The practicalities of managing beta-blocker toxicity – a District General Hospital experience of a severe propranolol overdose

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Case

A 54 year old patient admitted to the Emergency department following an intentional mixed overdose thought to have consisted of over 2g of propranolol along with lower but unknown quantities of sertraline, amitriptyline and tramadol. The patient was first seen approximately three hours post ingestion due to Glasgow coma score of less than 8 with a Heart rate of 55 beats per minute and mild QT prolongation (QTc 470ms) with no haemodynamic instability. Pupils were 5mm and sluggish bilaterally.

In hour four a rapid deterioration of physiology was witnessed with severe bradycardias down to 28 beats per minute associated with hypotension of 65mmHg systolic and prolongation of the QTc to 486ms. Initial resuscitation measures included 1L IV fluids, 3mg of atropine and increasing doses of peripheral adrenaline, all of which had little to no effect on heart rate or blood pressure. Treatment escalated aggressively as per overview below prior to transfer up to intensive care.

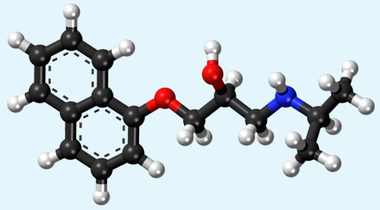
TOXBASE PROPRANOLOL OVERVIEW (2)

Preparations

- IR tablets (mg): 10, 40, 80, 160mg
- SR capsules (mg): 80, 160
- Oral solution

Properties

- Non-selective beta blockade
- Na+-channel blocker



Kinetics

- PEAK PLASMA CONC. @ 2 hours
- HALF-LIFE 3-6 hrs therapeutic use, 10-20 hrs with MR preps

Death — **Toxicity** — Survival

2g — 8g

Outcome and learning

The patient was off vasopressor support and extubated after 24 hours then discharged home 36 hours later. Severe propranolol toxicity works on both Beta Adrenergic receptors and sodium channels (1). Treating severe overdose is challenging due to complex pharmacology and therefore guidelines are a helpful tool to guide management. The practicalities of this can be difficult. TOXBASE (1) suggests a bolus of glucagon followed by a high dose infusion. We had difficulties with supply of glucagon in such quantities which meant a delay in administration and limited infusion doses before hospital supply ran out at around hour 9. It is thought that Glucagon is affective by bypassing the blocked Beta adrenoceptors to activate adenyl cyclase (2), Glucagon therapy in this setting has a limited evidence (2). Given this and the impracticality of its use at the doses required should it still feature so prominently in the TOXBASE guidelines when other more accessible and easily administered drugs such as intralipid could also be of benefit but do not feature in the TOXBASE guidelines (3)?

Management overview

- **Arterial line** & **Central venous access**
- **Atropine** boluses
- **Adrenaline** boluses then infusion
- Intubation and ventilation.
- 8.4% **sodium bicarbonate** bolus
- **Calcium gluconate** bolus
- **Intralipid** bolus followed by an infusion
- **Glucagon** bolus followed by infusion
- **High dose insulin euglycaemic therapy** (HIET) Bolus followed by Infusion (80 units/Hr)
- **Isoprenaline** infusion
- Close monitoring of glucose, K+ and pH (every 30 minutes)

Pharmacological Basis of Treatments

Treatment	Pharmacological and proposed physiological mechanisms	Summary of doses and management
Atropine	- Anti-cholinergic, antagonises parasympathetic tone at the muscarinic acetylcholine receptors.	Bradycardia management, 500mcg boluses up to 3mg total.
Adrenaline	- Directly compete at the beta receptors blocked by propranolol or other beta blocker. Adrenaline will increase afterload due to alpha adrenoceptor mediated vasoconstriction and may increase oxidative stress on the myocardium (4).	5 to 50mcg IV boluses, to affect. Infusion @ 0.01-0.1 mcg/kg/min. Bradycardia/negative inotropy may be refractory with overdose.
Glucagon	- Increases intracellular cAMP via G-protein stimulatory receptor that bypasses the beta-adrenoreceptor. Positive chronotropy/inotropy. (2&4)	Given as a 5mg bolus, followed by an infusion of 0.1mg/kg per hour
High-dose insulin euglycaemic treatment (HIET)	- Potent inotropy at high doses, increases calcium handling via the PI3K pathway. - Assists uptake of carbohydrate for the stressed myocardium. - Improves local microcirculation via endothelial nitric oxide synthase (eNOS) (4)	Given as a bolus dose of 1iu/kg (ensure K+ > 4.5mmol, glucose > 10mmol >L) and then infusion commenced 0.5 to 1.0iu/kg/hr up to 10iu/kg/hr. Becoming increasingly preferred. (4)
Sodium bicarbonate	- Mechanism is not fully appreciated, will vary by toxin and type of channel - high concentration gradient of Na+ and rise in pH may aid modulation at the Na+ channel (5). - Increased protein binding due to alkalaemia – possibly reduces free drug (5).	50 to 100ml boluses NaHCO3 8.4%. Aiming for pH 7.5 to 7.55, continue treatment if QRS complex widened (1).
Intralipid	- Propranolol is highly lipophilic. Proposed binding to reduce the availability of free drug, increases clearance (6).	1.5ml/kg 20% intralipid bolus. Followed by infusion at 15ml/kg/hr.

References
1) TOXBASE (2020) Propranolol guideline, www.toxbase.org
2) Bailey (2003) Glucagon in Beta blocker and calcium channel overdoses: A systematic review, Journal of toxicology, clinical toxicology, Vol 41 (5), p595-602
3) Walter et al. (2018), Review of management of cardiotoxic overdose and efficacy of delayed intralipid use, Journal of the intensive care society, Vol 19 (1), p50-55
4) Deranged physiology. Beta blocker overdose. Website: https://derangedphysiology.com/main/required-reading/pharmacology-and-toxicology/Chapter%205.2.5/beta-blocker-overdose
5) Bruccoleri et al. (2016). A Literature Review of the Use of Sodium Bicarbonate for the Treatment of QRS Widening. J Med Toxicol. 2016 Mar; 12(1): 121–129.
6) Macala et al. (2018) Low dose Intralipid resuscitation improves survival compared to ClinOleic in propranolol overdose in rats. PLoS One. 2018; 13(8): e0202871.