“Antidotal Hormone Therapy in Toxicology”

A webcast by **Alberto Perez MD**

Moderated by **KATHLEEN BRODERICK**

2:00pm - 4:00 pm EDT

On your telephone please dial:

1-866-835-7973

The webcast will begin shortly.

Hormonal Therapy in Toxicology

Alberto Perez MD
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WINDHAM HOSPITAL
HARTFORD HEALTHCARE

Hormonal Therapy in Toxicology

This webcast was developed in partnership with:

The American Association of Poison Control Centers (AAPCC)

AAPCC's Specialist in Poison Information Committee

The Children's Safety Network (CSN)

And funded by a contract from Health Resources and Services Administration (HRSA)

Objectives

- Definitions
- Case Presentation
- Review mechanism of actions and hormonal treatment regimens for certain overdoses

- **Definition of Hormone**

- **Hormone:** A chemical substance that originates in an organ or gland, which is conveyed through the blood stream to another part of the body to control and regulate the activity of certain cells or organs.

- **Hormones in Toxicology**

- Glucagon
- Insulin
- Octreotide
- Vasopressin

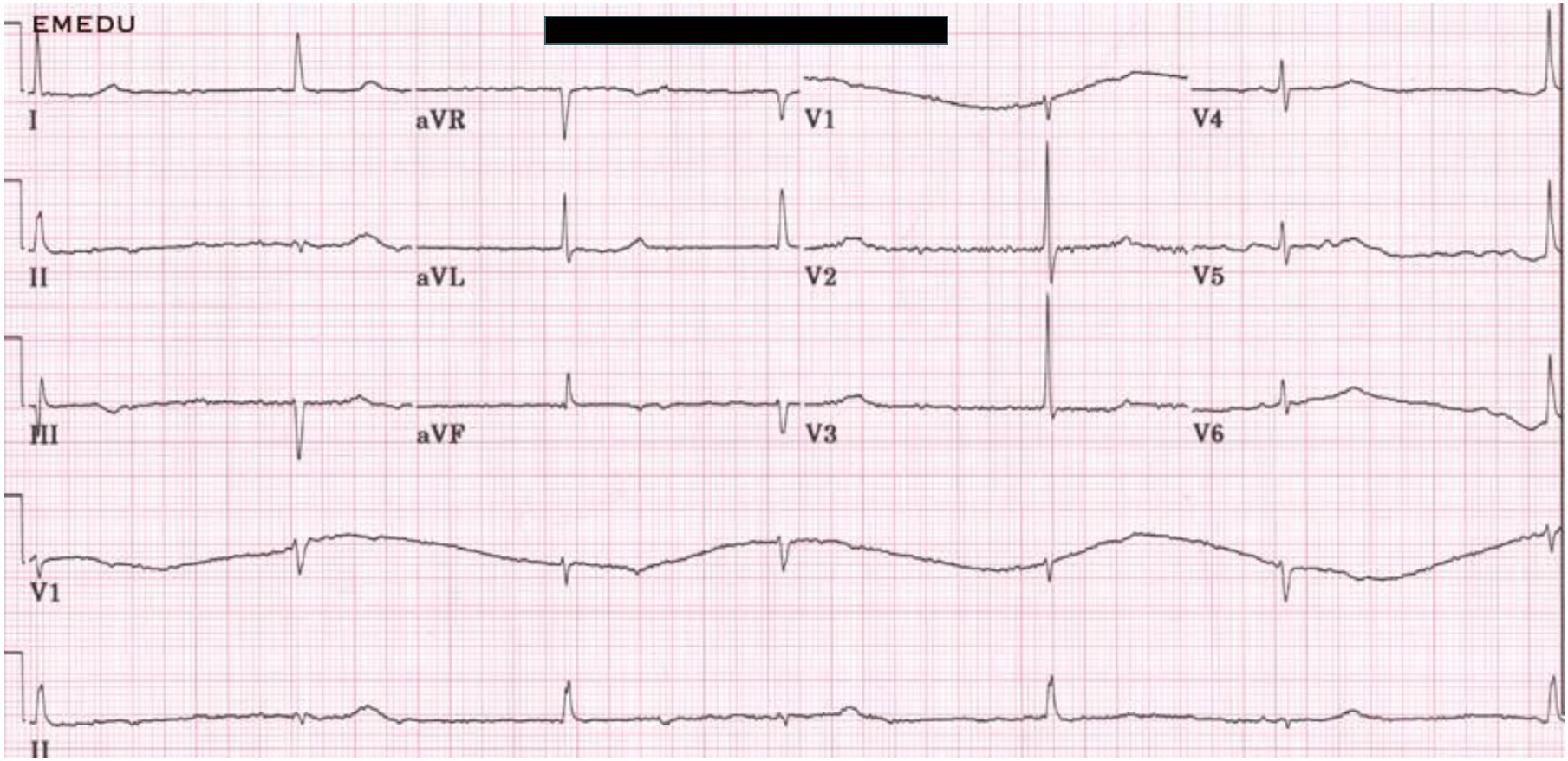
Case 1

- A 74 year-old man is brought in by his son for dizziness that is worse with standing
- Pt has a history of mild dementia and hypertension
- He lives alone and doesn't remember his meds
- Initial vitals are: 90/55 75 18 37.4
- He seems mildly confused

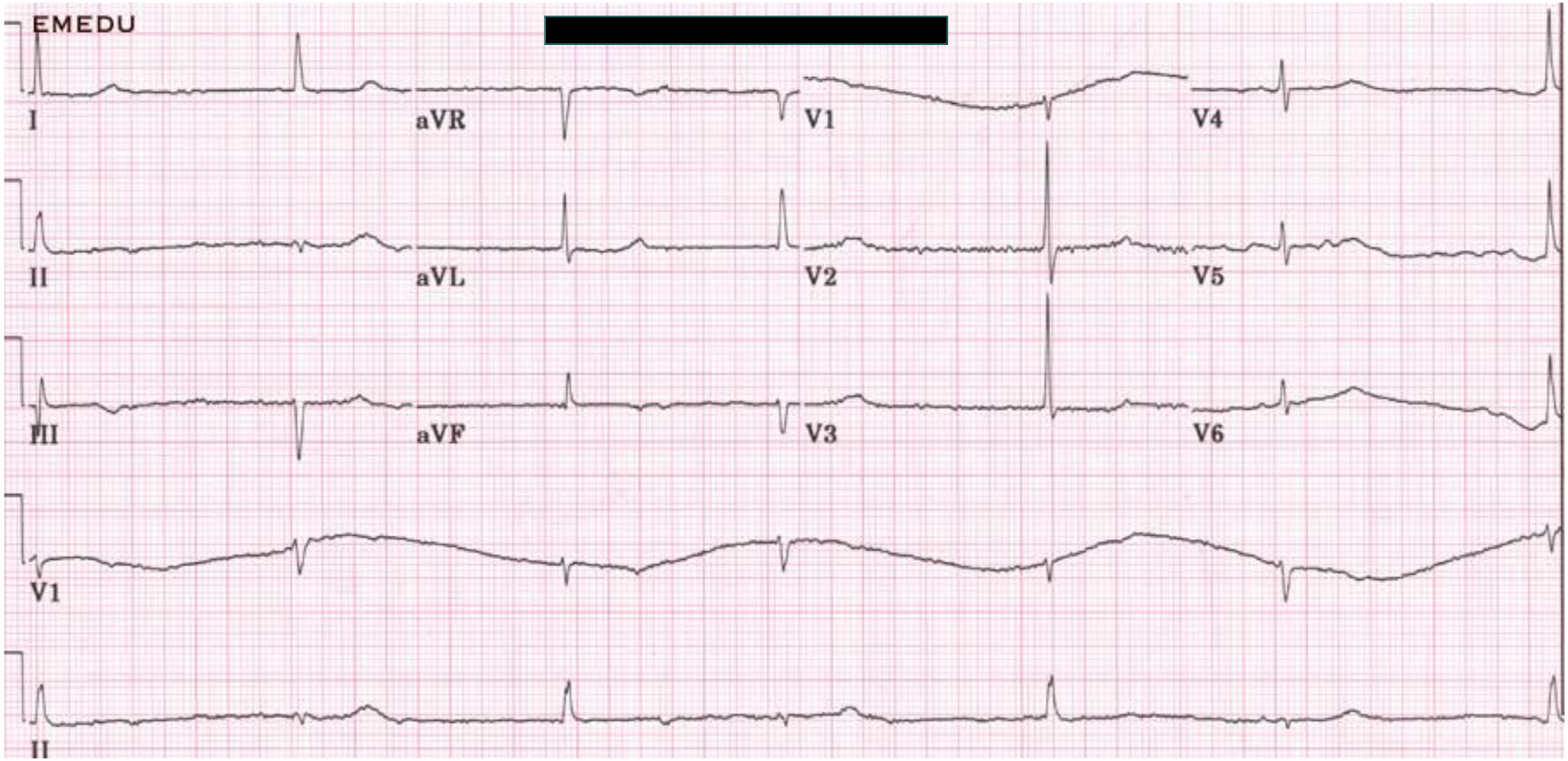
Case 1

- In the ED, he becomes progressively more bradycardic, hypotensive, and disoriented
- His vitals now are BP=72/34 and HR=30

Case 1

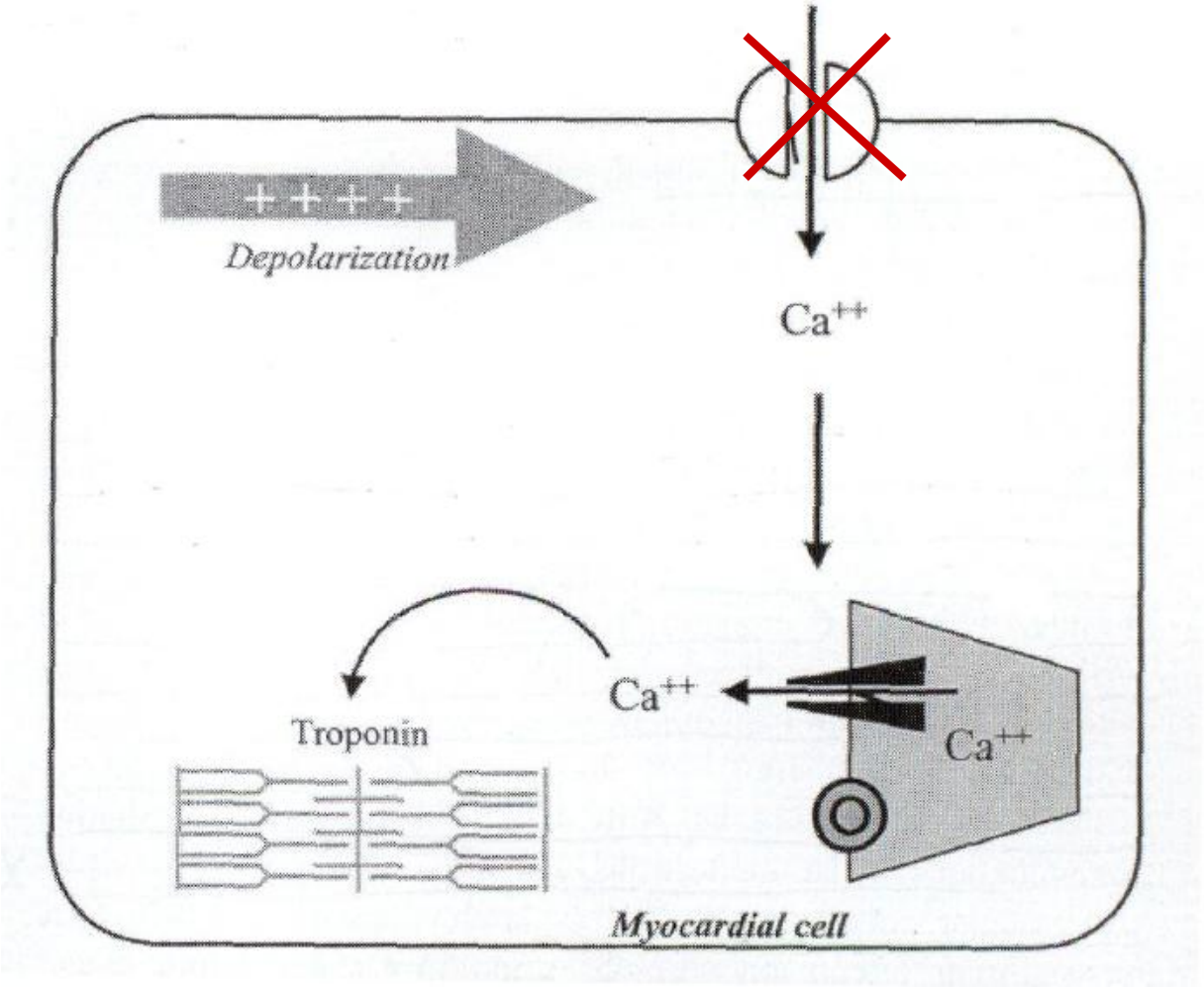


Case 1



List of meds included CCB…

CALCIUM CHANNEL BLOCKERS



Effects of impaired Ca influx

Myocardial

- Negative Inotrope
- Negative Dronotrope
- Negative Chronotrope

Smooth Muscle

- Relaxation
- Vasodilatation

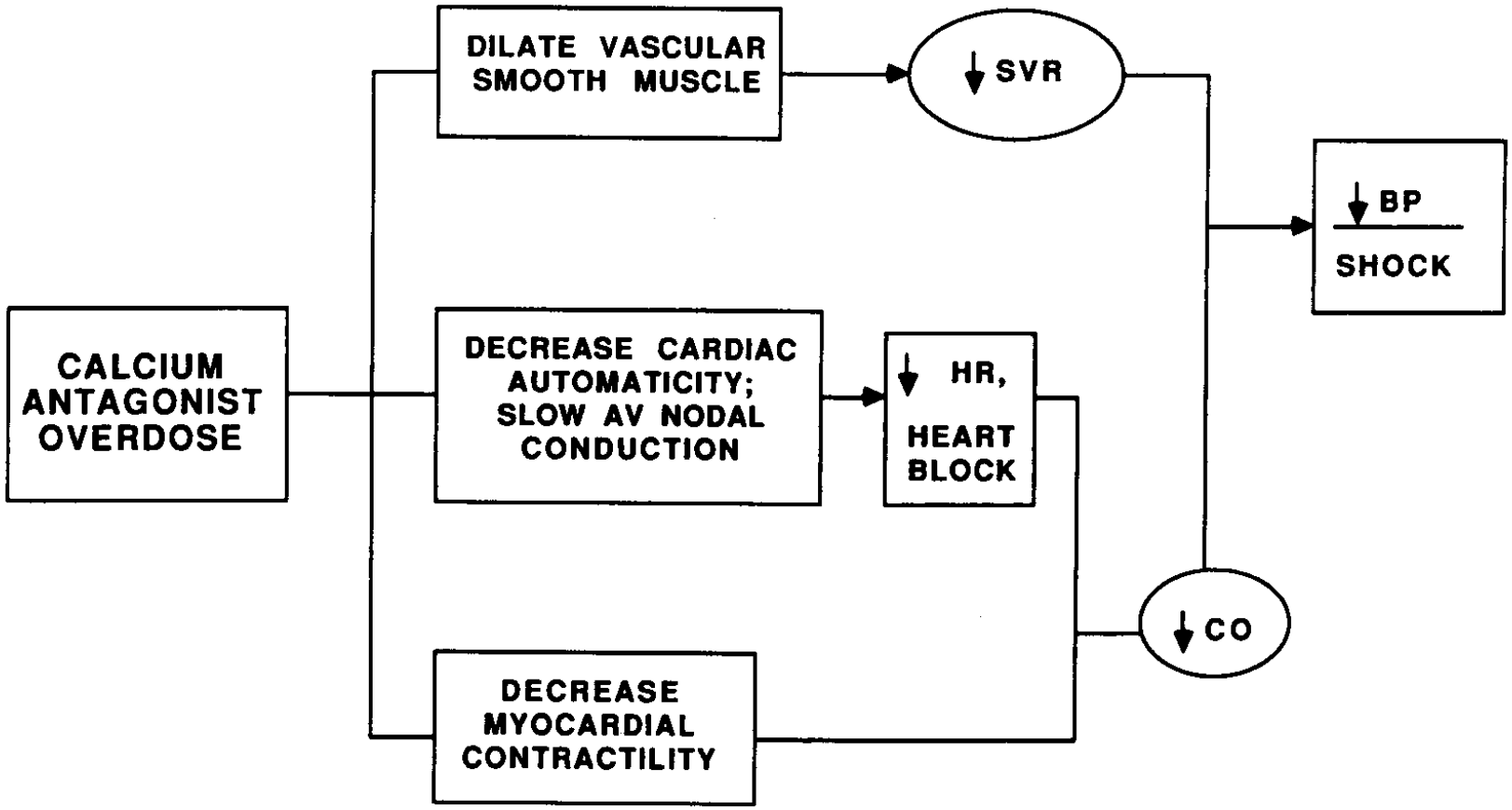
Pancreas

- Impaired insulin release

CCB - Manifestations

CCB	Conduction	Contractility	SVR
Verapramil	**+++**	++	+
Diltiazem	++	+	+
“depine”	+	+	**+++**

CCB - Pathophysiology



CALCIUM CHANNEL BLOCKERS

- Commonly prescribed cardiovascular drug class
  - 5% of toxic deaths in 2004

ARTICLE

Determining Triage Guidelines for Unintentional Overdoses with Calcium Channel Antagonists

F. Lee Cantrell, Pharm.D.
California Poison Control System, San Diego, California, USA and
San Francisco School of Pharmacy, University of California, San Francisco, California, USA

Richard F. Clark, M.D.
California Poison Control System, San Diego, California, USA,
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San Diego Medical Center, San Diego, California, USA, and

CCB MANAGEMENT

- Initial / Supportive
  - ABCs
  - Fluids
  - Atropine?
  - Decontamination
- Pharmacotherapy
  - Calcium
  - Catecholamines
  - Glucagon
  - Insulin/Glucose (HIE)
  - PDE inhibitors
  - Cardiac pacing
  - IA Balloon Pump

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- Initial / Supportive
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CCB DECON

- BE AGGRESSIVE!!
  - Gastric Lavage (???)
  - SD Activated Charcoal (all)
  - MD Activated Charcoal (SR preps)
  - Whole Bowel Irrigation (SR preps)
  - Hemodialysis – No role for CCBs

CALCIUM THERAPY

- **Calcium Chloride** (Inotropic agent)
  - 1g bolus (10 mL of 10% sol'n)
  - Drip at 1-3g per hour in Normal Saline
    - Central Line
    - Monitor ionized Ca
      (Goal = 2.5-3 mEq/L)

*** Calcium gluconate can be used but 1/3 calcium load per mg*

CALCIUM THERAPY

- Calcium Chloride (Inotropic agent)
  - Also reverses impaired conduction and hypotension
  - Short lived effect, in severe poisoning - poor response

HIE THERAPY

0749-5161/02/1801-0036
PEDIATRIC EMERGENCY CARE

Vol. 18, No. 1
Printed in U.S.A.

Hyperinsulinemia/euglycemia therapy for calcium channel blocker poisoning

EDWARD W. BOYER, MD, PhD, PETER A. DUIC, MD, ADELAIDE EVANS, MD

INTRODUCTION

Calcium channel blocker (CCB) overdose remains a significant cause of poisoning death (1). Conventional therapy consisting of intravenous (IV) fluids, calcium, dopamine, dobutamine, norepinephrine, and glucagon often fails to improve hemodynamic parameters in severely intoxicated patients (2). Because of these failures, efforts have focused on the development of novel treatments for this poisoning (3, 4). One, hyperinsulinemia/euglycemia

presentation, was 1094 ng/mL; a corresponding norverapamil level was 1253 ng/ mL (therapeutic concentration: 100–600 ng/mL) (6).

Patient 3. A 48-year-old nondiabetic male with hypertension, chronic obstructive pulmonary disease, congestive heart failure, and depression, ingested an unknown amount of extended-release diltiazem in a witnessed ingestion. He became hemodynamically unstable in the emergency department, failing to respond to calcium, IV fluids, dopamine, and dobutamine. He received an insulin infusion at a rate of 75 IU/kg/h, which improved his blood pressure

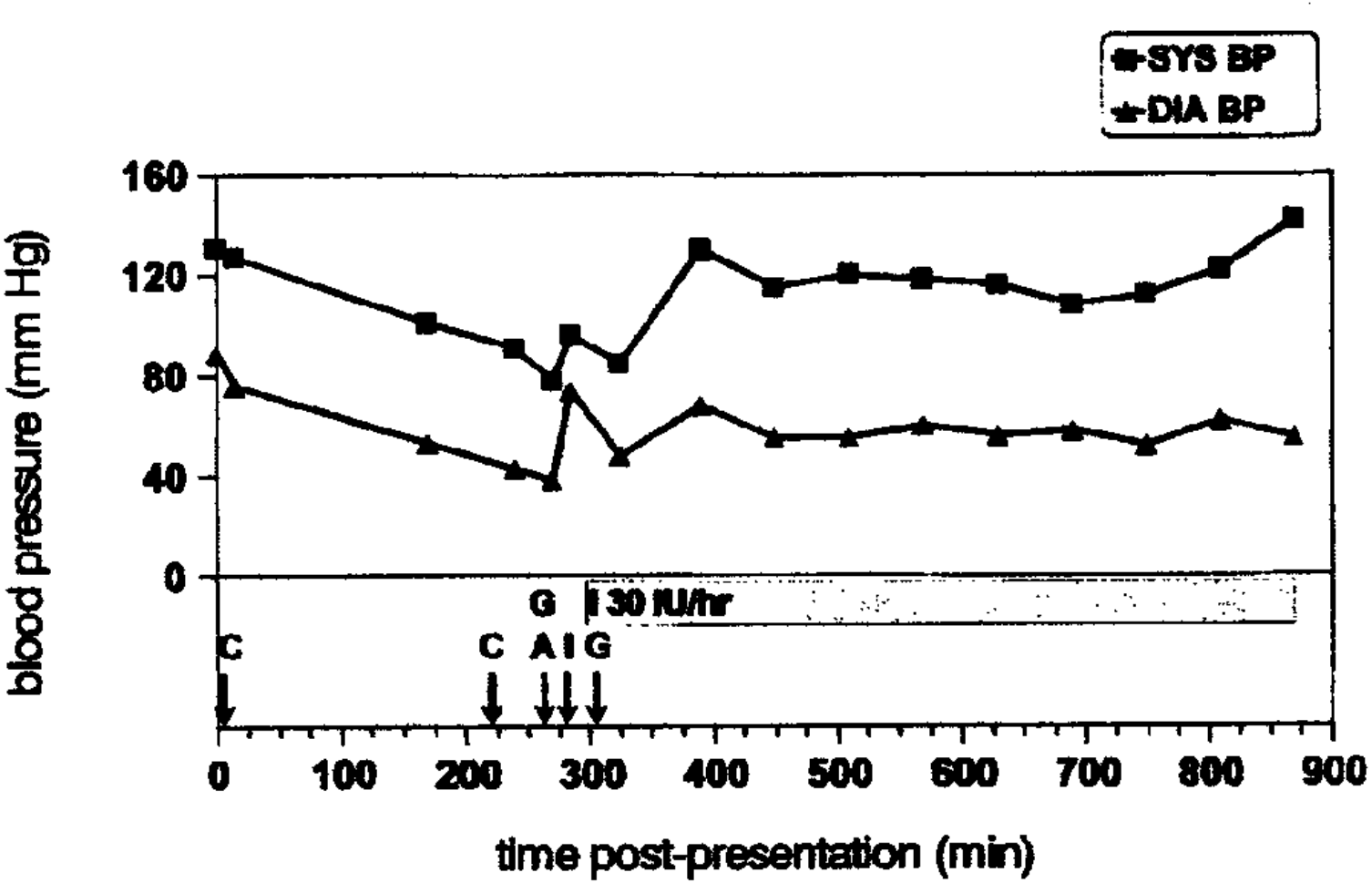
Boyer et al. Ped Emerg Care 2002; 18: 36

HIE THERAPY

- Insulin / Glucose
  - Animal data
  - Human case series and reports
  - Exact mechanism unknown – ?
    Improved cardiac CHO utilization

- High Dose !!
  - Insulin 1 U/kg bolus
  - Insulin infusion 0.5 – 1 U/kg/hour

High Dose Insulin / Euglycemia



CCB/BB Poisoning - Insulin

TABLE 1

Protocol for hyperinsulinemia/euglycemia in the treatment of calcium channel antagonist poisoning

1. Measure bedside capillary glucose; measure electrolytes, including potassium:
   a. If glucose <200, administer 1 ampule D_{50} (for adults); or 0.25 gm/kg dextrose as a D25 solution (for children).
   b. If potassium <2.5 mEq/dL, administer 40 mEq.
2. Administer intravenous bolus of insulin (1 U/kg).

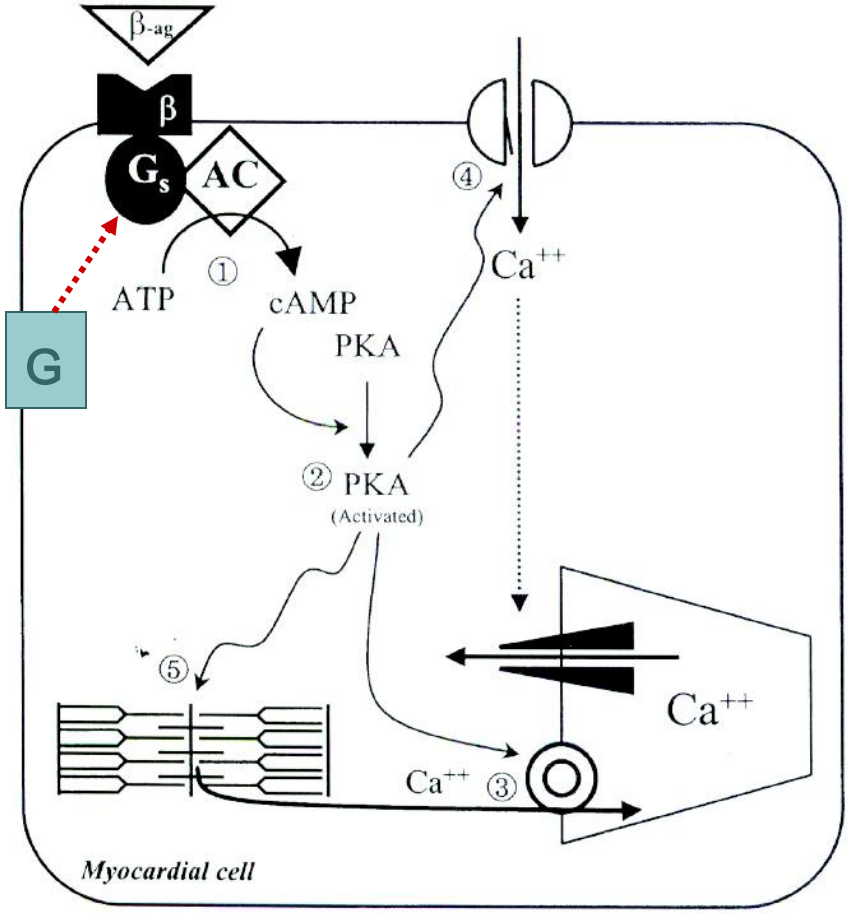
For adult and pediatric patients, start D_{10} ½ NSS infusion at a rate equal to 80% of maintenance rate.

Add 250 U regular insulin to 250 cc normal saline to make a solution of 1 U/mL. Infuse this solution at a rate of 0.5 U/kg/hr. Infusion rate may be increased to 1 U/kg/hr depending upon clinical response. Targets for therapy are systolic blood pressure greater than 100 mm/Hg and heart rate greater than 50.

Recheck serum capillary glucose every 20 minutes for the first hour of the insulin infusion, and hourly thereafter. Recheck serum potassium hourly; replete if <2.5 mEq/dL.

Boyer et al. Ped Emerg Care 2002; 18: 36

Glucagon Mechanism



Glucagon

Liver
Adipose → cAMP → glycogenolysis
gluconeogenesis
ketogenesis

HEART → cAMP → INOTROPY
CHRONOTROPY

GI → Relaxation

Glucagon – Mechanism Action

Cardiac Mechanism

1. Glucagon Receptor (Gs/GTP)
   - Increase in cAMP

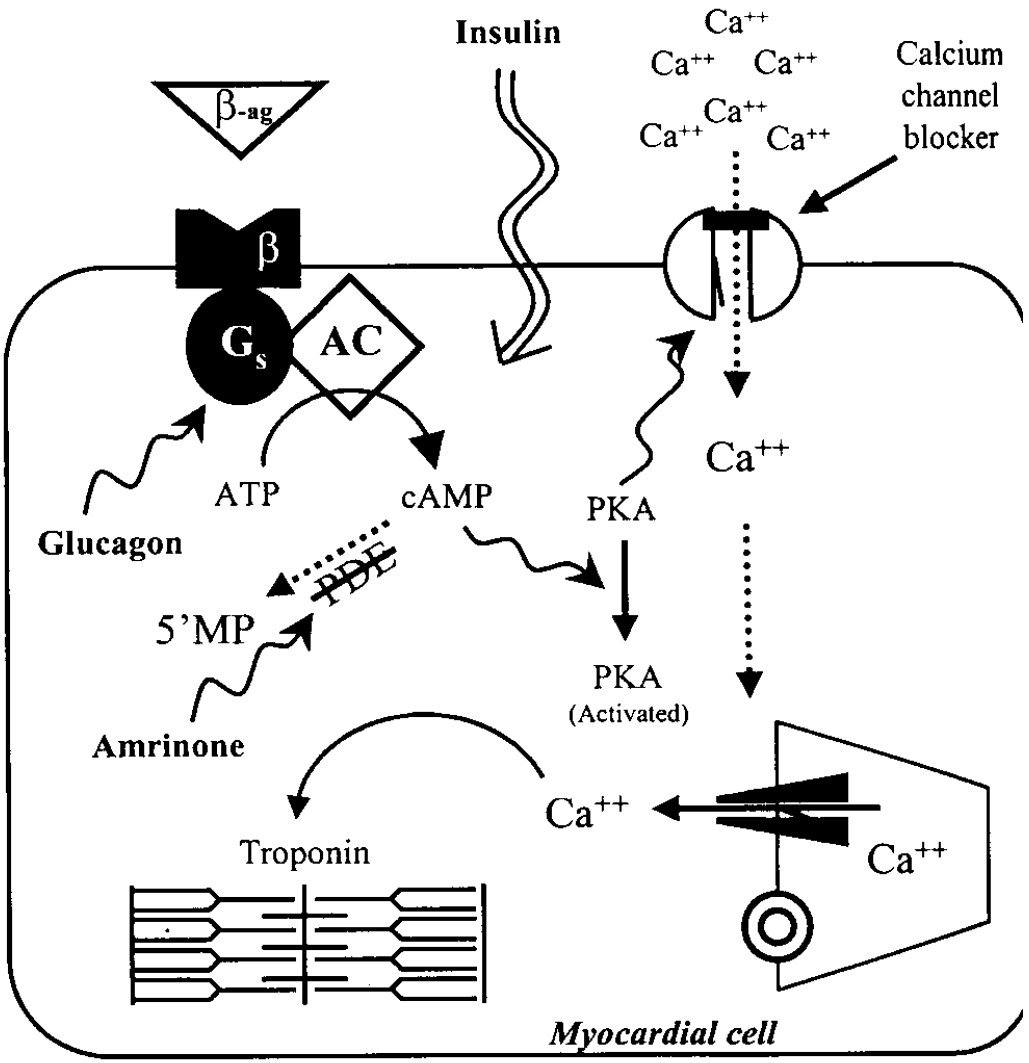
2. Mini-Glucagon
   - Phopholipase A2 → ↑Arachidonic Ac.

GLUCAGON

- Dose
  - 5-10 mg over 1-2 minutes
  - Infusion: Response dose / hour
- Adverse effects
  - Nausea / vomiting
  - Hyperglycemia
  - Rare allergy (recombinant)

CCB - Antidotes

- Calcium
- Catecholamine
- Insulin
- Glucagon
- PDE



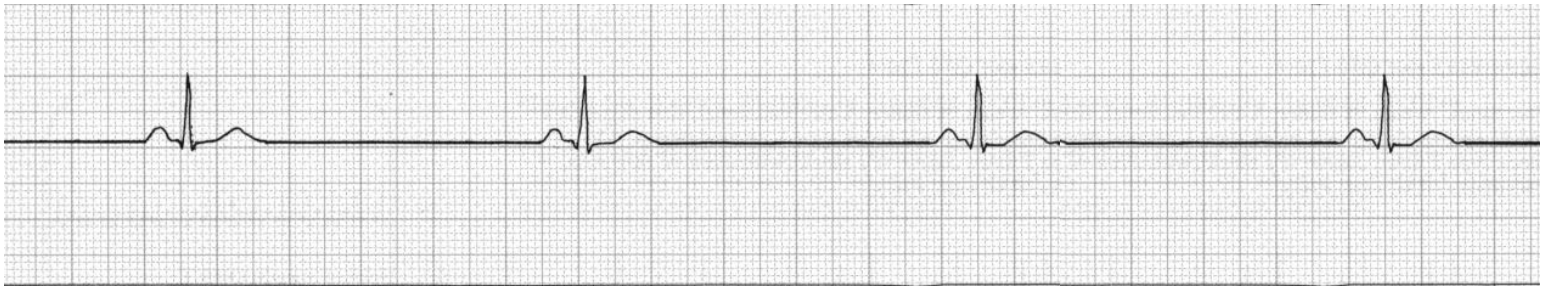
Case 2: ……..

- 65 year old male found comatose at home
- En route: BP 80/s HR: 30 RR: 10
- On arrival, he is ….

Case 2: ……..

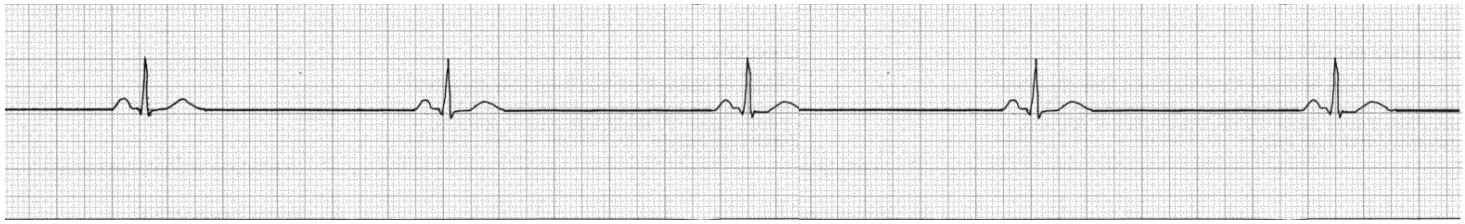
- 65 year old male found comatose at home
- En route: BP 80/s HR: 30 RR: 10
- On arrival, he is …. intubated

Case 2. "……　　"



Case 2:

1. Atropine 1 mg given → no response
2. Bolus 500 cc NS → no response



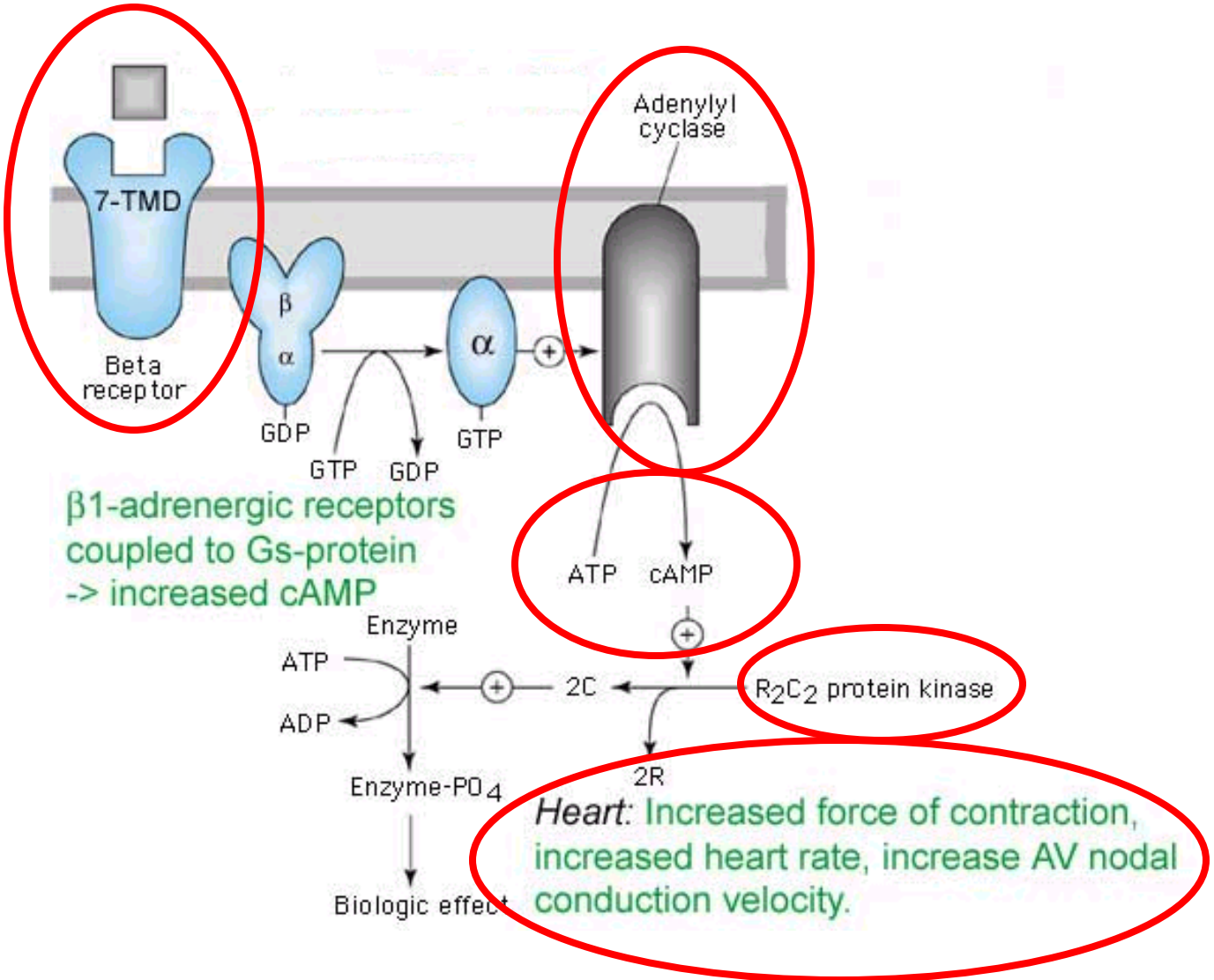
3. Atropine – 2mg → no response
4. Pacing Paddles placed → BP drops
5. Dopamine infusion started (at 20 ug/kg/min) →HR at 40

Case 2: .....

- Finally, family member brings in an empty bottle of propranalol (~ 5 grams missing)

Diagnosis: Beta Blocker overdose

Beta Blockers



BB MANAGEMENT

- Initial / Supportive
  - ABCs
  - Fluids
  - Atropine?
  - Decontamination
- Pharmacotherapy
  - Catecholamines
  - Glucagon
  - Insulin/Glucose (HIE)
  - Cardiac pacing
  - IA Balloon Pump

BB DECON

- BE AGGRESSIVE!!
  - Gastric Lavage (???)
  - SD Activated Charcoal (all)
  - MD Activated Charcoal (SR preps)
  - Whole Bowel Irrigation (SR preps)
  - Hemodialysis – No role for BB except….

BB DECON

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  - Hemodialysis – No role for BB except…. …..ATENOLOL

Beta Blockers

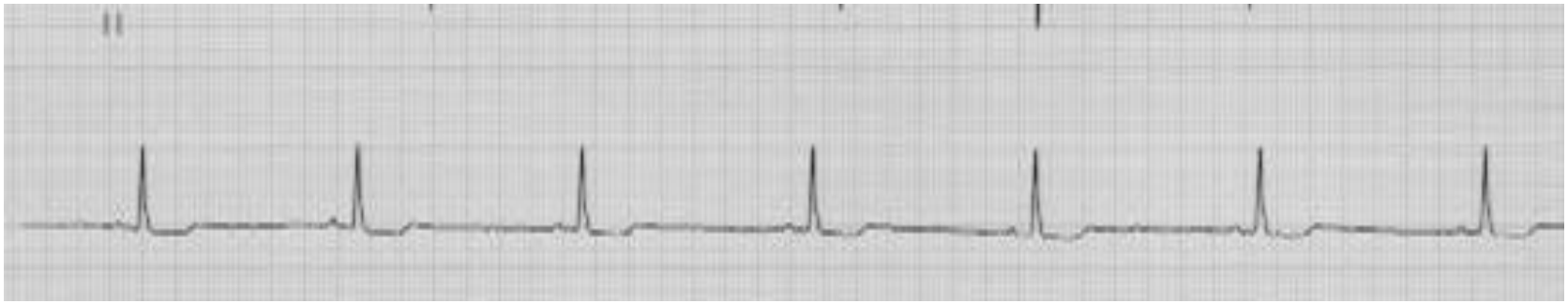
Treatment of Bradycardia:

- ABC's
- Circulatory support
  - ACLS guidelines:
    - hypotension: fluids, dopamine
    - bradycardia: atropine, pacers, dopamine

Beta Blockers

1. Atropine: limited effects

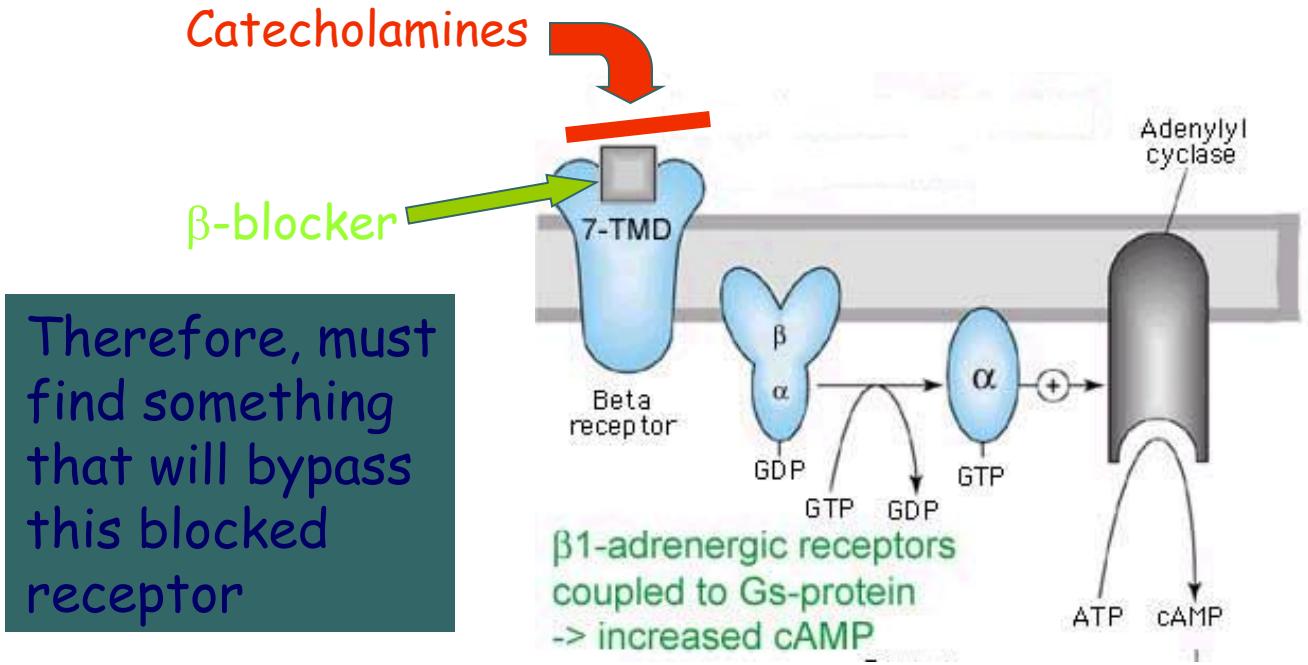
→ Increases HR only 22% of the time



Beta Blockers

2. Catecholamines (epi, dobutamine, dopamine) often are ineffective in treating β-blocker effect.

→ Dopamine: 25% effective, Epi: 67% effective



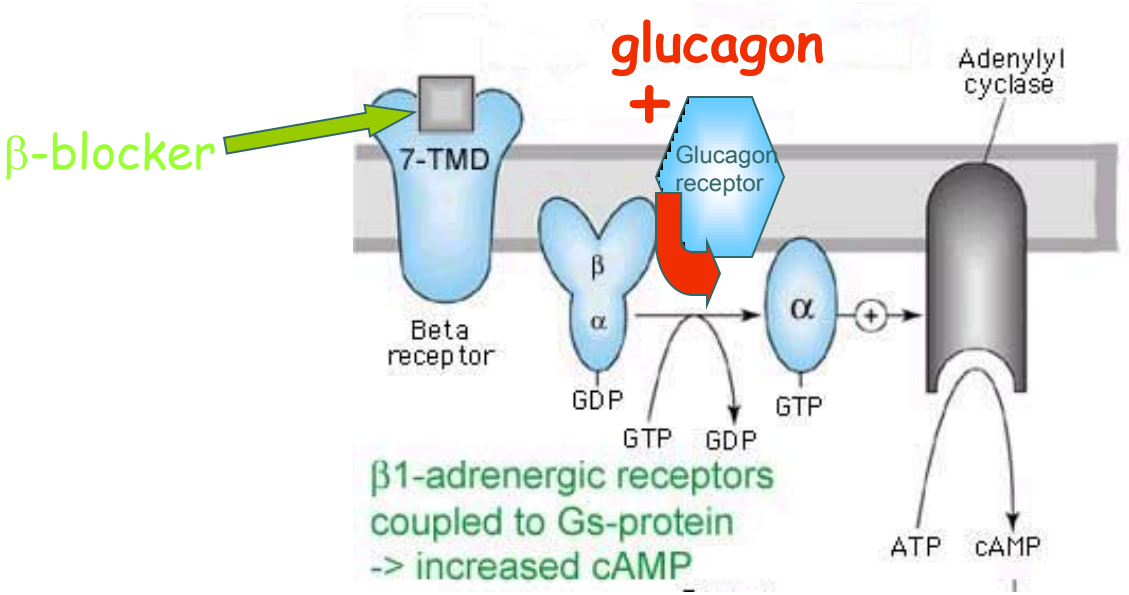
Therefore, must find something that will bypass this blocked receptor

Beta Blockers

3. Glucagon

→Drug of choice for β-blocker (& CCB) O.D.

- Secreted by pancreas secondary to hypoglycemia
- Glucagon Receptors found in heart muscle
- Acts by stimulating adenylate cyclase.
  - independent of β-receptor



Beta Blockers

Glucagon

- The final outcome:
  - ➢ Positive chronotropic and inotropic effects despite β-adrenergic blockade.
  - ➢ Onset within minutes, peak levels in 5-7 minutes, duration of action of 10-15 minutes.

Beta Blockers

Glucagon - evidence

Many animal studies of glucagon's cardiac effects

Human Studies

→About 15-20 case reports of glucagon benefit, when other modalities failed.

→Only two case reports of glucagon benefit where glucagon was the sole agent used.

No prospective studies exist

Beta Blockers

Glucagon - How to give

- Available as a 1-unit (1-mg) or 10-unit (10-mg) lyophilized powder accompanied by 1 cc or 10 cc diluent

- Initial dose (adults or pediatrics):
  - 50ug/kg (3.5 mg in 70 kg) infused over 1 min.
    - If ineffective, higher doses (up to 10 mg) can be tried.

- infusion:
  - 2-5 mg/hr in D5W (0.1 mg/kg/hr – Peds). ("response dose"/hr)

Beta Blockers

Glucagon - precautions

Side effects from glucagon include:

i. Dose-dependent nausea and vomiting → aspiration
ii. Hyperglycemia, hypokalemia (not clinically important)
iii. Some reports of treatment failure

Beta Blockers

4. Insulin??

Shown to have positive inotropic effects on animal and human myocardium

Beta Blockers

Insulin in Acute Beta Blocker OD.

Kerns, *et al.* Ann Em Medicine. 1997. 29:748-757

24 dogs, anesthetized and infused with Inderal.

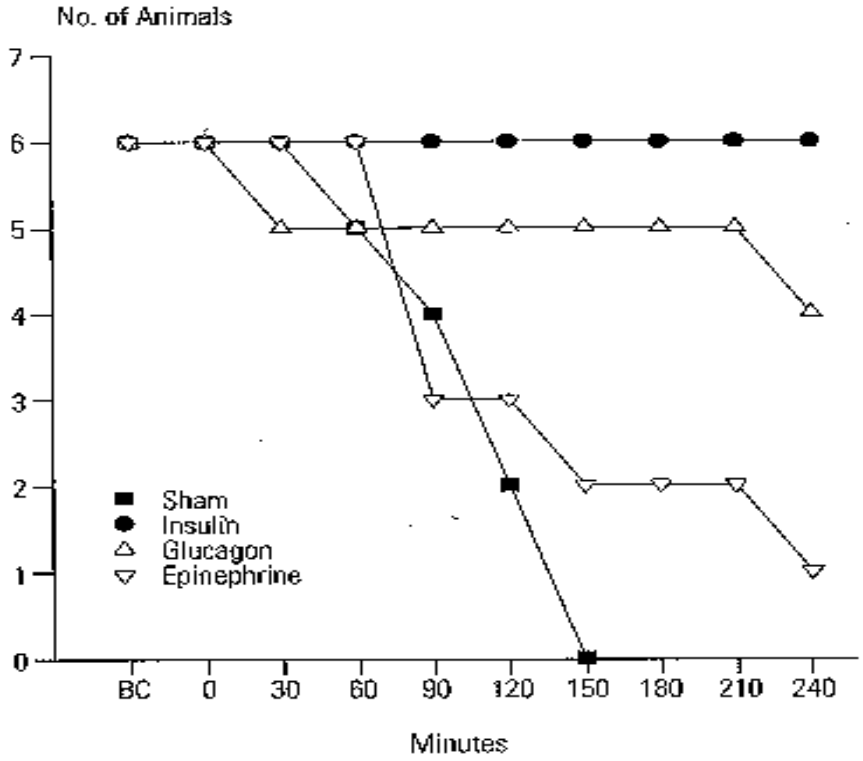
Hemodynamics before & after treatment with:

i. Normal Saline (n=6)
ii. Insulin (4IU/min) + glucose PRN (n=6)
iii. Glucagon (50 ug/kg) + infusion (n=6)
iv. Epinephrine (1ug/kg/min) + titrated (n=6)

Beta Blockers

Results:

6/6 Controls died within 150 min
5/6 Epinephrine animals died after 240 min
2/6 Glucagon animals died " " "
0/6 Insulin animals died " " "



Kaplan-Meier Survival Curve
Insulin vs. Glucagon ($p<0.05$)
Insulin vs. Epinephrine ($p<0.02$)

Beta Blockers

Insulin in Acute Beta Blocker OD.

Pathophysiology

1. May enhance catecholamine release
2. May enhance myocardial substrate use
   - In normal myocardium, FFA are preferred substrate.
   - In poisoned myocardium, glucose becomes 1º substrate
3. May increase cytosolic calcium

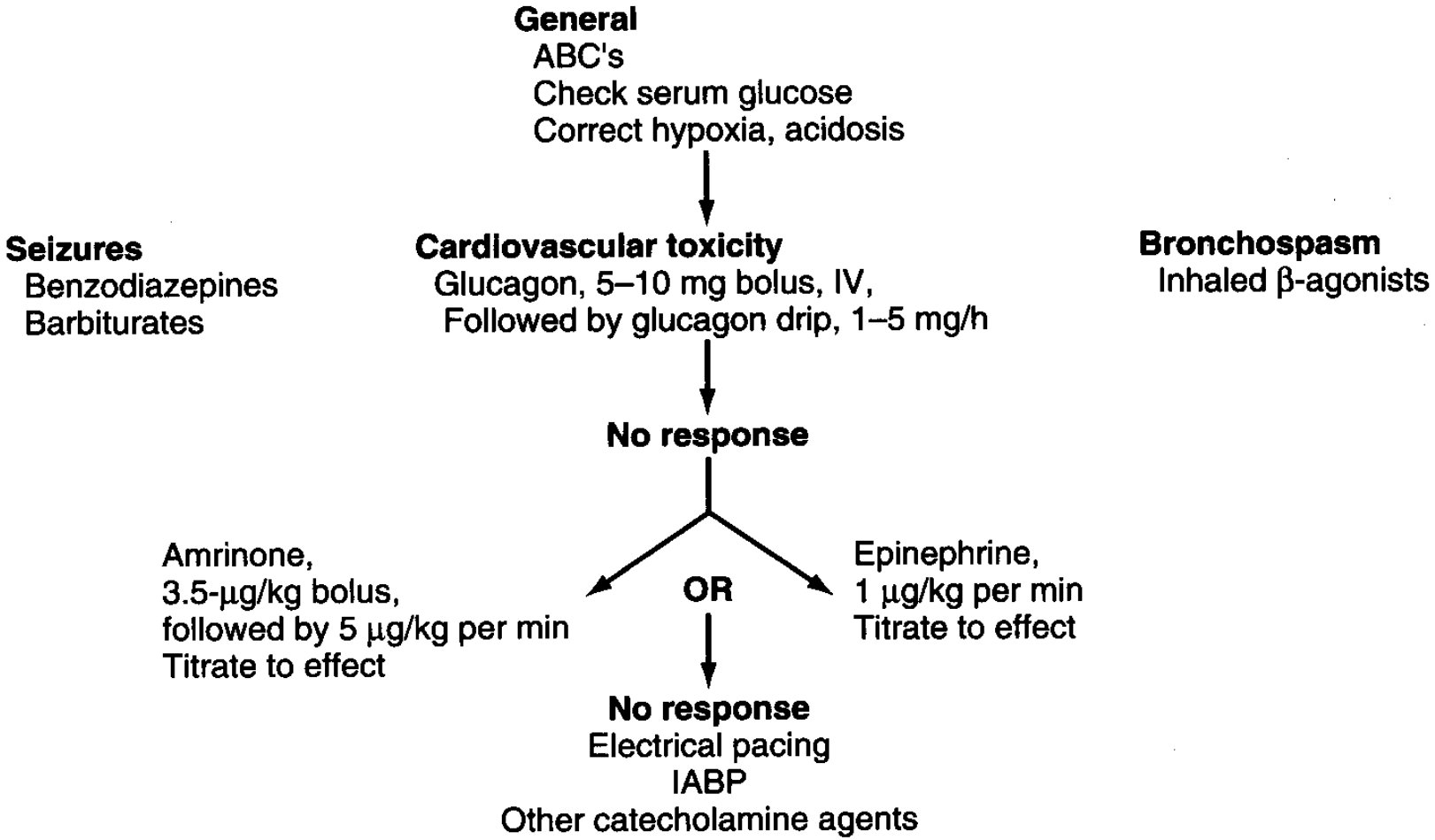
Beta Blockers

The Use of High Dose Insulin –Glucose Euglycemia in Beta-Blocker Overdose: A Case Report

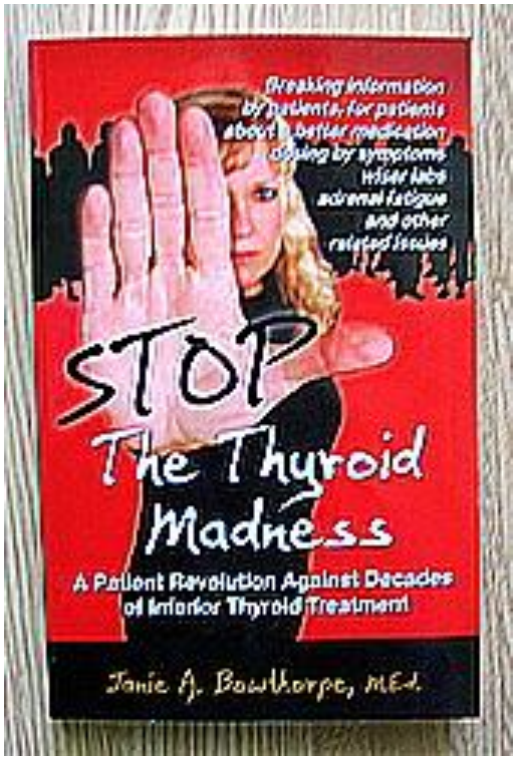
Page CB, Hacket LP, Isbister GK. J Med Tox 2009;5(3):139-142.

- Utilized 4 boluses of 1-2 IU/Kg and infusions of 10 IU/kg/hr

β Blocker - Management



- **Major Pharmaceuticals Discontinuing Their Natural Desiccated Thyroid Drugs**
- August 2009



The pharmaceutical manufacturer Major has reportedly received notice from the FDA that their complete line of natural desiccated thyroid drugs can no longer be manufactured, and that the designation of DESI -- Drug Efficacy Study Implementation -- can no longer be used for these drugs

Case 3

- 54 year old male brought in by police because of extreme agitation.
- While being subdued, patient becomes lethargic, and begins to show bizarre focal neurological deficits.
- Vitals: BP: 120/80 HR: 110 RR: 20 T=37.5
- Glucose: 30
- After 1 amp of D50, patient's neuro findings resolve, and he becomes more alert.

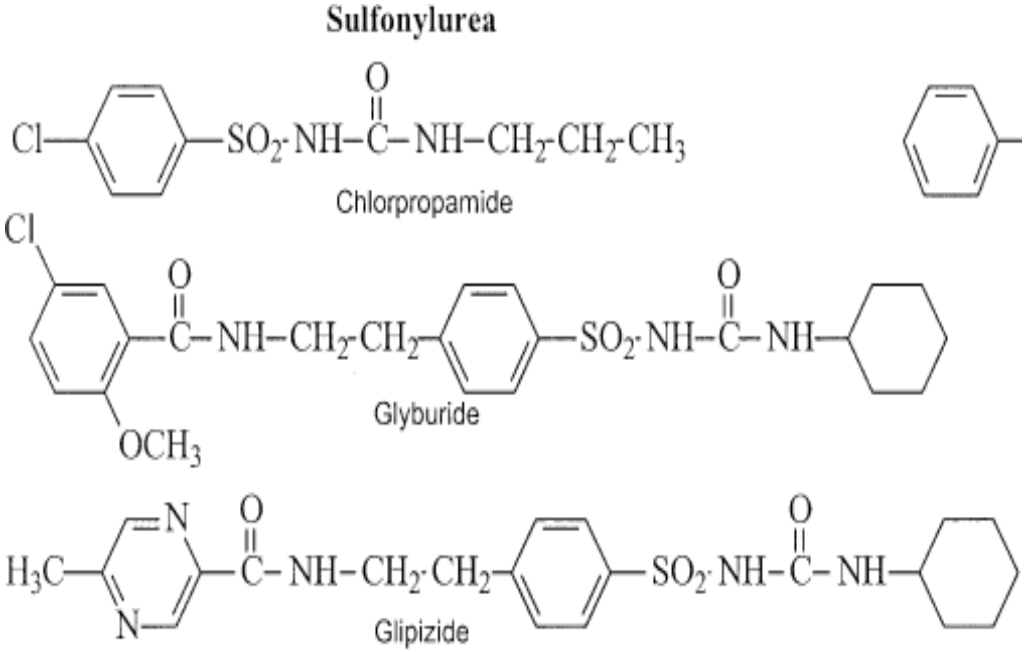
Case 3

- After an hour on a dextrose drip, patient again becomes lethargic and agitated.
- Repeated glucose: 40
- Another D50 given with resolution of Sx
- This cycle of hypoglycemia-induced symptoms returns several times

Case 3

- Inside patient's pocket is an empty bottle of glipizide XL
- Diagnosis: Sulfonylurea overdose

Sulfonylureas

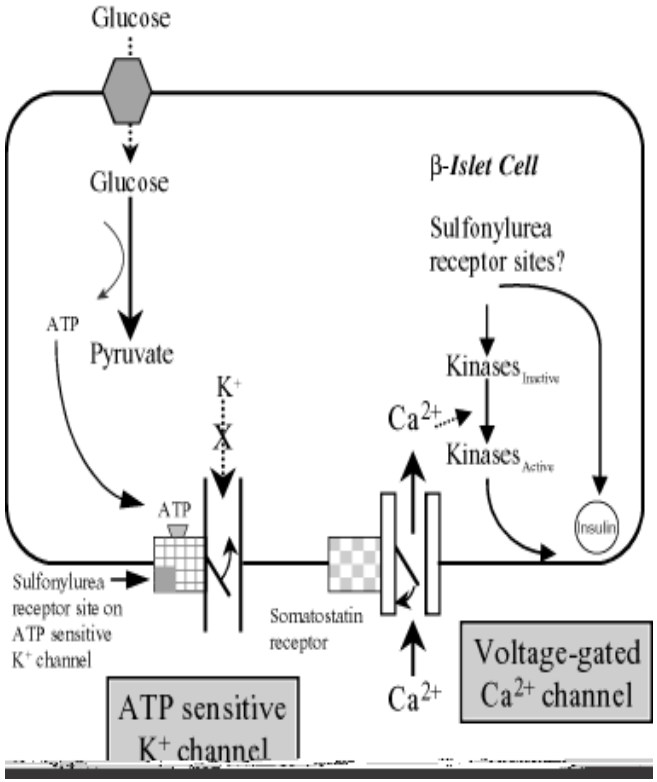


Sulfonylureas

Gen.	Generic name	Trade name	Time to peak (hr)	Duration of Action (hr)
First	Chlorpropamide	Diabinase	2-7	60
First	Tolbutamide	Orinase	3-4	6-12
Second	Glipizide	Glucatrol (XL)	1-3 (6-12)	12-24 (24)
Second	Glyburide	Micronase DiaBeta	2-6	12-24
Third	Glimepiride	Amaryl	2-3	16-24

Mechanism of Action

- Sulfonylureas keep the potassium efflux channel closed.
- This keeps the cell depolarized which allows the voltage-gated calcium channel to remain open.
- This stimulates insulin release.



Sulfonylureas

- Since sulfonylureas stimulate insulin release, this can result in prolonged hypoglycemia.
- Continued doses of dextrose will continue to stimulate insulin release.
- Octreotide works by antagonizing insulin release. Exact mechanism is still being debated.

Key Facts

- A retrospective study showed 4 of 25 patients developed delayed hypoglycemia including 1 at 16 hours post ingestion.
- If a sulfonylurea is ingested, a minimum of 24 hours of observation is recommended.

- Dextrose
  - Initial management for all hypoglycemia. BUT:
  - Glucose itself stimulates release of insulin.
  - Results in recurrent, rebound hypoglycemia.
  - Requires ICU monitoring, blood glucose measurements q 20-60 minutes
  - Duration of treatment can be very long (>2-4 days)

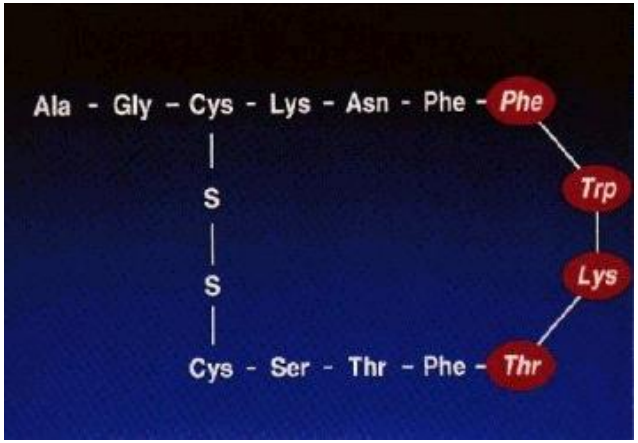
Glucagon

- Raises glucose levels by stimulating glycogenolysis.
- Effective only if sufficient glycogen present, has no effects in starvation, chronic hypoglycemia.
- Since it stimulates Insulin secretion, it is detrimental and contraindicated in Sulfonylurea O.D.

Octreotide

- The dose is 1-2 mcg / Kg bolus IV or SC.
- Some papers suggest a continuous infusion while others suggest an every 8 hour dosing regimen.
- If placed on an octreotide regimen, the octreotide must be off a minimum of 24 hours without another episode of hypoglycemia before discharge.

Octreotide:



- Long-acting somatostatin analogue
- suppresses hormone release
  - GH, gastrin, glucagon, and, most interestingly,

INSULIN

Sulfonylureas

1. Boyle PJ. J Clin Endocrin Metab. 1993

- 8 normal subjects received O.D. of glipizide on 3 occasions.
  1. D50 + dextrose infusion
  2. D50 + octreotide (30 ng/kg/min)
  3. D50 + diazoxide (300 mg q4h)

- Number of patients with hypoglycemic episodes
- Frequency of rebound hypoglycemia after treatment end

- Dextrose requirement significantly lower in octreotide group ($p<0001$)
- Rebound hypoglycemia occurred in all patients receiving dextrose or diazoxide, but only 2/8 in octreotide group.

Sulfonylureas

2. McLaughlin, et al Ann Em Med, Aug. 2000

- 9 patients treated with Octreotide for sulfonylurea-induced hypoglycemia

- Before Octreotide therapy:
  - Number of rebound hypoglycemic events : 28
  - Number of amps of D50 given: 25

- Following the administration of Octreotide (SC):
  - Number of hypoglycemic events: 2
  - Number of amps of D50 given: 2

- NO MAJOR SIDE effects reported!!

Sulfonylureas

Octreotide - How to give

- Can be given IV or SQ
- Initial dose: 50 μg q 6 hours
  (Infusion doses: 100 μg /hr)
- Pediatric dose: 1.0 μg /kg (single case report)
- End point: 24-48 hrs (remember: PO intake is the optimal glucose source)

Sulfonylureas

Octreotide: Advantages/Side effects

- Can be given both IV or SC.
- Very inexpensive, → $11 for a 100 ug vial
- Highly efficacious and safe in multiple studies
  - argued that the use of octreotide can prevent admission to the ICU
- NO MAJOR SIDE effects reported

Comparison of Octreotide and Standard Therapy Versus Standard Therapy Alone for the Treatment of Sulfonylurea-Induced Hypoglycemia

Charles J. Fasano, DO
Gerald O'Malley, DO
Paul Dominici, MD
Elizabeth Aguilera, MD
Daniel R. Latta, BS

From the Department of Emergency Medicine, Albert Einstein Medical Center, Philadelphia, PA.

- Prospective, double-blind, placebo controlled trial of all patients with hypoglycemia on a sulfonylurea

- Randomized to:
  - 1 ampule of 50% dextrose IV and carbohydrates orally plus placebo (1 mL of 0.9% NS SQ)
  - OR
  - Above plus1 dose of octreotide 75 mcg SQ

- 40 patients (18 placebo; 22 octreotide)
  - Mean glucose similar
    - Placebo, 35 mg/dL
    - Octreotide 39 mg/dL
- Octreotide patients consistently higher during the first 8 hours
- Recurrent hypoglycemia occurred less frequently in octreotide group

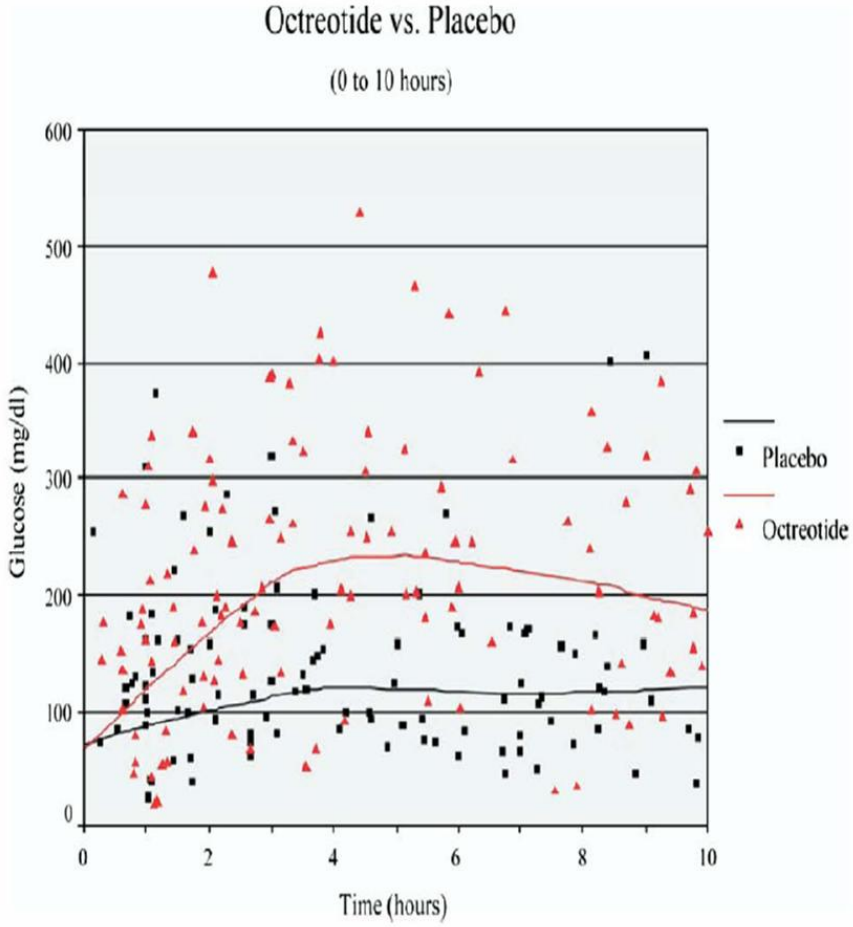


Figure 2. Serum glucose octreotide versus placebo.

Vasopressin

- Vasopressin treatment for cyclic antidepressant overdose.
  - Barry JD, Durkovich DW, Williams SR. J Emerg Med. 2006 Jul;31(1):65-8.
- Massive caffeine overdose requiring vasopressin infusion and hemodialysis.
  - Holstege CP, Hunter Y, Baer AB, Savory J, Bruns DE, Boyd JC. J Toxicol Clin Toxicol. 2003;41(7):1003-7.

Vasopressin

- The use of vasopressin in the setting of recalcitrant hypotension due to calcium channel blocker overdose. Kanagarajan K et al., Clin Tox 2007:45; 56-59
- successful use of vasopressin in two patients with massive CCB overdoses in whom hypotension was unresponsive to calcium, glucagon, insulin, and conventional vasopressor therapies

Conclusions

- CCB and BB are different
- BB – reach for glucagon
- CCB - reach for HIE

Conclusions

- Octreotide is essential for Sulfonylureas overdoses
- Octreotide may save an ICU admission
- Vasopressin as a pressor … when everything else fails or even consider starting its use earlier

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- The American Association of Poison Control Centers (AAPCC)
- AAPCC's Specialist in Poison Information (SPI) Committee
- The Children's Safety Network (CSN)
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