rhomboid tablet of an unnamed product with packaging that was the same as D1; G1: the package of Lu Quan "鹿泉" with red-yellow capsules but otherwise like C; G2: another package of Lu Quan "鹿泉" with red-yellow capsules akin to C

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Hong Kong Med J. 2009

Cialis

Glucose, insulin and C-peptide levels during admission

	Day 1	Day 2	Day 9
Glucose (RR, 3.0–6.0), mmol/L	2.4	2.8	4.7
Insulin (RR, 2–23), mU/L	17	11	0.3
C-peptide (RR, 0.3–1.4), nmol/L	2.6	Not done	0.7

RR = reference range.

One tablet of counterfeit Cialis contained 152.8 mg of glibenclamide and 0.5 mg of sildenafil

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Chaubey et al, Medical Journal of Australia, 2010

Clinical Question

- No sulfonylurea drugs were detected when the patient's blood was tested. What should we do?

An Unusual Cause of Hyperinsulinemic Hypoglycemia Syndrome

- 47-year-old woman was admitted comatose in the overnight fasted state
- No significant past medical history, no medication
- She was a trained physiotherapist and married to a local consultant psychiatrist in New Zealand
- Denied any access to hypoglycemic medication

Manning et al, Diabet Med, 2003, Marks and Richmond, J RSoc Med, 2008

An Unusual Cause of Hyperinsulinemic Hypoglycemia Syndrome

Table 1 Chronology of events

Day	Event	Comment
1		
5	First admission—hypoglycemic coma	Plasma venous glucose 1.9 mmol/l Plasma insulin 105 pmol/l[b] Plasma C-peptide 1060 pmol/l[b] Plasma sulphonylurea screen negative
10	Discharged to care of spouse	
12		
14	Second admission—hypoglycaemic coma	
16	Calcium stimulation test (see Fig. 1)	Insulinoma suspected

Plasma insulin > 36 pmol/l and C-Peptide > 200 pmol/l in the presence of hypoglycaemia (plasma glucose < 2.5 mmol/l) is indicative of endogenous hyperinsulinemia

- 1st admission 5 days: intravenous 10% dextrose
  - Sulfonylurea screen was reported as negative and drug-induced hypoglycemia was felt to have been excluded
- 2nd admission 29 days: prolonged intravenous dextrose, normal growth hormone and cortisol
  - Normal CT scan of the pancreas
  - An insulinoma was suspected as the most likely diagnosis and, as hypoglycemia had been documented on two separate occasions, a formal fast was deemed unnecessary
  - Endocrine consult

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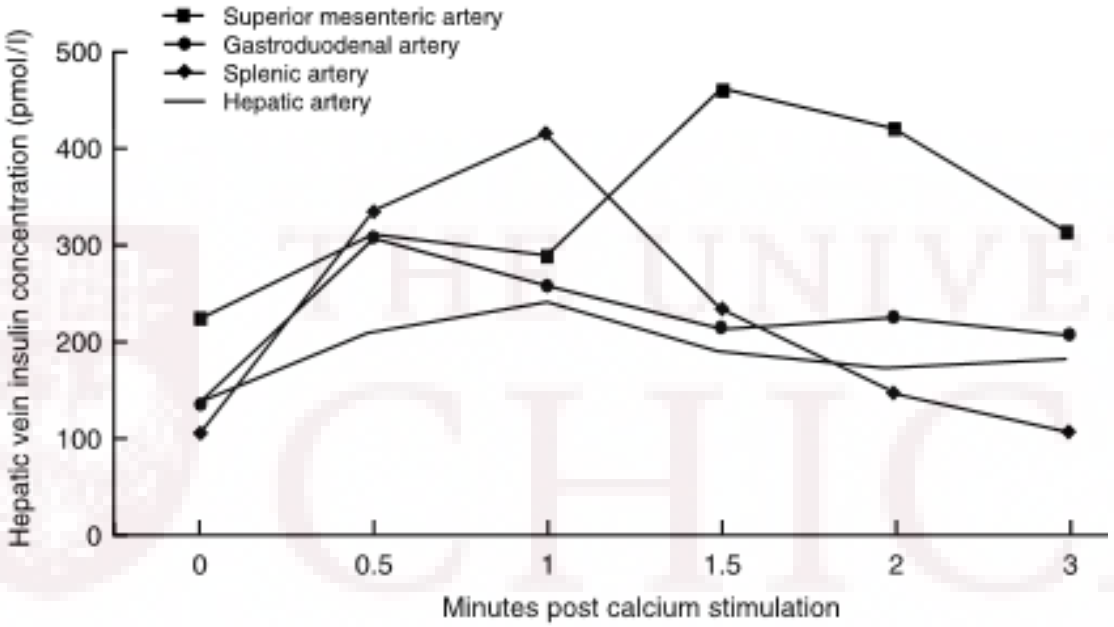
Manning et al, Diabet Med, 2003, Marks and Richmond, J RSoc Med, 2008

An Unusual Cause of Hyperinsulinemic Hypoglycemia Syndrome



- Selective arterial calcium stimulation test
- Positive result (a doubling of hepatic venous insulin concentration in response to calcium) was detected in all arterial territories

- Generalized pattern of response with calcium stimulation, plan for distal pancreatectomy if no insulinoma was identified
- Intra-operative ultrasound, no insulinoma was detected, and a two-thirds distal pancreatectomy was performed

Manning et al, Diabet Med, 2003, Marks and Richmond, J RSoc Med, 2008

An Unusual Cause of Hyperinsulinemic Hypoglycemia Syndrome

16	Calcium stimulation test (see Fig. 1	Insulinoma suspected
28	Subtotal pancreatectomy	Normal histology (no insulinoma)
35		
36	Capillary BSL 2.1 mmol/l	
37	36-h supervised fast	Euglycaemic throughout
39	Discharged to care of spouse	
43		
45		
46		
48		
49		
50		Plasma venous glucose 1.9 mmol/l Glibenclamide and Glipizide present in same sample
51	Patient found dead 06.15 h	Autopsy toxicology positive for Glibenclamide, Glipizide and Metformin

Plasma insulin > 36 pmol/l and C-Peptide > 200 pmol/l in the presence of hypoglycaemia (plasma glucose < 2.5 mmol/l) is indicative of endogenous hyperinsulinemia

- POD #9 had hypoglycemia. Despite patient reluctance, a formal supervised fast was commenced but was discontinued at 36 h because of co-morbidity associated with recent abdominal surgery
- Euglycemia until discharge on POD#12
- Multiple hypoglycemia at home, patient passed away 12 days after discharge

Manning et al, Diabet Med, 2003, Marks and Richmond, J RSoc Med, 2008

An Unusual Cause of Hyperinsulinemic Hypoglycemia Syndrome

Table 1 Chronology of events

Day	Event	False prescriptions[a]
1		Glibenclamide 225 mg
5	First admission—hypoglycemic coma	
10	Discharged to care of spouse	
12		Glibenclamide 450 mg
14	Second admission—hypoglycaemic coma	
16	Calcium stimulation test (see Fig. 1)	
28	Subtotal pancreatectomy	
35		Glibenclamide 600 mg
36	Capillary BSL 2.1 mmol/l	
37	36-h supervised fast	
39	Discharged to care of spouse	
43		Glibenclamide 400 mg
45		Glibenclamide 600 mg
46		Glibenclamide 600 mg
48		Glibenclamide 600 mg Metformin 102 g
49		Glipizide 600 mg
50		Glibenclamide 100 mg Humalog 1000 units
51	Patient found dead 06.15 h	

[a]Only hypoglycaemic drugs are listed. Numerous other false scripts were written (commencing day −48) for a variety of sedatives, e.g. clonazepam, throughout the illness.

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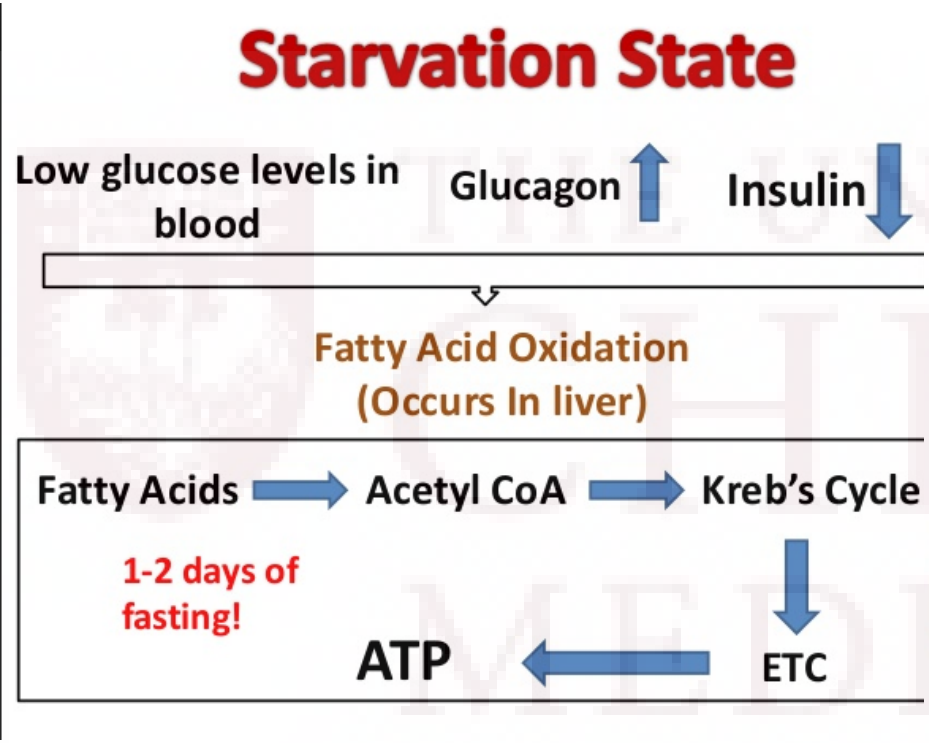
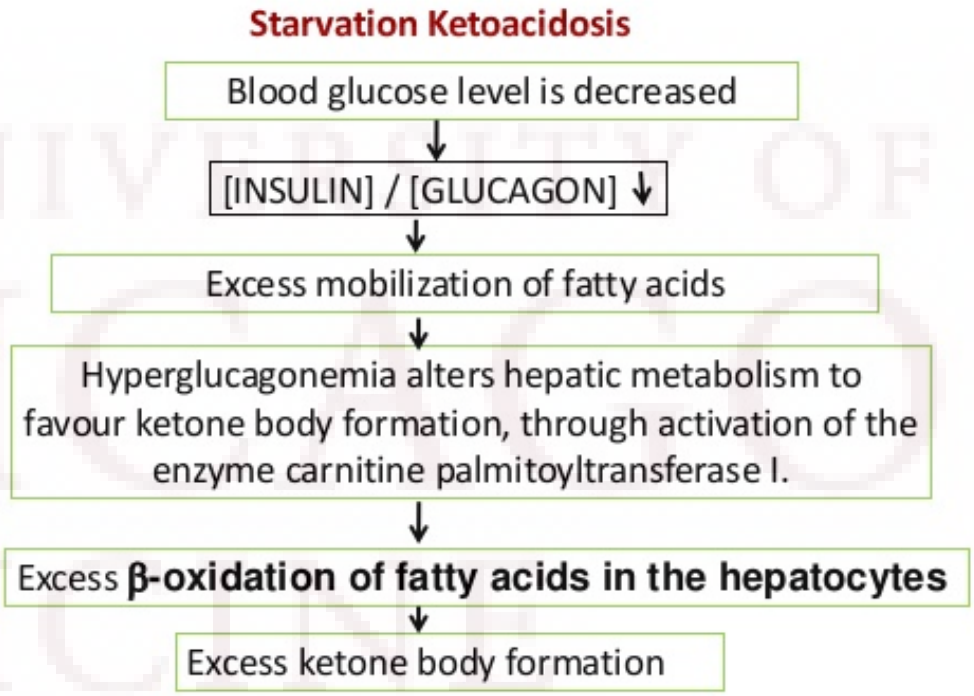
Manning et al, Diabet Med, 2003, Marks and Richmond, J RSoc Med, 2008

Clinical Question

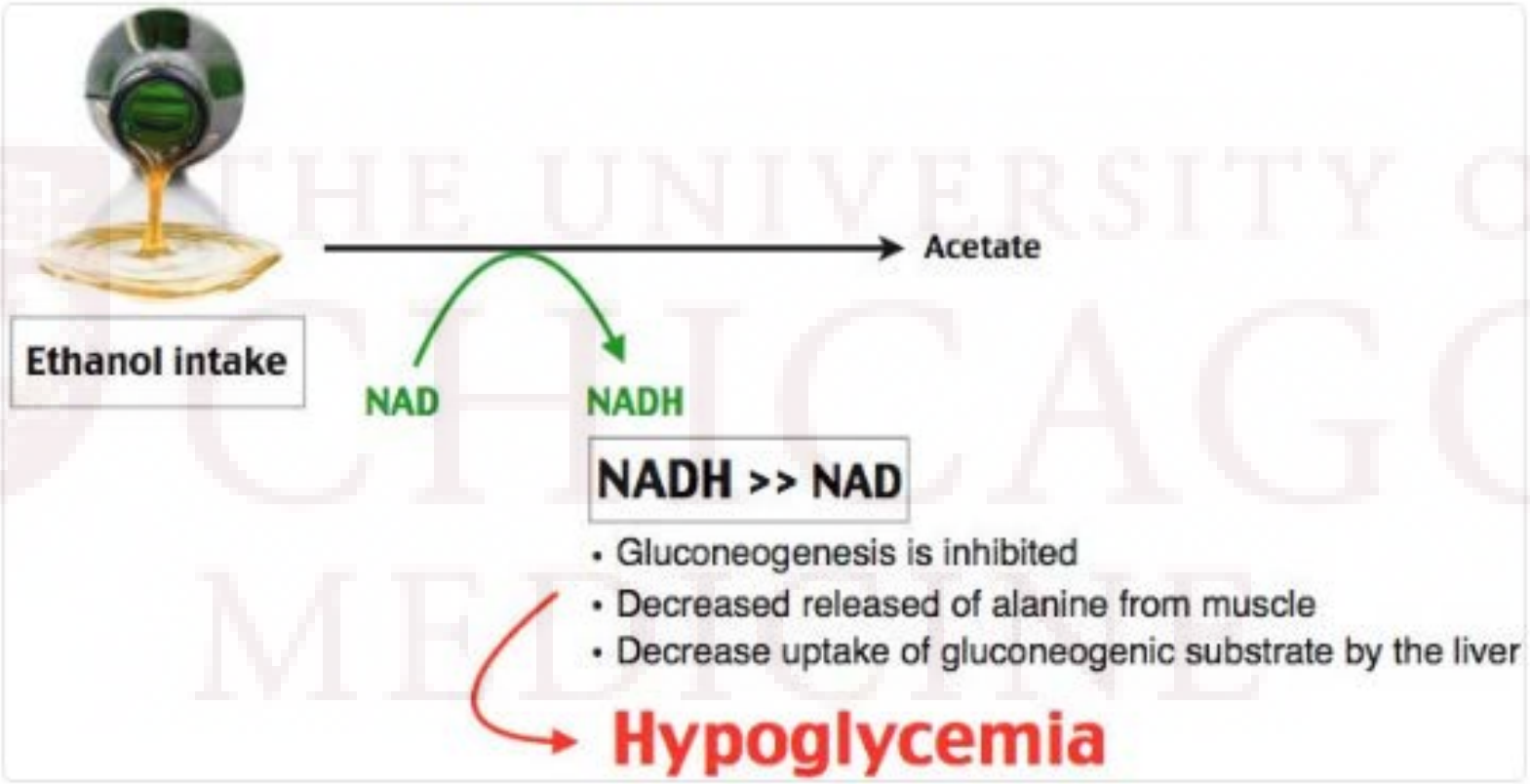
- Sulfonylurea may have been undetectable for the following reasons:
  - Not sensitive
  - Hypoglycemic effects of sulfonylureas may persist after the elimination of the drug
  - Blood sample may have been sent after the initial presentation

Starvation Ketosis





Alcohol Induced Hypoglycemia



Drug induced Hypoglycemia

Moderate quality of evidence
Cibenzoline
Gatifloxacin
Pentamidine
Quinine
Indomethacin
Glucagon (during endoscopy)
Low quality of evidence
Chloroquineoxaline sulfonamide
Artesunate/artemisin/artemether
IGF-1
Lithium
Propoxyphene/dextropropoxyphene
Very low quality of evidence
Drugs with >25 cases of hypoglycemia identified
Angiotensin-converting enzyme inhibitors
Angiotensin receptor antagonists
Beta-adrenergic receptor antagonists
Levofloxacin
Mifepristone
Disopyramide
Trimethoprim-sulfamethoxazole
Heparin
6-mercaptopurine

IGF-1: insulin-like growth factor 1.

Marks V. Endocrinol Metab Clin North Am. 1999;28(3):555.

Assessment and Plan

- Improved after dextrose solution, no octreotide or glucagon
- Diagnosis: hypoglycemia induced by glyburide, worsening with alcohol intake with possible starvation ketosis

Take Home Messages

- Patients with insulinoma and insulin secretagogue-induced hypoglycemia can have plasma insulin, C-peptide, and proinsulin values above or within the normal overnight fasting range with low plasma glucose
- Many techniques for detection of first-generation sulfonylureas do not detect second-generation sulfonylureas or meglitinides

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February 22, 2018

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