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

Dr S Bhattacharjee CT2, Dr N Stafford ST3
Anaesthetic Department, Dorset County Hospital

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 sluggishly 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.

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 adenylyl cyclase (2), Glucagon therapy in this setting has a limited evidence (2). Given this and the impracticality of its use at the doses required 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 treatment (HIET) Bolus followed by Infusion (80 units/hr)
- Isoprenaline infusion
- Close monitoring of glucose, K+ and pH (every 30 minutes)

Pharmacological Basis of Treatments

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<tr>
<th>Treatment</th>
<th>Pharmacological and proposed physiological mechanisms</th>
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<tr>
<td>Atropine</td>
<td>Anti-cholinergic, antagonises parasympathetic tone at the muscarinic acetylcholine receptors.</td>
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<tr>
<td>Adrenaline</td>
<td>Directly competes at the beta receptors blocked by propranolol or other beta blocker.</td>
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| Glucagon                   | Increases intracellular cAMP via G protein stimulatory receptor that bypasses the beta-adrenergic receptor. Positive chronotropy/inotropy (28A)
| High-dose insulin euglycaemic treatment (HIET) | Potent inotropy at high doses, increases calcium handling via the PI3K pathway. Supports uptake of carbohydrate for the stressed myocardium. |
| 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. Increased protein binding due to alakalemia – possibly reduces free drug. |
| Intralipid                 | Propranolol is highly lipophilic. Proposed binding to reduce the availability of free drug, increases clearance. |

Summary of doses and management
- Bradycardia management, 500mcg boluses up to 3mg total. 5 to 50mcg IV boluses, to affect. Infusion @ 0.01-0.1 mcg/kg/min. Bradycardia/negative inotropy may be refractory with overdose.
- Given as a 5mg bolus, followed by an infusion of 0.1mg/kg per hour
- Given as a bolus dose of 1iu/kg (ensure K+ > 4.5mmol, glucose > 10mmol >4, then infusion commenced 0.5 to 1.0iu/kg/hr up to 10iu/kg/hr. Becoming increasingly preferred. (4)
- 50 to 100ml boluses NaHCO3 3.4%. Aiming for pH 7.5 to 7.55, continue treatment if QRS complex widened (1).
- 1.5ml/kg 20% intralipid bolus. Followed by infusion at 15ml/kg/hr.

References
1) TOXBASE (2020) Propranolol guideline. www.toxbase.org