My Therapy is Killing the Patient Faster Than the Overdose

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April 2025

Conflict of Interest

- No one involved in the development of the educational content has a relevant financial relationship to disclose

Objectives

- Evaluate clinical scenarios to identify when escalating therapy may paradoxically lead to patient harm rather than benefit.
- Apply risk-benefit analysis to adjust therapeutic regimens, ensuring that selected interventions are both safe and efficacious.

- P.S. I would like to acknowledge and thank everyone (JP) who created these objectives

Frank opinions

- We are too excited to use antidotes to use them properly
- We use them too infrequently to know the nuances
- We don’t use or have time to use Poison Control enough
- Most of our literature is case reports/series or retrospective database mining rife with confounding errors and confirmation biases
  - *In an era now too of rampant academic dishonesty in the medical literature*
- So I bring you more of the same from my perspective which is a bit different

Overall stats – importance of supportive care

- ~3,000,000 poison center calls a year
  - At most 400,000 intentionals
  - At most 3,000 deaths (remember these are calls, who calls on opiates or alcohol or so on?)
- *So 0.1% mortality for all or 1% for intentionals –*
  - *I rounded down to 300k*
- ~300k admission, 35k-40k major effects, ~70k ICU, 35k-40k major effects
  - Let's call it 365,000 admission 73k ICU and 36.5 major effects
  - In 2023 there were 6,120 hosps
  - So any one hospital averages 60 adm, 2 ICU and 6 major effect patients/year

Numbers are conservative estimations I generated from numerous NPDS summaries of past 10years and online browser searches- VOODOO numbers if you will

CCB HIE case with oops

- So, shortly after I was removed from the ER I was again sadly (but fortunate in the practice change it caused) to be involved with an oops case
- And it taught me a new way to look at how I had been approaching antidotes and the medical literature I was using for them
- Let’s see the case

180 HYPERINSULIN THERAPY IN THE TREATMENT OF VERAPAMIL OVERDOSE.

Place R, Carlson A, Leiken J, Hanashiro P. *Rush-Presbyterian-St. Luke's Medical Center, Toxikon, Chicago, IL.*

Background: Hyperinsulinemia-euglycemia (HIE) has been demonstrated to be useful in the treatment of calcium antagonist (CA) overdose. We present a case of CA toxicity in which hemodynamic data was obtained, and in which the patient responded to a higher dose of insulin than previously reported. Case Report: A 49-year-old male (100 kg) ingested 80 tablets of 240 mg Verapamil SR. At presentation he was alert but hypotensive, requiring dopamine. At hour 18 he developed 3° AV block, which required transvenous pacing. Serum verapamil level was 4620 ng/mL (norverapamil 2180 ng/mLl). Cardiogenic shock worsened despite therapy with calcium chloride (4 g), glucagon (15 mg), and norepinephrine (20 µg/kg/min). HIE therapy with 1 U/kg of insulin and continuous glucose was planned. Inadvertently, 1000 U of insulin was administered. Rapid hemodynamic improvement ensued: Hemodynamic data (Swan-Ganz)

What have we observed about HIE – hyperinsulinemic euglycemia in this oops

- It works quickly …*“but wait Frank it may have been the timing”*
- So why didn’t the glucose drop? Or anything else?
- If the hyperglycemia and the CV effects go hand in hand then we can use glucose+BP+HR as monitoring parameters for efficacy effect and toxicity…
  - *“so, you don’t use concomitant D10 or D20?”*
- We don’t but ultimate decision rests with primary team
  - *“is there any support for this approach”*
  - *There are no comparative trials, just circumstantial and empiric evidence*

continued

- *But why risk it, let's just give the dextrose*
- Recommended as D10W-D20W at 100ml/hr so 2.4-4.8L/day
  - On top of the fluid from pressors
  - *How many of you have titrated up as you titrate up the insulin dose?*
  - *How many have seen the reports of prolonged hypoglycemia afterwards because of insulin accumulation?*
  - *Who has ever calculated the caloric value of that prophylactic dextrose?*
- D20W at 100ml/hr = 3.3gm dextrose/hr = 80gm/day =272 kcal
  - How is that protective against even the first 1 unit/kg bolus?

So the Brady Hypo patient

- Could be CCB, BB, dig, alpha agonists, late sodium channel blockers…along with many others
- Only one with lab confirmation is digoxin
- If > one class in the history or there is no history or …who believes the history anyway… how should we approach
- The thoughtful way using probabilities, timing, access, onset AND time to peak effects of the agents we will use
- Most prescribed, speed of diagnosis, stocking location, speed of prep and administration,

Nuances (voodoo) for selecting treatment in brady hypo

- Is the glucose between 200-300 and mental status is remarkably good for MAP?
  - Use HIE early (caution if known to be amlodipine)
  - With Hx of DM give bolus and watch for 5-15minutes before infusion
- Evidence of QRS widening
  - Bolus bicarb and look for narrowing within 1-3 minutes
- All this can be done while waiting for dig
  - With suggestive ECG and strong Hx – give 1-2 vials and observe for an hour.
- Best pressor to use is the formulary one in your ED

General issues

- Fluid volumes
- Treating known adverse effects with prophylactic treatment can be
  - unnecessary,
  - interfere with monitoring parameters,
  - add or obscure findings of adverse effects

- On to aspirin (aka most iatrogenic)

ASA and alkalinization

- Conventional start is 3 amps in 1LD5W at 150ml/hr that usually ends up at 200-250ml/hr
- But what is the predominant form of OD? Chronic
- Who OD's on ASA? *Old people*
- Do old people like 3.6-6l of fluid a day?
- A good addition to persuading renal to do dialysis if indicated.
  - *For the tox nerds in audience…how is this not also forced diuresis?*
- And think about baseline urine pH. The higher it is the less benefit likely to occur suggest the transition to dialysis needs to be quicker

ASA – Intubation most dangerous time

- No ventilator can match a young healthy adult's ventilation capability
- Intubating them because of tachypnea without recognizing concomitant hypernea and appropriate compensation artificially generating respiratory failure and air trapping
- The bar for prophylactic intubation needs to be higher with ASA Ods
- We may perform intubation but we can be present for 5 minutes (that is all it takes) and recommend… Yikes …..Extubation

Another procedure we don’t own but could do better with is RRT

- Criteria for what is dialyzable is based on studies in CKD patients on maintenance RRT (HD)
- These studies were done when at steady-state therapeutic conditions, fasting without that day’s medications and using formulas designed for post absorptive, post-distributive conditions.
- Are all overdose patients post-absorptive, post-distributive when they present? (let alone are there SR dosage forms out there)
- The data is predominantly underestimating the impact HD could have earlier on or during high likelihood prolonged absorptive states
- This should be a research area we explore

Gibson TP. Designing dialysis drug studies. Int J Artif Organs. 1985 Mar;8(2):69-70. PMID: 3988364. Gibson TP. Problems in designing hemodialysis drug studies. Pharmacotherapy. 1985 Jan-Feb;5(1):23-9. doi: 10.1002/j.1875-9114.1985.tb04453.x. PMID: 3982975.

APAP and NAC

- Many people know I could go on forever on this topic
- I don’t know if there is risk with too much NAC but in animal models there is evidence of thresholds beyond which no improvement is seen. If true in humans we may be risking fluid issues at a minimum
- Empirically in the days before FDA approval of Acetadote, IV bags of oral NAC 70mg/kg to be given every 4 hours over one hour were in 250ml bags which was doubled with simultaneous HD
  - Not really published anywhere I can find because we never though it important to publish since everyone knew

the bolus – infusion dilemma

- It is soooo popular these days to bolus something then start an infusion because everyone is too busy to stand there and wait and see how long the bolus might last.
  - Please remember that sometimes the mechanisms require it to be one of the other not both
    - QRS widening from Na-channel blockers requires bolus therapy
    - Systemic or urinary alkalinization requires infusion
  - Please at least try to wait for a need to retreat with naloxone to better gauge the need for an infusion and be more confident of the rate selection
  - Intravenous Lipid Emulsion works by bolus (as per lipid shuttle mechanism) than infusions
  - Think back on HIE and concomitant dextrose

Indication without drug therapy?

- In 2023 more flumazenil (858) was used in PCC cases than HIE (688), ILE (492), l-carnitine (607), and digoxin immune fragment (364).
  - *PCC data so with all the cautions of selection bias being applicable*
- With everyone tell me how dangerous benzos are and all the respiratory failure all around b/c of them, why isn't it used as commonly as naloxone?
  - *Seizures?* Might seize vs respiratory failure, is that really a question? Why not use barbs then?
  - BTW, I am not afraid of flumazenil but in specific settings associated with known benzo use not in undifferentiated possibly overdosed patients
  - Also, and with limited clinical experience and some conflicting case series…flumazenil works for paradoxical agitation in pediatrics (voodoo)
- *Gummin DD, Mowry JB, Beuhler MC, et all. 2023 Annual Report of the National Poison Center Data System (NPDS) from America's Poison Centers: 41st Annual Report. DOI: 10.1080/15563650.2024.2412423*

Financial iatrogenics

- The targeting of old past patent protection drugs with low volume sales but high acuity patient status identifications has made antidotes a priority target for predatory acquisition for aggressive pricing
  - Fomepizole $10k/4 vial package
  - Glucagon 10mg/hr infusion costing up to $2,000/hr

Heindel GA, Trella JD, Osterhoult KC. Rising cost of antidotes in the U.S: cost comparison 2010-2015 Clin Tox DOI: 10-1080/15563650.2017.1286014

Other things to watch

- ILE and hydroxycobalamin can interfere with common lab assays (and why doesn’t anyone consider this when we try to assess how it works)
- HIE (with D20W running alongside) probably does too
- Speaking of ILE, why aren’t we considering the possibility it is affecting concomitant therapies? It does not know to only bind toxins

The ones that don’t kill that people fear do kill

- Flumazenil
- EDTA without prior BAL for lead poisoning
- Charcoal

General factors to consider

- Is the antidote actually indicated? Or am I treating ourselves?
- Is there a need for therapy I am not using?
- What are the anticipated adverse effects (and are they the desired effects such as methemoglobinemia in carbon monoxide therapy)
- What drugs or labs may this interfere with?
- Are the unusual doses used giving us excipient or fluid risks not normally seen?
- What is the appropriate dose? (too often we dose to get rid of everything, experience shows that isn’t often necessary, give what you can)

I probably never even got to this slide so

- I left a lot unsaid b/c I wanted to give a sense of how much there is to consider for therapies infrequently used in highly acute situations
  - So call your PCC. Even if it doesn't help this patient it may help your next one or help you help someone else late on night when they call you for help
- I am happy to answer questions anytime
  - paloucek@uic.edu or on social media (Frank Paloucek in Pharmacist Hive Mind)

Case #1

A 58 y/o suspected CCB OD. MAP 62, HR 48. Has received 1 u/kg insulin bolus followed by 5 units/kg/hr (HIE). Primary team starts simultaneous D20W at 100 mL/hr. Over 6 hours, MAP, HR improve slightly, glucose is stable (180–220 mg/dL) but his u/o drops and peripheral edema is noted.

Which of the following best reflects the primary concern with the current management?

A. The insulin dose is too low to provide effective inotropy.

B. The patient should be transitioned to glucagon infusion instead of insulin.

C. The volume from D20W may be excessive and obscure hemodynamic assessment.

D. The patient's stable glucose indicates the need to increase the insulin infusion.

Answer and Rationale

Correct Answer:

C. The volume from D20W may be excessive and obscure hemodynamic assessment.

Rationale:

- Prophylactic dextrose infusions at high volumes (e.g., D20W at 100 mL/hr = ~2.4 L/day) may contribute to fluid overload, especially in patients already receiving pressors or other IV fluids.
- This can interfere with accurate monitoring of MAP, urine output, and mental status—critical parameters for titrating HIE therapy.
- Additionally, this fluid burden increases risk for iatrogenic harm.
- The glucose range suggests adequate support without need for escalation or substitution.

Case #2

An 81 y/o with confusion and tinnitus. She admits to “a few extra aspirin” x7d arthritis pain. RR 44 pCO_2 21 mmHg, pH 7.47. ASA is 48 mg/dL .

Standard 3 amps NaHCO3 in 1 L D5W at 200 mL/hr started. Six hours later, she is anuric and volume overloaded, with worsening mental status.

What was the most likely contributor to clinical worsening in this patient?

A. Underestimation of aspirin’s CNS effects due to low pCO_2.

B. Use of bicarbonate therapy in the absence of confirmed acidosis.

C. Failure to initiate hemodialysis early in chronic salicylate toxicity.

D. Inadequate alkalinization due to low fluid rate.

Answer and rationale

Correct Answer:

C. Failure to initiate hemodialysis early in chronic salicylate toxicity.

Rationale:

- Elderly patients with chronic salicylate toxicity are at increased risk for volume overload and neurotoxicity.
- Standard alkalinization protocols can introduce several liters of fluid, which may worsen renal clearance and obscure the clinical picture.
- In these cases, early transition to dialysis is often more appropriate. The presentation and labs point to ongoing accumulation, and high fluid volumes are not well tolerated.
- This highlights the risk of following a “standard protocol” without individualization.