Therapeutics Bulletin

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UNIVERSITEIT STELLENBOSCH UNIVERSITY

Division of Clinical Pharmacology • Department of Medicine
Faculty of Medicine and Health Sciences

PO Box 241 • Cape Town • 8000 • South Africa
Tel: +27 21 938 9045/9335 • Fax: +27 21 938 9860

Contributors:
Clinical Pharmacology
(Dr Memela Makiwane, Dr Ahmed Abulfathi, Dr Eric Decloedt)
Toxicology (Dr Gerbus Müller)

Calcium channel and ß-blocker toxicity

Overdoses with beta-adrenergic blockers (ß-blockers) and calcium-channel blockers (CCBs) are associated with significant morbidity and mortality. Adult intentional self-harming ingestions and accidental ingestions by exploring toddlers constitute the majority of cases; whereas medication errors are rarely implicated. Severely poisoned patients may have profound bradycardia and hypotension refractory to standard vasopressors and in this therapeutic bulletin will review the additional treatment options that could be considered.

Mechanism of toxicity

Calcium (Ca) is crucial for cardiovascular function as its flow across cell membranes is necessary for cardiac automaticity, conduction, contraction and maintenance of vascular tone. ß-blockers and CCBs interfere with Ca flux across cell membranes via different mechanisms. CCBs directly block L-type calcium channels found in the heart, vasculature and pancreas; whereas ß-blockers decrease Ca flow by modifying the L-type calcium channels via second messenger systems.

The resultant decreased intracellular Ca produces cardiovascular dysfunction which results in cardiovascular collapse in severe overdose situations. The physiological and toxic effects of ß-blockers and CCBs are similar despite their different mechanisms of action and are therefore reviewed together.
CCBs exhibit different selectivity for cardiac Ca versus vascular Ca channels. Dihydropyridines (e.g. amlodipine and nifedipine) are predominantly peripheral vasodilators and are less cardiotoxic compared with non-dihydropyridines (diltiazem and verapamil) which may cause pronounced negative chronotropic, inotropic and dromotropic effects. In addition, Ca mediated insulin secretion by pancreatic tissue and decreased free fatty acid utilization by the myocardium may be impaired in all types of CCB toxicity and cause hyperglycaemia, acidosis and further depress cardiac contractility.

Classification of ß-blockers to predict toxicity is less clear as the toxicity of ß-blockers vary according to various molecule properties (lipophilicity, membrane stabilising activity, α-blockade etc).

Treatment

ß-blockers and /or CCBs toxicity may produce difficult to treat hypotension and bradycardia and often requires simultaneous therapies of intravenous fluids, vasopressors, calcium, glucagon, high-dose insulin and intravenous lipid emulsion therapy.

First line therapy:

- **For hypotension and bradycardia:**
  - ***Intravenous fluid boluses*** should be given by taking weight and fluid status into account.
  - ***Atropine*** 0.5–1 mg i.v. every 2-3 minutes (max. 3mg).
  - ***Vasopressors***: adrenalin and dopamine.
- **Additional treatment in patients with ß-blocker toxicity:**
  - ***High-dose glucagon***
    - An initial bolus dose of 50–150 µg/kg should be administered i.v. over one to two minutes. This initial dose may have a transient effect occurring within approximately five minutes. If no benefit is seen, repeat the dose until effect is seen.
    - Convert the total bolus dose into a continuous infusion (maximum: 10 mg/hr) diluted in 5% dextrose.
- **Additional treatment in patients with CCB toxicity with cardiotoxicity:**
  - ***Calcium*** dosed as 10–20 mL of 10% calcium gluconate via peripherial venous access or 5–10 mL of 10% calcium chloride via central venous access. Calcium chloride contains three times the available calcium per gram compared to calcium gluconate.
  - Consider ***glucagon*** if cardiac contractility is impaired (cardiac ultrasound may be considered).

Second line therapy:

Above treatments yield a poor response in moderate to severe toxicity and ***high-dose insulin euglycaemic therapy (HIET)*** simultaneously administered with above treatments should be considered.

- Short acting insulin administered as a 1unit/ kg bolus dose, followed by 0.5–1.0 units/kg/hr adjusted to clinical response (tapered off once signs of cardiotoxicity begin to resolve).
- Potential adverse effects of insulin infusion include **hypoglycaemia** and **hypokalemia**. Start dextrose infusion of 0.5 g/kg/h concomitantly with the insulin infusion. Monitor glucose every 20 minutes and adjust infusion or administer bolus dextrose as needed. Monitor potassium frequently (some experts recommend hourly) and administer potassium chloride when potassium <2.5 meq/L.

ß-blockers with effects on cardiac sodium channels may prolong the QRS interval. Stabilise the myocardium with ***sodium bicarbonate*** 1–2 mEq/kg IV bolus when the QRS >120 ms. Repeat sodium bicarbonate for recurrent QRS widening.

Third line therapy:

Should the above treatment not succeed, ***intravenous lipid emulsion (ILE)*** may be attempted. ILE expands the plasma compartment and sequesters lipophilic ß-blockers and CCBs (also referred to as the lipid sink). This is administered as

- Intralipid 20%: 1.5 mL/kg over 1 minute.
- Follow immediately with an infusion at a rate of 0.25 – 0.5 mL/kg/min.
- Repeat bolus every 3-5 minutes (3 mL/kg total dose).

Maximum total dose of 8 mL/kg is recommended.

Therapeutic objectives may include the following:

- Systolic blood pressure ≥ 90 mm Hg.
- Heart rate ≥ 60 bpm.
- Adequate organ perfusion (urine output of 1–2 mL/kg/hour and improved mentation).
- Reversal of cardiac conduction abnormalities (QRS < 120 milliseconds).

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