Hypoglycemia, diabetic medications

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No financial disclosures with regards this presentation

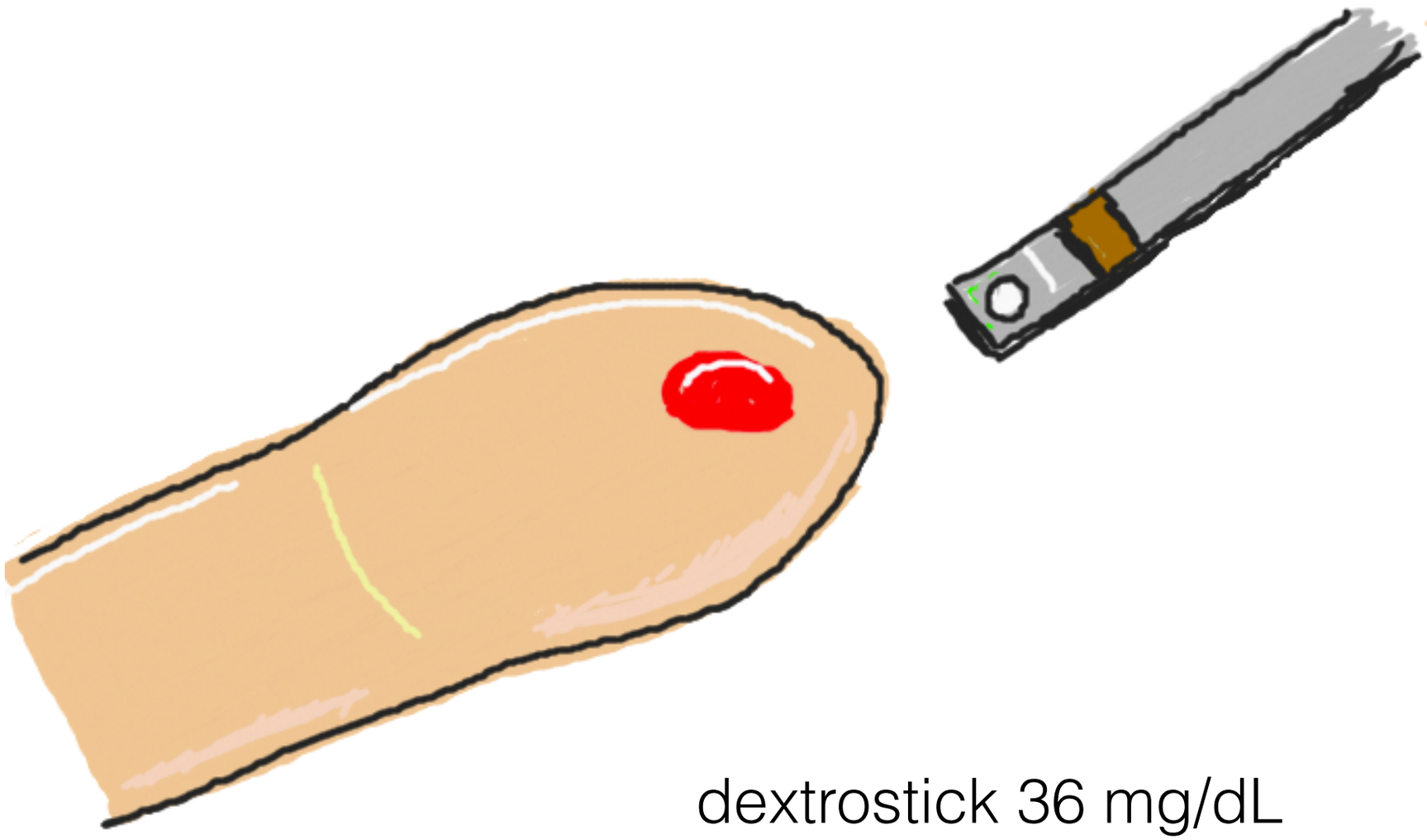
- Unidentified male in 20s. Driver and only passenger car, struck tree, extensive front end damage, starred windshield.

- Unresponsive, vitals unremarkable (as best I recall!). Large hematoma forehead, no other apparent injury.

- Time of day: mid-afternoon, sunny with dry roads, summer

- 78 yo male brought to ED by EMS with right sided hemiparesis and garbled speech. Family discovered at 18:30, last seen prior 90 minutes earlier. PH: HTN and DM, meds: losartan and glyburide. No ethanol.

- Exam: Awake but apathetic. BP, RR and pulse all normal, T 35.8^{o} C rectally. Neuro exam shows right hemiparesis UE > LE, unintelligible speech.



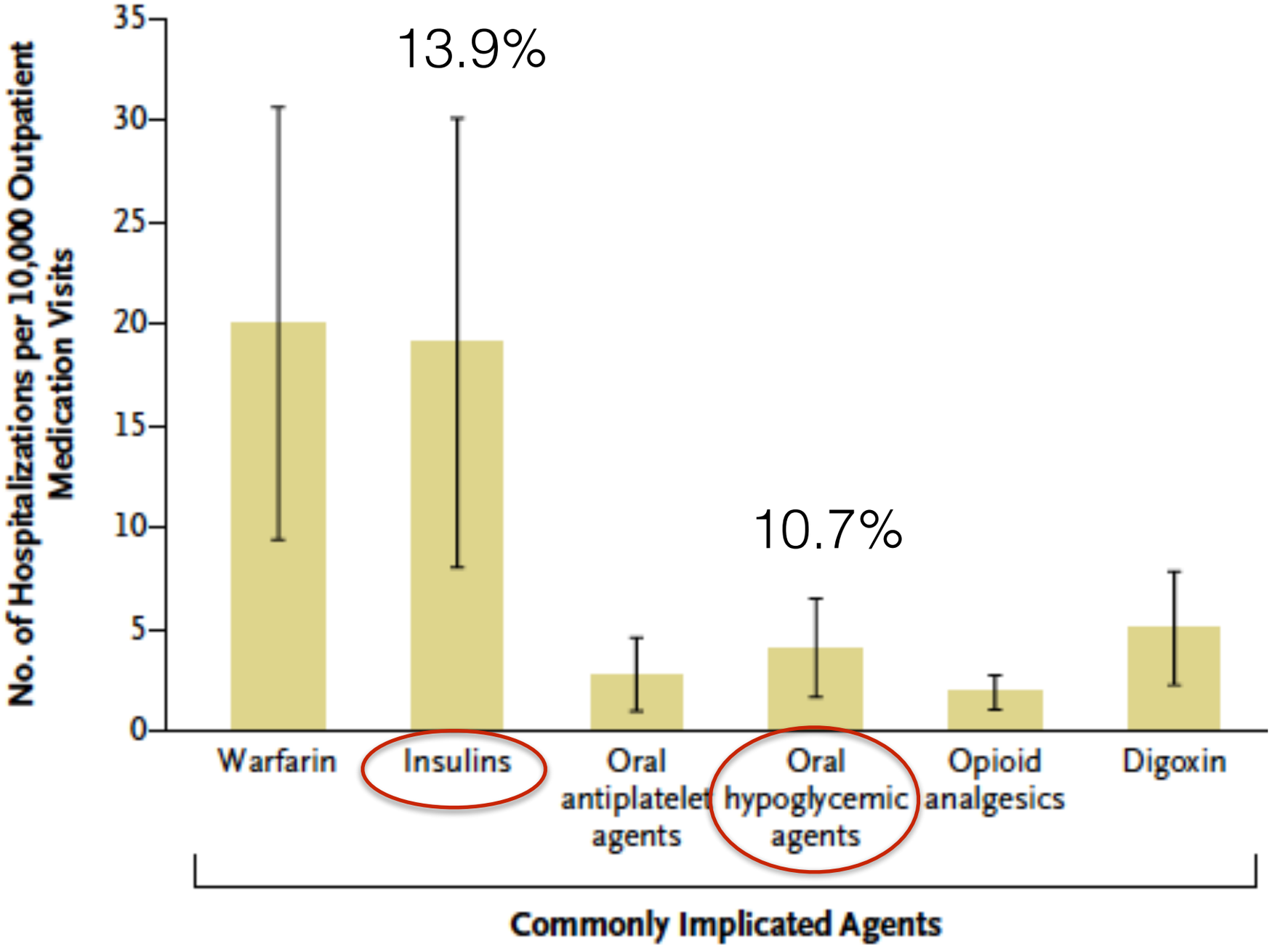
dextrostick 36 mg/dL

- Today
  - hypoglycemia
  - etiology and management
  - emphasis diabetic medications

Hypoglycemia

- Drugs
  - diabetic medications
  - insulin secretagogues: quinine
  - interfere with gluconeogenesis
    - ethanol, salicylates
  - drug interactions
- Other
  - critical illness, starvation
  - fulminant hepatic failure
  - infants and neonates: inborn error metabolism, hormonal disturbances
  - insulinoma

Emergency Hospitalizations for Adults ≥ 65 y for adverse drug events



N Engl J Med 2011;365:2002-12

Hypoglycemia

- lab definition: venous glucose ≤ 50- 60 mg/dL
    - in neonates: first 24° as low as 30 mg/dl, first week as low as 45 mg/dL

- symptom defined: adrenergic symptoms, neuroglycopenic symptoms

- Autonomic signs
  - adrenergic: palpitations, tremor, anxiety
  - cholinergic: nausea, sweat, hunger

- Neuroglycopenia
  - confusion, concentration
  - blurred vision
  - behavioral change
  - weakness, fatigue
  - focal weakness
  - seizures, coma

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Hypoglycemia

- onset of symptoms hypoglycemia
  - non-diabetics: 55 +/- 2 mg/dL
  - poorly controlled diabetics 77 +/- 5 mg/dL
- tightly controlled diabetics may lose appropriate early warning signs, neuroglycopenia without sympathomimetic warning signs
- long standing diabetes mellitus: loss glucagon response to hypoglycemia and autonomic failure

N Engl J Med 1988;318:1487-92
N Engl J Med 1995;333:1726-31

- A 49 yo male with longstanding IDDM with nephropathy and neuropathy brought to ED following a hypoglycemic episode

- Prehospital FS glucose was < 20 mg/dL, treated 1 amp D50. On arrival to ED he is lethargic and has a repeat dextrostick of 36 mg/dL.

- He receives a 2nd amp D50 with arousal and is given a meal. One hour later his dextrostick is 168 mg/dL.

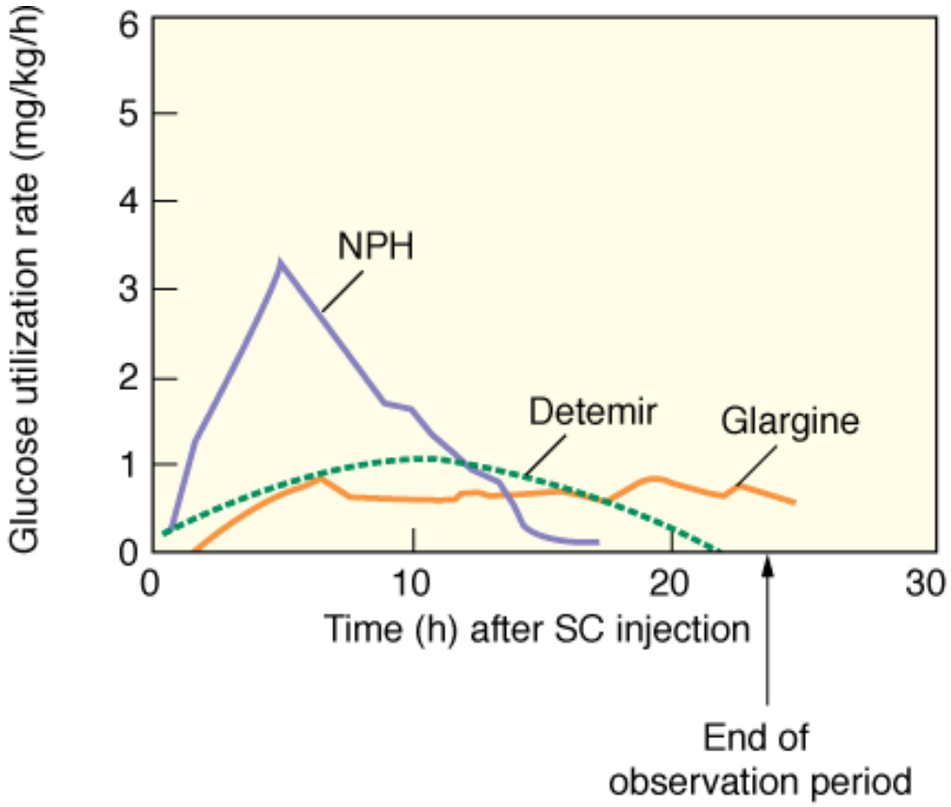
141	107	54	20
3,8	25	5,2	

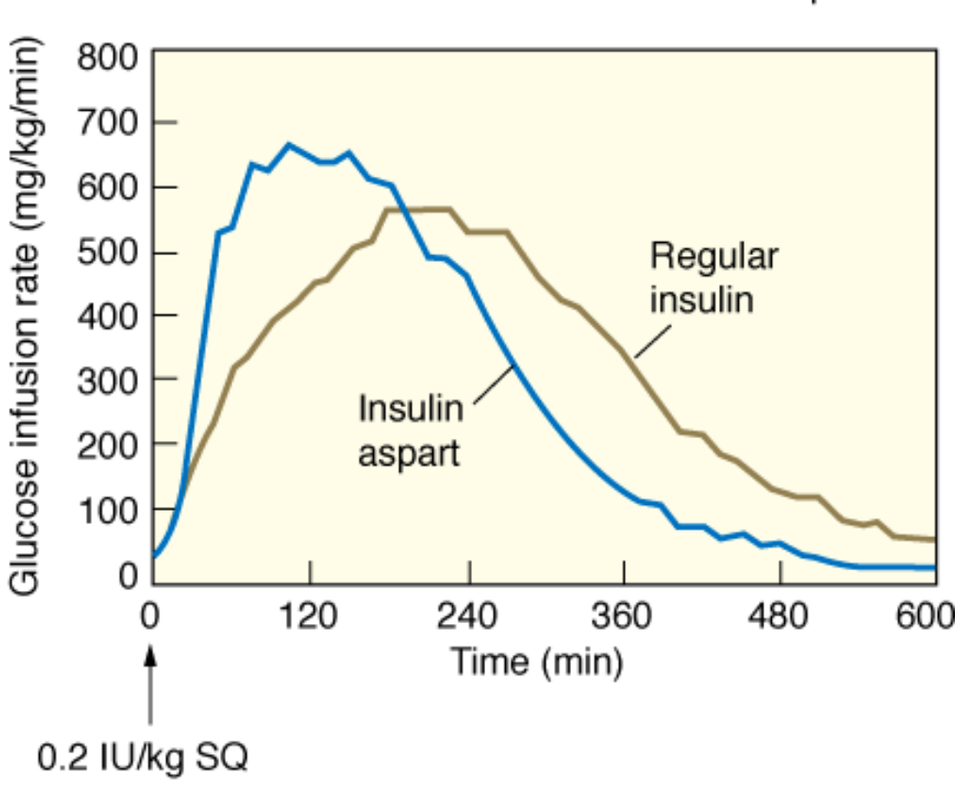
- Careful interview reveals appropriate use of insulin and normal caloric intake. Despite this, second episode in past week.

- Insulin clearance
  - hepatic ~60%
  - renal ~ 30%
  - remainder adipocytes, skeletal muscle, placenta

Hypoglycemia

- why did it happen?
  - intentional
  - dose change, double dose
  - visual issues
  - change in renal function
  - concomitant illness
- what are kinetics of product?





Preparation	Onset (SQ administration)	Peak	Duration
lispro, aspart, glulisine	5-15 min	1.5 h	3-4 h
regular	30-60	2 h	6-8 h
NPH	2-4 h	6-7 h	10-20 h
glargine	1.5 h	flat	~ 24 h
detemir	1 h	flat	17 h

Greenspan's Basic & Clinical Endocrinology 9th ed

- A 37 yo female with Type II DM presents after injecting self with 240 U Lantus at 13:00 and then another 90 U Lantus at midnight.

(Lantus® = glargine)

- Her usual dose?, i.e. insulin resistance?
- One site, multiple site injection?
- Kinetics insulin product
- Her renal function

- Intentional overdose insulin
  - large depot: kinetics different, duration effects may last for days
  - admission, observation
    - initial hypoglycemia following overdose long acting insulin may be delayed, up to 18 h later reported with glargine

- Admission following insulin overdose
  - intentional overdose
  - hypoglycemia following use of longer acting insulin
  - recurrent hypoglycemia after use any insulin product
  - hypoglycemia with renal or hepatic impairment

- Safe for discharge
    - accidental extra dose/ double dose
        - euglycemia for 4-6 hours in ED, alert and with good po intake
        - good social support

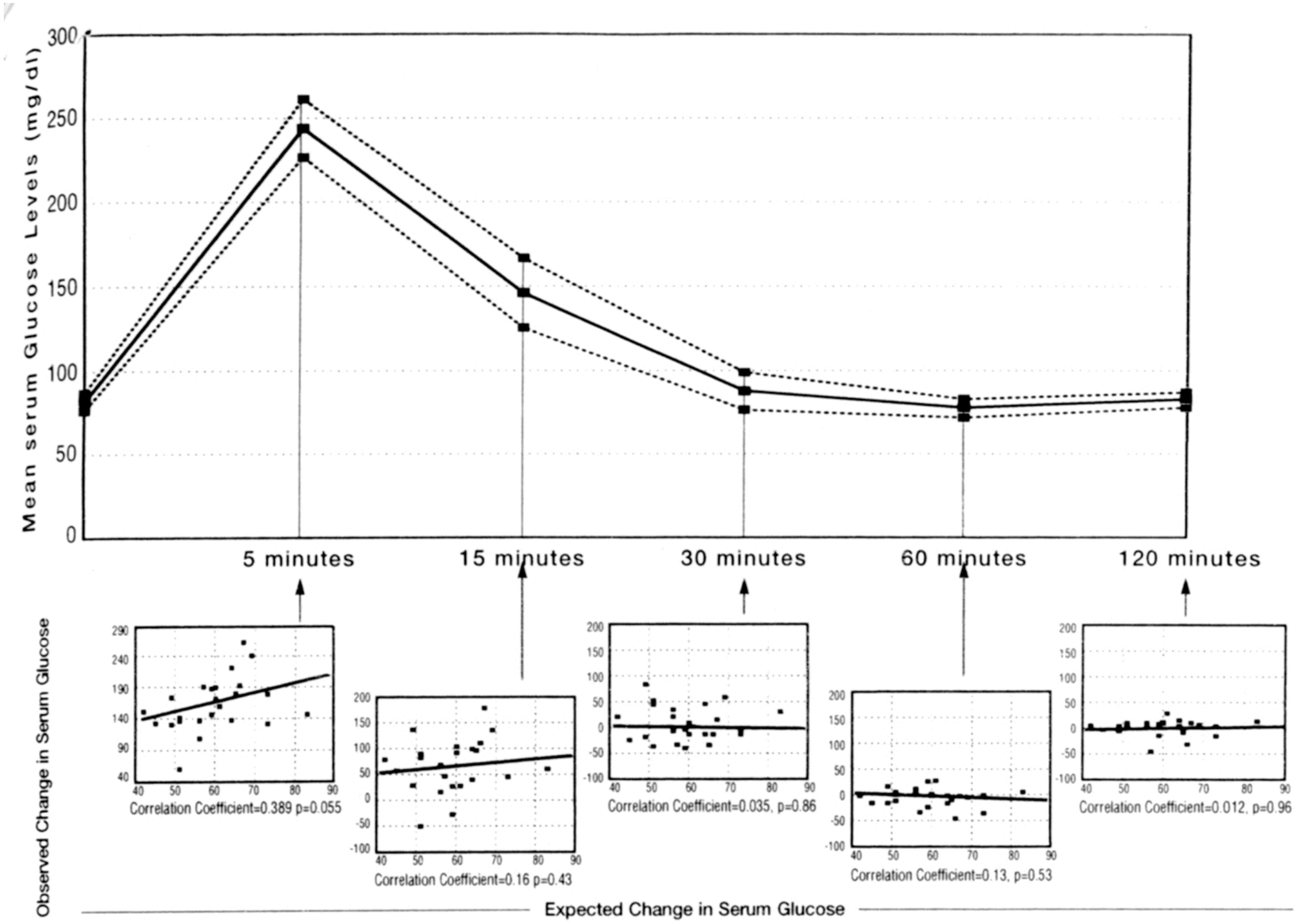


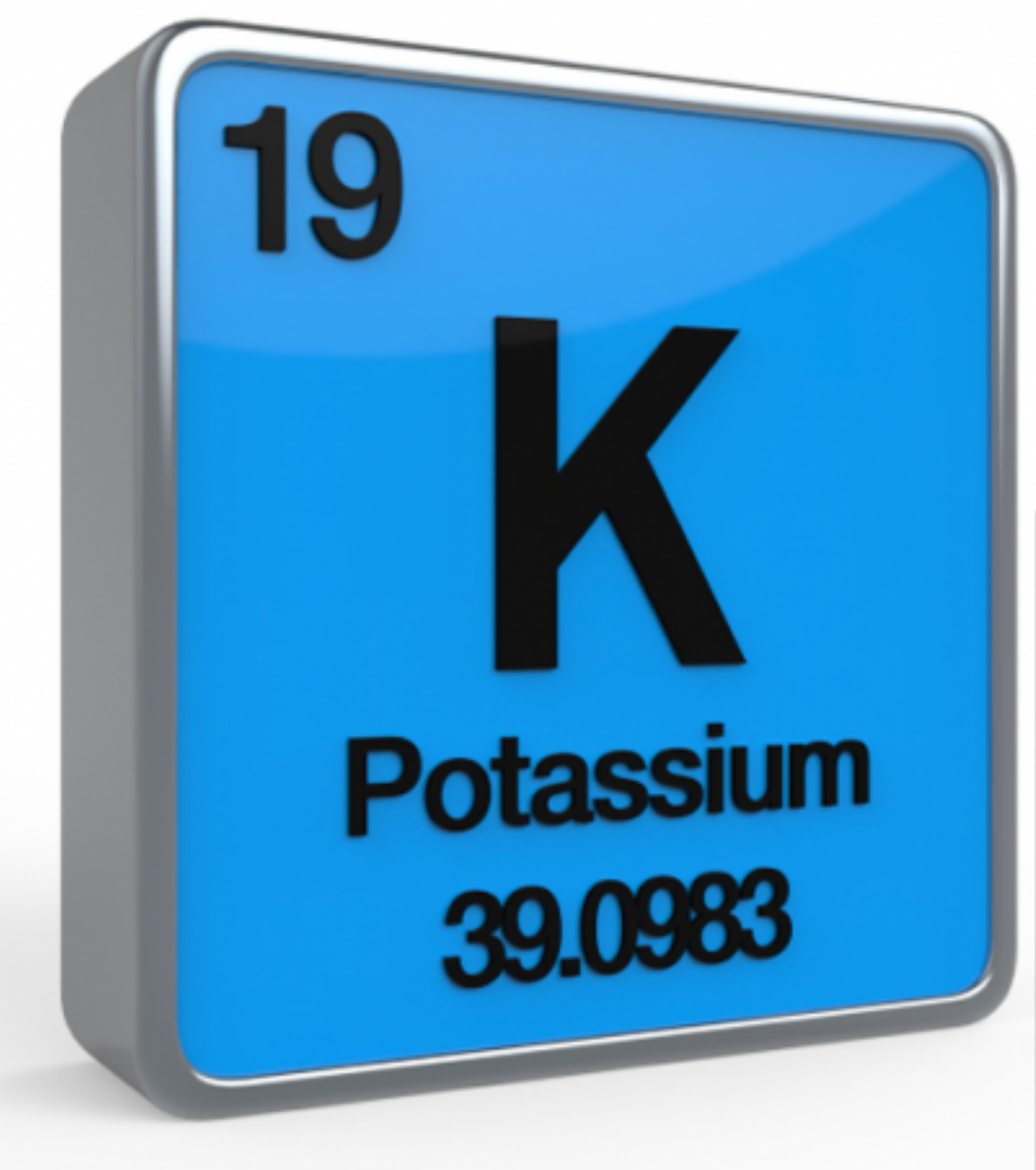
Figure 1. (*Top*) Mean serum glucose levels and their 95% confidence intervals with respect to time. (*Bottom*) Correlation analysis with Pearson's correlation coefficients for *observed* and *expected* changes in serum glucose.

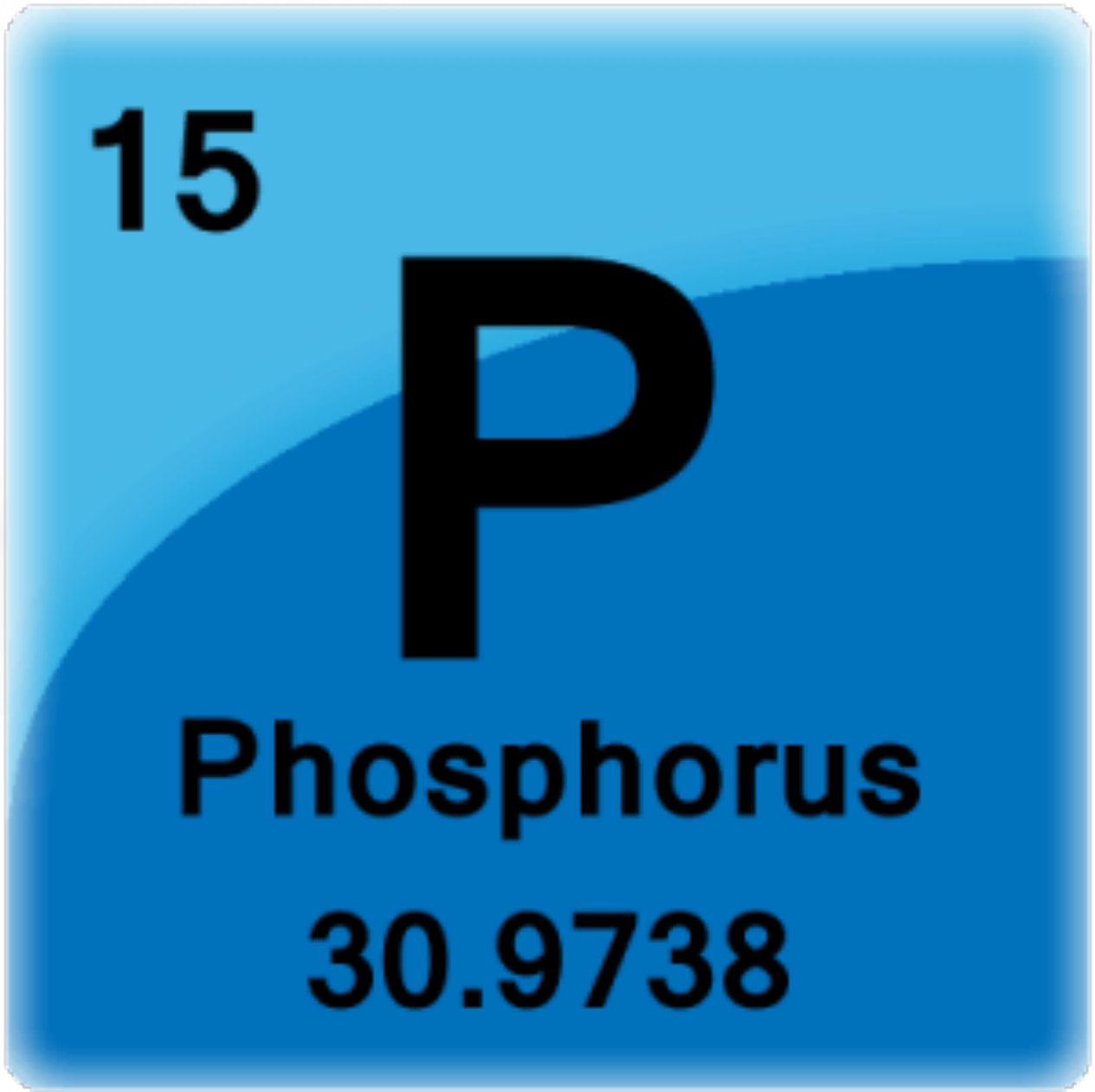
Acad Emerg Med 1998;5:691-694

- Adults: 0.5 -1 g/kg D50 (1-2 mL/kg)
- Children: D25, D10
- Toddlers, neonates: D10, 0.2 mg/kg (2 mL D10/kg)

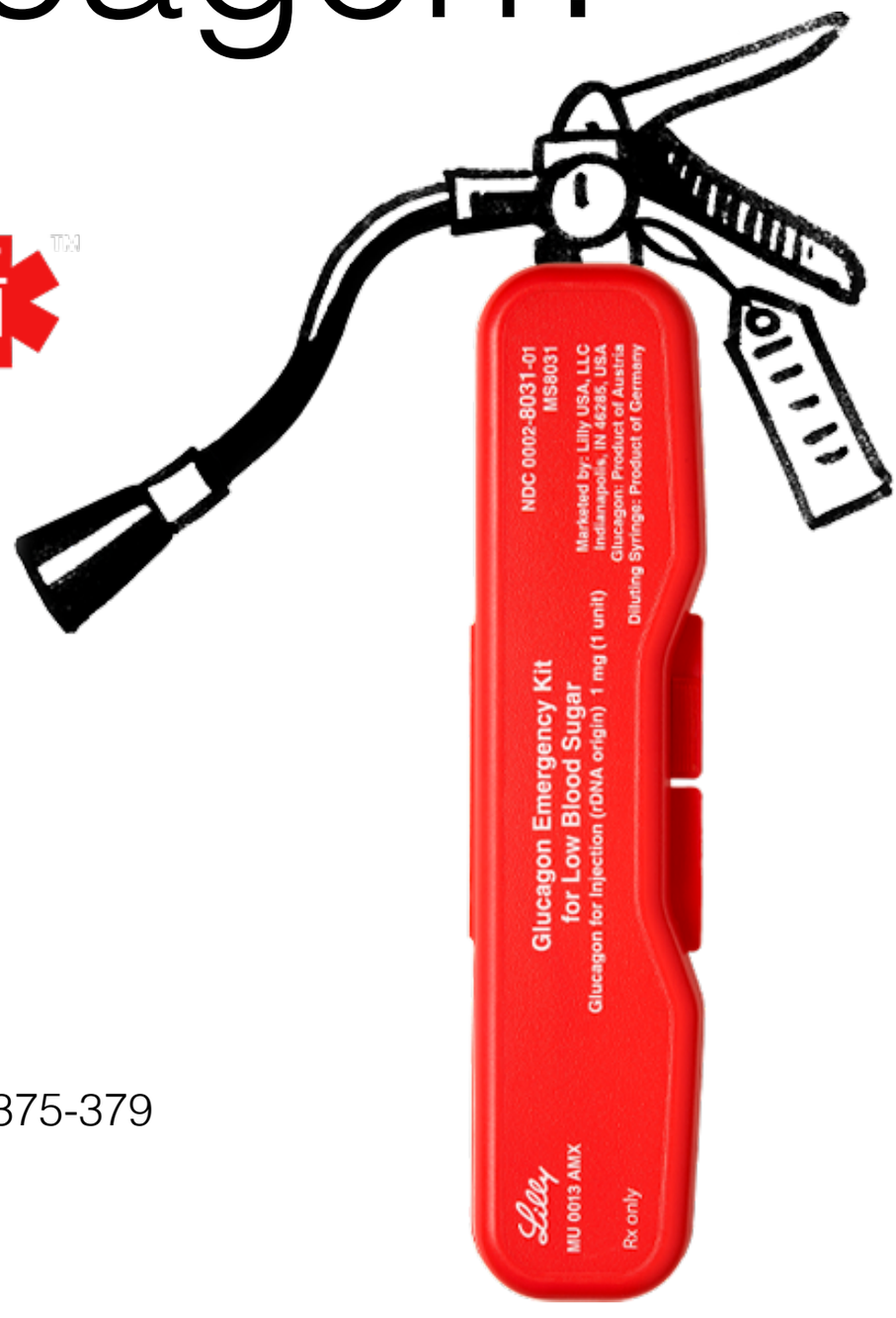
- Hyperosmolar risks:
  - local: phlebitis, thrombophlebitis
  - kids: hyperosmolar coma, neurologic injury

	dextrose per 100 mL	osmolarity
D50	50 g	2,525 mOsm/L
D25	25 g	1,330 mOsm/L
D10	10 g	505 mOsm/L


19
K
Potassium
39.0983


15
P
Phosphorus
30.9738

What about glucagon?



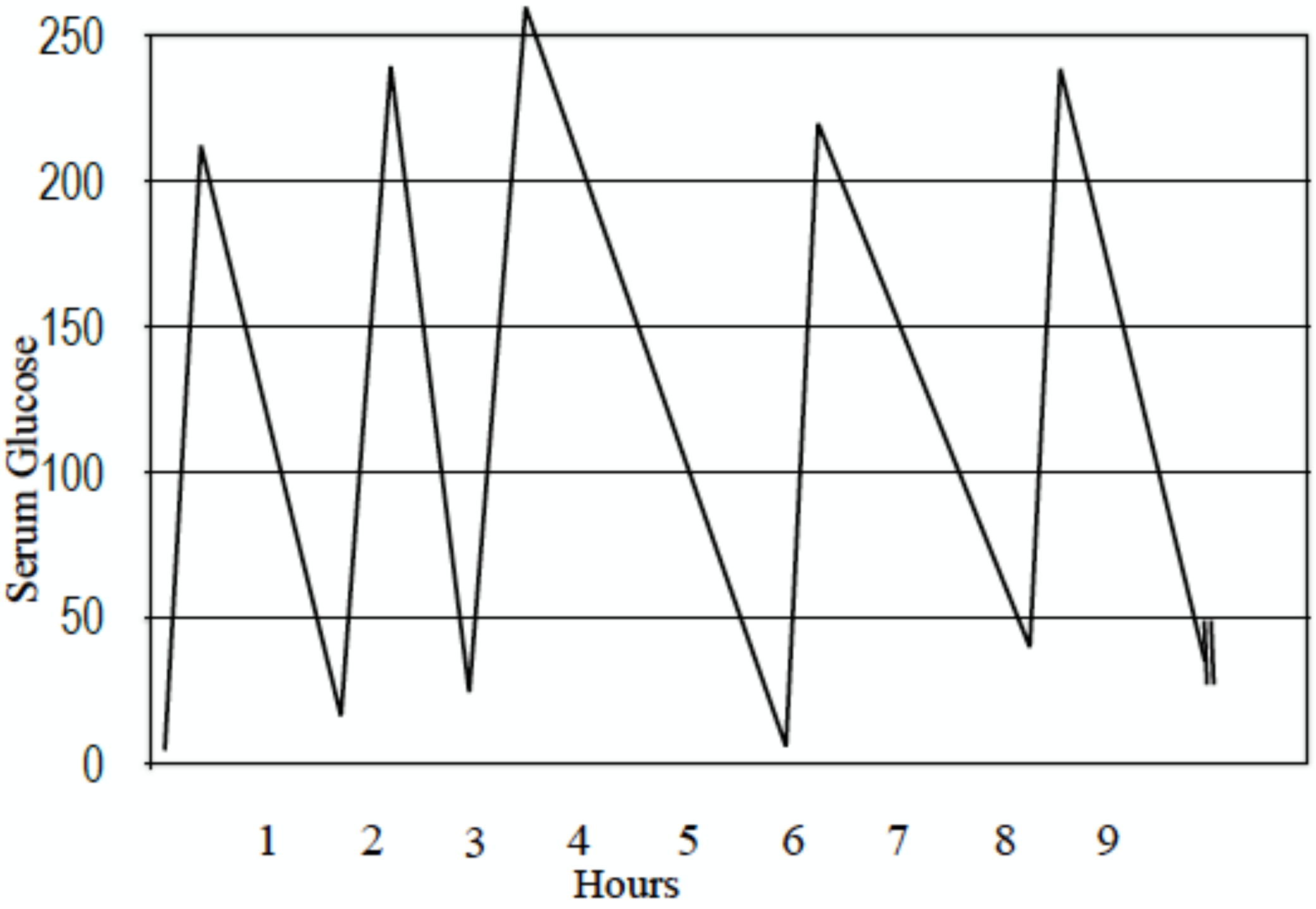
- stimulates gluconeogenesis, glycogenolysis
  - and, beta cells
- prehospital glucagon (1 mg IM) for hypoglycemia
  - mean increase glucose ~ 100 mg/dL
  - improvement mental status ~ 8 minutes

Ann Emerg Med 1991;20:375-379

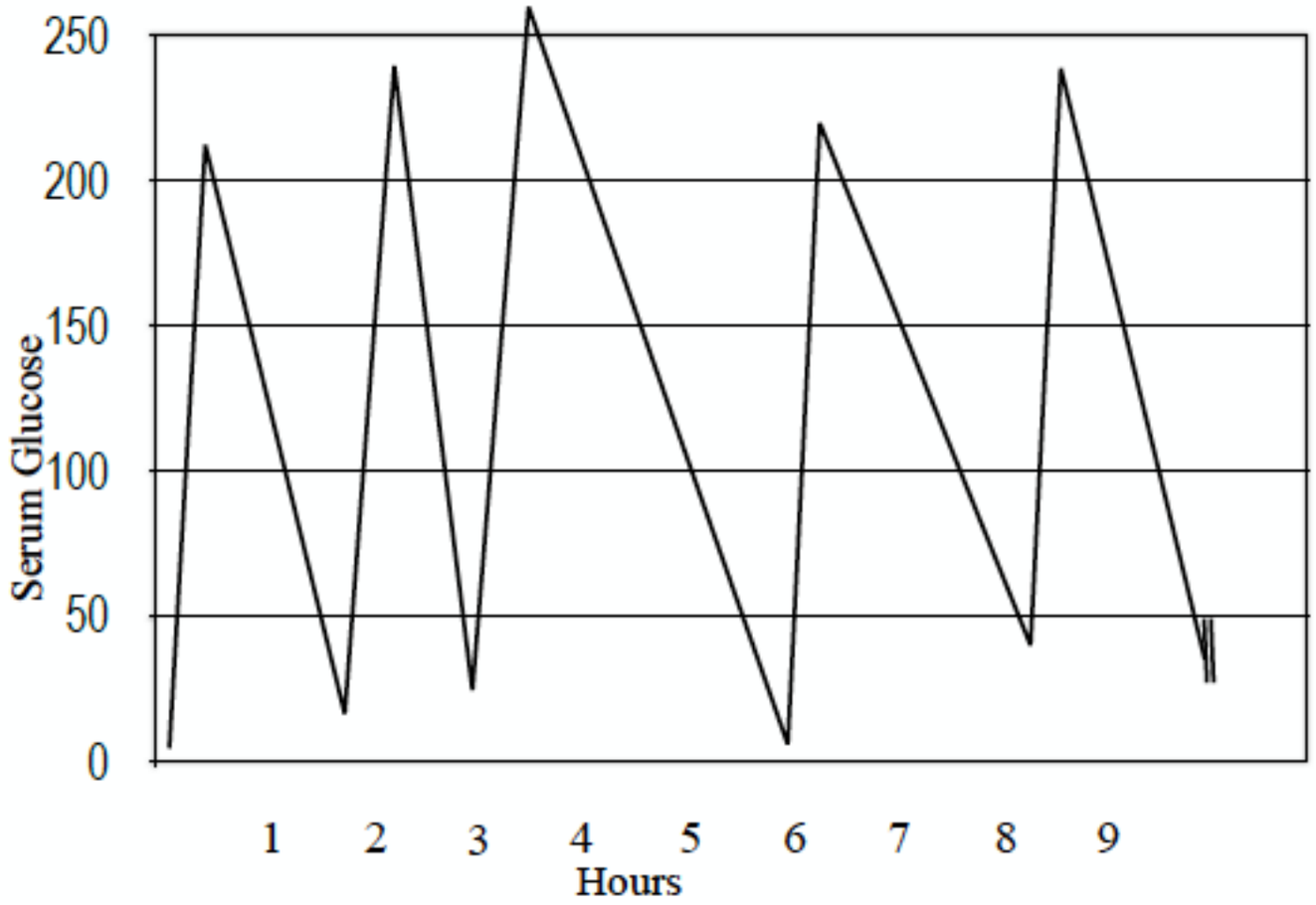
- Dextrose v glucagon prehospital setting
  - recovery to full orientation faster with dextrose (11 min v 28 min)

J Accid Emerg Med 1997;14:30-32

- 50 yo male ingests 10 x 5 mg glyburide
- two hours later lethargic, seizure
- dextrose 0.5 g/kg IV prehospital for glucose of 12 mg/dL
- in ED placed on D10 infusion, despite this several more episodes of symptomatic hypoglycemia treated with bolus dextrose with good response, D10 infusion increased



courtesy of Lewis Nelson MD

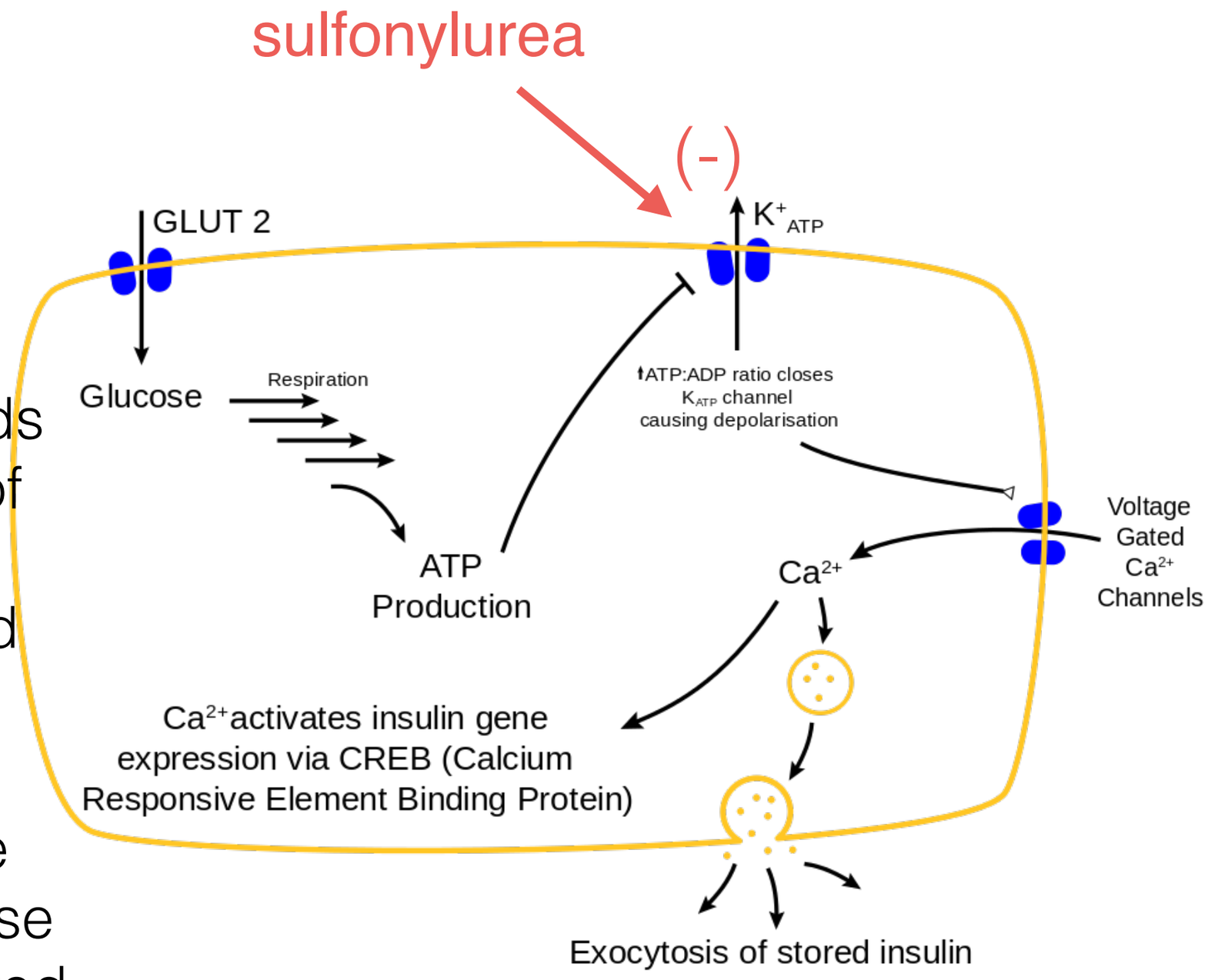


courtesy of Lewis Nelson MD

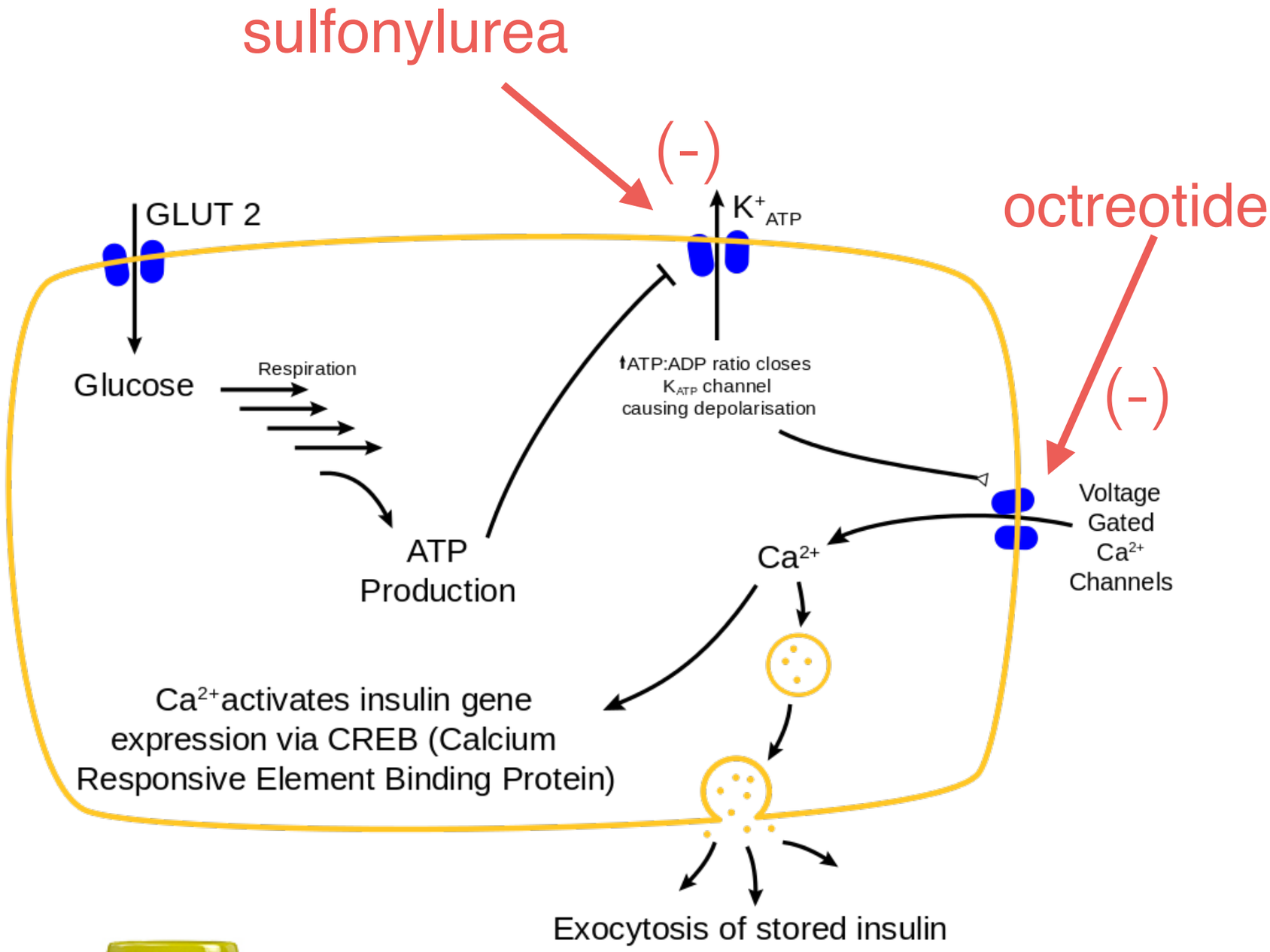
- glucose induced insulin release from pancreas
- non-diabetics, diabetics with preserved beta-cell function

- antagonism of K efflux channel leads to depolarization of beta cell, opening Ca^{++} channels and release insulin

- beta-cell response response to glucose loading exaggerated with sulfonylurea present



en.wikibooks.org



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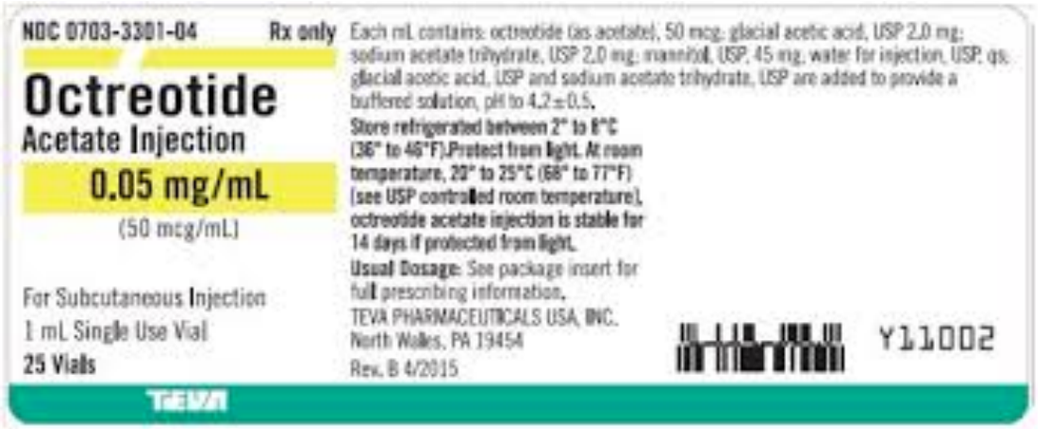
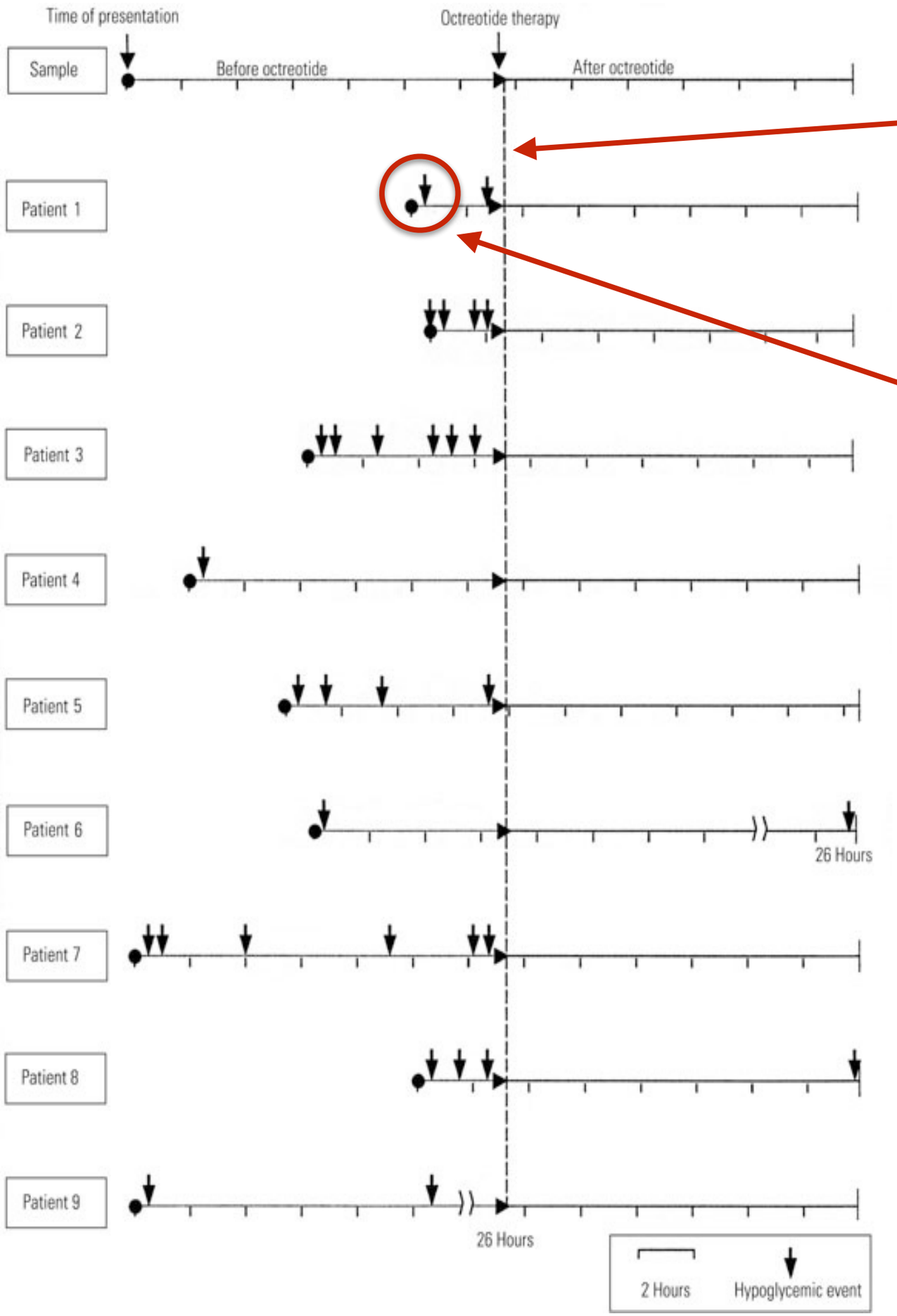


Octreotide

- Indication (off label)
  - symptomatic hypoglycemia due to sulfonylurea OD
  - recurrent hypoglycemia unknown etiology
- Dose: 50- 75 ug **SQ** (or IV) q 6 to 8 h
- Duration of action?
  - not well defined for this indication, believed to be about 6-12 hours
- How many doses?
  - in a known sulfonylurea OD 2-3 additional doses should be considered after first dose

	peak	t 1/2	duration action	active metabolites
glipizide	1-3 h	7	12-24 h	no
glipizide_GITS	6-12 h	7	24+ h	no
glyburide	2-6 h	10 h	16-24 h	yes
glimepiride	2-3 h	5-9 h	24+ h	yes



Octreotide

Hypoglycemic episode

Ann Emerg Med 2000;36:133-138

- Observation period after last dose octreotide?
  - not well defined, we recommend 12 hours, and: normally alert and taking po well
- Caveats:
  - massive overdose
  - avoid medically clearing in evening in patient previously symptomatic

Sulfonylurea ingestion adults

- Intentional overdose: admit
- Naive adult with accidental exposure: admission with observation
    - hypoglycemia onset typically rapid, within hours, nearly all within 6-8 h
    - avoid medically clearing in evening, at night……
- Adult diabetic with accidental double dose: home management an option **if** good social setting.
    - Greater than double dose, or hypoglycemia: hospital observation

- A 3 yo female maybe ingests a single tablet of ER glipizide
- She arrives in ED 60 minutes post ingestion, alert, happy, playful. Dextrostick 88 mg/dL

- When does hypoglycemia occur post sulfonylurea ingestion in children?
  - mean time 4-6 h; exceptional cases delays up to 16-21 h post exposure

Clin Toxicol 1996;34:267-70
J Ped 1997;131:141-46

Sulfonylurea ingestion in children

- We recommend 24 h observation
  - ad lib diet
  - no supplemental dextrose unless hypoglycemia
  - if supplemental dextrose needed, add octreotide

Table 3. Association Between Hospital Admission for Hypoglycemia and Use of Co-trimoxazole in Patients Receiving Glyburide

	No. (%) Exposed			
	Cases (n = 909)	Controls (n = 43 766)	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
Hospitalization Within 1 Week of Exposure to Second Drug				
Co-trimoxazole	35 (3.9)	189 (0.4)	8.5 (5.8-12.4)	6.6 (4.5-9.7)
Amoxicillin†	10 (1.1)	246 (0.6)	1.8 (1.0-3.5)	1.5 (0.8-2.9)
Hospitalization Within 2 Weeks of Exposure to Second Drug				
Co-trimoxazole	49 (5.4)	319 (0.7)	7.3 (5.4-10.0)	5.7 (4.1-7.9)
Amoxicillin†	13 (1.4)	433 (1.0)	1.4 (0.8-2.5)	1.1 (0.6-2.0)
Hospitalization Within 3 Weeks of Exposure to Second Drug				
Co-trimoxazole	56 (6.2)	447 (1.0)	6.1 (4.6-8.1)	4.9 (3.6-6.6)
Amoxicillin†	19 (2.1)	611 (1.4)	1.5 (0.9-2.3)	1.2 (0.8-1.9)

Abbreviation: CI, confidence interval.
*Multivariate analysis adjusted for factors in Table 1.
†Comparable noninteracting drug for comparison.

JAMA 2003;289:1652-1658

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- CYP 2C9 substrate: sulfonylureas
- CYP 2C9 inhibitor: TMP/SMX

JAMA 2003;289:1652-1658

Sulfonylurea related hypoglycemia risk factors

- elderly, esp. with concurrent illness
- recent hospitalization
- poor nutrition
- alcoholism
- renal and liver disease
- polypharmacy

Meglitinides v sufonylureas

- similar mechanism of action
- rapid onset, short duration action
- published experience limited
- persistent PD effect for 24 h reported with repaglinide overdose in a teenager

Clin Toxicol 2016;54:158-160

Other diabetic medications

- Subtype 2 sodium-glucose transport protein (SGLT2) inhibitors: canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®)

- glycosuria: volume issues

- alpha glucosidase inhibitors: acarbose, meglitol
  - binds intestinal disaccharidases, **nada risk**
- thiazolidinediones (the glitazones, Actos®, Avandia®)
  - acute overdose: limited experience
  - very **unlikely** hypoglycemic risk

GLP-1 agonists (SQ)
1. exenatide
2. liraglutide

Beta cell

+

GLP-1
glucagon like peptide 1

+

inactivates

DPP-4
dipeptidyl peptidase 4

-

slows gastric
emptying

DPP-4 inhibitors
1. sitagliptin
2. saxagliptin

GLP-1 agonists

1. exenatide
2. liraglutide

Beta cell

+

GLP-1

glucagon like pepti

vates

+

DPP-4

dipeptidyl peptidase 4

Observation for 8 hours

-

slows gastric emptying

DPP-4 inhibitors

1. sitagliptin
2. saxagliptin


850 mg
30 film-tableta
METFORMIN
metformin
FARMAKOS PRIZREN
30 film-tableta
850 mg
METFORMIN
metformin
FARMAKOS PRIZREN
850 mg
30 film-obložene tablete
METFORMIN
metformin
FARMAKOS PRIZREN

- 3 yo male brought to ED lethargic about 20:30. Mom reports child sleepy midafternoon, put him to bed for nap. At 20:00 unable to arouse.

- Unresponsive, smells “minty”. Shortly post arrival suffers grand mal seizure

- Glucose is unmeasurable

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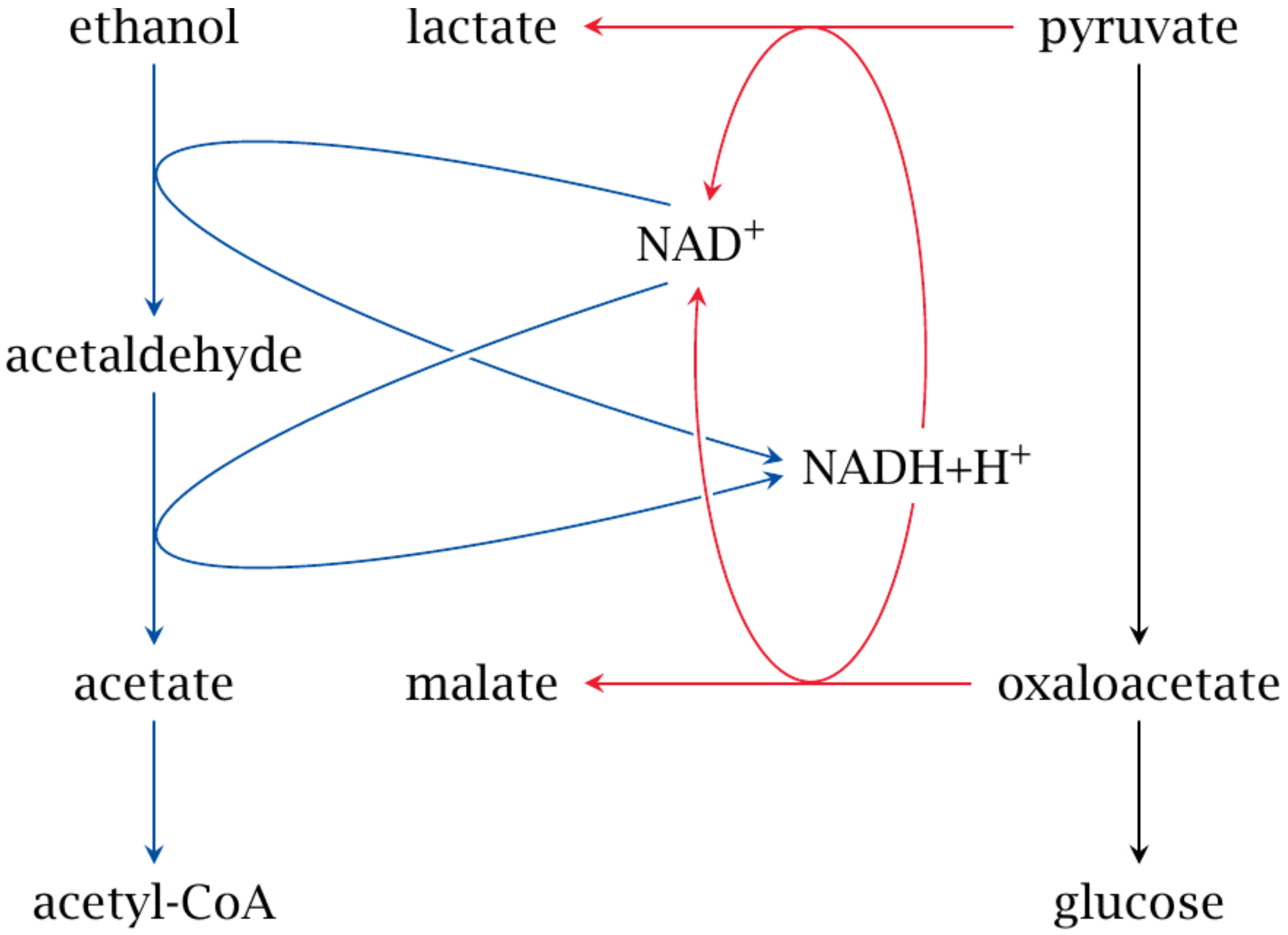
Scope original mint mouthwash 15% ethanol



http://watcut.uwaterloo.ca/webnotes/Metabolism/gneoInteractions.html

Children: Ethanol and hypoglycemia

- 10 y retrospective review in England, 143 intoxicated children
    - age < 7 y, 10/53 (19%) presented with symptomatic hypoglycemia (blood glucoses 9- 47 mg/dL)
    - age 7- 14 y, 2/90 with symptomatic hypoglycemia
    - selected population (??? true denominator)
- Charity Hospital New Orleans
    - over 4 1/2 years, 3/88 children with a measurable ethanol had a glucose < 67 mg/dL, all were teens (0/8 age < 5 y)

BMJ 1986;292:519-522
Acad Emerg Med 1996;3:46-49

Bariatric surgery and hypoglycemia

- Recent literature on the association of hypoglycemia in bariatric surgery patients, Roux-en-Y procedure in particular

- Typically occurs > 12 months post procedure

- one study with continuous glucose monitoring detected hypoglycemia (≤ 55 mg/dL) in 30/40 over 120 h (do not discuss if/ how often symptomatic…..)

  - 29% also with abnormal mixed meal tolerance test

Surg Obes Relat Dis, in press, http://dx.doi.org/10.1016/j.soard.2014.11.003

Unexplained hypoglycemia

- suspect covert use insulin or sulfonylurea
    - healthcare worker
    - relative, house mate with diabetes
    - psychiatric history
    - abrupt onset symptoms

Laboratory Investigation

- insulin
- C-peptide
- proinsulin
- anti-insulin antibodies
- sulfonylurea assay (and meglitinides)

Glucometer type	Glucose oxidase method	Glucose Dehydrogenase method
Hypoxemia	falsely increase	falsely increase
galactose xylose, maltose ★ icodextrin		**falsely increase**
acetaminophen	variable, toxic APAP: **may falsely increase significantly**	falsely increased, **may be significant** at toxic concentration
vitamin C (high dose)	variable	falsely increased

Diabetes Care 2007;30:403-409
Clin Chem 1998;44:893-894
Am J Clin Pathol 2000;113:75–86

Continuous home glucose monitors

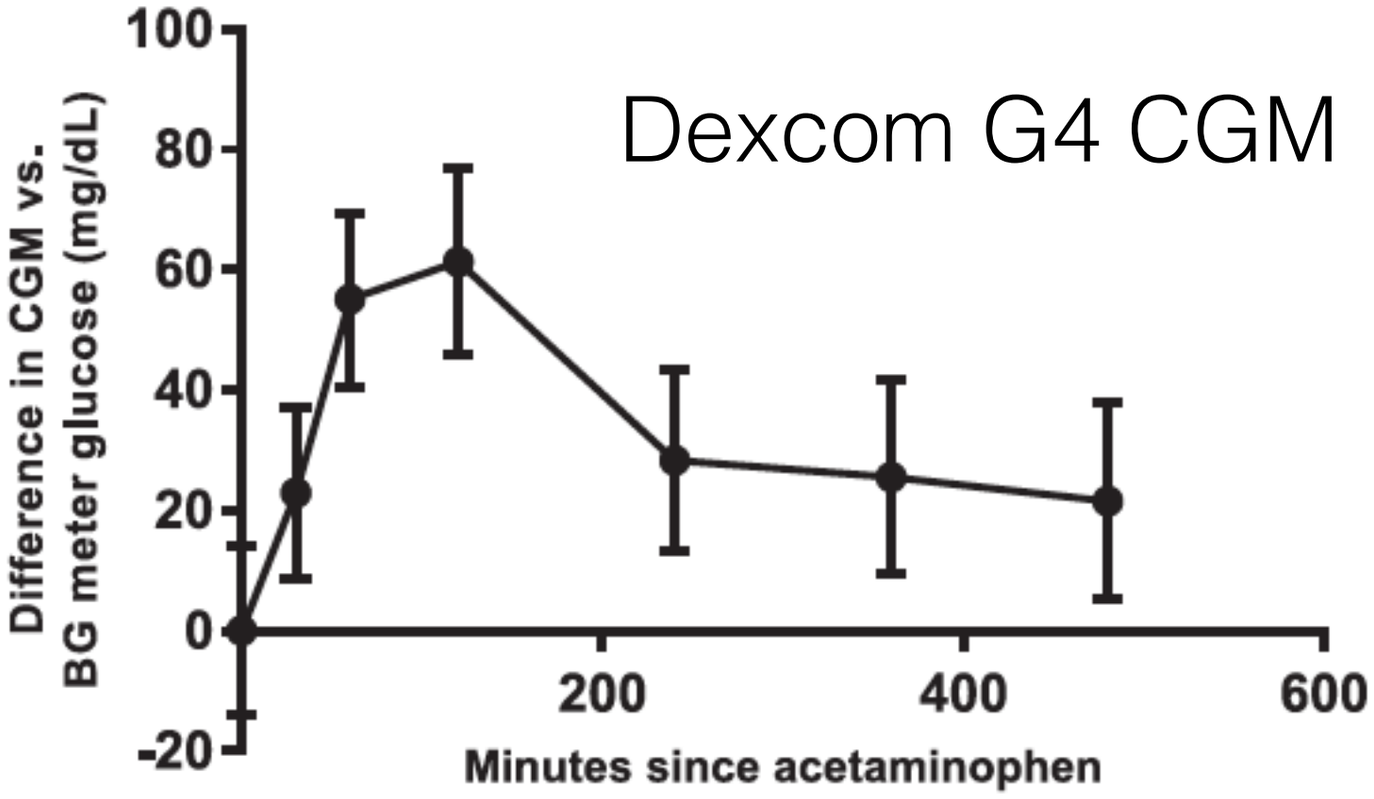


Figure 1—Least squares means and 95% CIs for difference between CGM glucose and BG meter glucose by time point.

Dexcom G4 CGM

1,000 mg dose acetaminophen false elevation glucose, compared to glucometer, up to 60+ mg/dL at 2 h

Diabetes Care 2015;38:e158–e159

- Ackee fruit, *Blighia sapida*
- Jamacian vomiting sickness
- hypoglycin A, inhibitor of beta oxidation fatty acids, ultimately interferes with gluconeogeneisis

Summary

- Insulin/ sulfonylurea intentional overdose: admit
- Naive adults and children with sulfonylurea ingestion: admit
    - adults: at least 8-12 h observation; children 24 h
    - (avoid “clearing” late evening or night)
- Accidental double dose in diabetic, no symptoms, can be managed at home if safe social situation

Summary

- Dextrose is first line antidote
    - sulfonylureas: rebound hypoglycemia with intact beta cells
- Octreotide: low threshold for use with sulfonylurea, meglitinide toxicity; recurrent hypoglycemia unknown etiology