Successful treatment of severe atenolol overdose with calcium chloride

John O'Grady, MD; Scott Anderson, MD; Derrick Pringle, MD

ABSTRACT

Atenolol, a selective β_1-adrenergic antagonist, is commonly used to treat hypertension, ischemic heart disease and cardiac dysrhythmias. Few cases of severe atenolol intoxication have been described, and only one of these reports discussed the use of calcium chloride as a treatment. We present a case of atenolol overdose associated with shock and first-degree heart block, in which administration of calcium chloride led to dramatic improvement after failure of conventional treatment. In addition, we discuss the pharmacokinetics, toxicology and management of β-blocker overdose, focusing on the possible role of calcium chloride.

RÉSUMÉ

L'aténolol, un inhibiteur des récepteurs β_1-adrénergiques, est utilisé couramment pour traiter l'hypertension, l'insuffisance coronarienne et les dysrythmies cardiaques. La littérature fait état de peu de cas d'intoxication à l'aténolol et un seul de ces rapports discutait du recours au chlorure de calcium comme forme de traitement. Nous présentons un cas d'intoxication à l'aténolol accompagnée d'un état de choc et d'un bloc cardiaque du premier degré pour lequel l'administration de chlorure de calcium eut des résultats remarquables après l'échec du traitement conventionnel. De plus, nous présentons la pharmacocinétique, la toxicologie et la prise en charge de l'intoxication aux β-bloquants, notre propos étant axé sur le rôle possible du chlorure de calcium.

Key words: atenolol, β-blocker, intoxication

Introduction

Atenolol is a selective β_1-adrenergic antagonist that lacks intrinsic sympathomimetic activity. It has a longer half-life than most similar agents,[1,2] it is hydrophilic, and its brain penetration is limited. Atenolol and other β_1-adrenergic receptor antagonists are widely prescribed for hypertension, ischemic heart disease and certain dysrhythmias.[1]

Only a few severe atenolol overdoses have been documented,[3–14] and in only one case[10] was therapeutic use of calcium chloride reported. In that case, calcium was administered 48 hours after atenolol ingestion, by which time the β-blocker levels may have been negligible. Also, only one report of overdose with propranolol, a nonselective β_1-adrenergic antagonist, described the use of calcium chloride as possible treatment.[15] Calcium has also been used in the treatment of acebutolol and nadolol intoxications. In the former case, there was a transient increase in blood pressure after calcium was administered,[16] while in the latter, blood pressure gradually increased to normal within 2 hours of the calcium gluconate infusion.[17]

We report a case in which atenolol overdose was successfully treated with calcium chloride. This case and previous reports suggest that calcium chloride has a role in the treatment of β-blocker toxicity and that it may, in some cases, obviate the need for nonpharmacologic measures such as hemodialysis.

From the Department of Emergency Medicine, University of Western Ontario, London Health Sciences Centre, London, Ont.

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Case report

A 50-year-old woman with a long-standing psychiatric history was left alone by her husband at 9 am. When he returned at 1 pm, he found her unresponsive on the floor, with a suicide note and several empty pill bottles nearby, including acetaminophen, clonazepam, desipramine (old prescription) and atenolol (recent prescription). Her past medical history was remarkable for remote coronary artery bypass grafting, peptic ulcer disease and migraine headaches.

The paramedics attending the patient found her bradycardic, hypotensive and responsive only to deep pain. On arrival at the emergency department (ED) her heart rate was 50 beats/min and her blood pressure was 70/50 mm Hg. Rhythm strip and electrocardiography (ECG) confirmed narrow complex bradycardia with first-degree heart block.

In the ED, she was promptly and easily intubated without medication, but aggressive attempts to increase her blood pressure were unsuccessful, and the following agents were administered without effect: normal saline boluses, atropine, ephedrine, high-dose titrated dopamine (in excess of 200 μg/kg per minute), high-dose epinephrine (in excess of 200 μg/kg per minute) and glucagon (11 mg, given as 1-, 5- and 5-mg boluses). Despite these, the patient's systolic blood pressure remained in the range of 50–60 mm Hg until 1 g of calcium chloride was administered, at which point it rose dramatically to 100–120 mm Hg. Thirty minutes later her hypotension recurred, and a second dose of calcium chloride resulted in an equally dramatic blood pressure response.

The remainder of the patient's hospital course was unremarkable. Inotropes were titrated off over the ensuing 3 hours, she was extubated during the first night, a psychiatric evaluation was completed, and she was discharged on day 4 with appropriate follow-up.

Discussion

Pharmacokinetics of β-blockers

Atenolol, a selective β_1-adrenergic receptor antagonist, has an oral bioavailability of about 56%. Although it is poorly absorbed, most of the absorbed drug reaches the systemic circulation because of the lack of a first-pass effect. Atenolol's volume of distribution is 0.95 L/kg and less than 5% is bound to plasma proteins.[1] Most of the drug is excreted unchanged in urine with an elimination half-life of 5 to 8 hours. The usual atenolol dose for hypertensive therapy is 50 to 100 mg daily but, for the reasons discussed above, this must be adjusted down in patients with low creatinine clearance.[2]

Wadworth and colleagues[2] determined that, to achieve a 15% reduction in exercise heart rate with atenolol, the required effective plasma concentration is 376 nmol/L, but to achieve a 30% reduction requires 3760 nmol/L — a 10-fold increase. Atenolol's therapeutic plasma concentration range is 752 to 1880 nmol/L,[1] but there is wide variability in patient responses to β_1-adrenergic antagonists, and blood levels correlate poorly with clinical manifestations.[18] To illustrate, atenolol doses up to 1200 mg and propranolol doses up to 4000 mg/day have been tolerated without significant clinical manifestations[8,11] but, in one case, a 500-mg atenolol overdose caused hemodynamic instability[6] and, in another, a 1000-mg atenolol overdose caused cardiac sinus pauses that persisted for 34 hours.[4] In a particularly severe case, 5000 mg of atenolol led to ventilatory suppression requiring mechanical ventilation, with a plasma concentration of 35 338 nmol/L.[3] Of note, hemodynamic stability was maintained in this case without pharmacologic treatment.

Clinical findings, pathophysiology and experimental models

β-Blockers inhibit adrenergic receptors and reduce sympathetic nerve activity in various body tissues. This leads to a predictable constellation of signs and symptoms, including bradycardia, hypotension, low cardiac output, cardiac failure, cardiogenic shock, bronchospasm, ventilatory depression, and hypoglycemia,[3,19] although the last of these occurs rarely.

Cardiotoxicity is mainly due to ion dyshomeostasis, cardiac hyperpolarization and membrane stabilization.[20] This mechanism was substantiated by Kerns and associates,[21] who perfused isolated rat hearts with either propranolol or atenolol. Both agents had negative chronotropic effects and rendered the hearts refractory to pacing, but atenolol also reduced myocardial contractility. Subsequent treatment with low extracellular potassium (K^+, 2.3 mmol/L) and high extracellular sodium (Na^+, 160 mmol/L) increased heart rate and restored the ability to pace.

Langemeijer and colleagues[22] treated isolated, spontaneously beating rat hearts with propranolol and demonstrated a dose-dependent decrease in myocardial contractility. They then repeated the experiment, comparing reserpine-treated and non-reserpine-treated hearts (reserpine is a catecholamine-depleting agent). Both responded in the same way, which suggests that propranolol's negative-inotropic effects are not explained by actions on the β-adrenergic receptor. Langemeijer and colleagues also

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showed that propranolol's effects on contractility were less pronounced in a medium enriched with calcium (Ca^{++}), which suggests that its negative inotropism is due to or at least influenced by calcium. Of interest, a little known metabolic manifestation of β-blocker overdose is hypocalcemia, probably mediated through blockage of parathyroid hormone.[23,24] Given what is known about the β-blocker and calcium interactions, it is not surprising that, in a canine β-blocker overdose model, calcium chloride administration significantly improved blood pressure, stroke volume and cardiac index.[25]

Drug interactions

The patient in this case had also ingested acetaminophen, clonazepam and desipramine, which might have affected the presentation. However, acetaminophen causes hepatotoxicity rather than cardiac effects and would not produce the degree of cardiovascular compromise seen in this patient.[26] Clonazepam, a benzodiazepine, has few cardiovascular effects and is relatively safe in overdoses.[1] It causes central nervous system (CNS) depression and is more likely to produce drowsiness or coma. Desipramine, a tricyclic antidepressant, causes anticholinergic effects, CNS depression, catecholamine depletion, cardiotoxicity and orthostatic hypotension, but tricyclic overdoses typically present with supraventricular tachycardia and, in significant cases, prolonged QRS duration on ECG.[27] Given that our patient had access to very little desipramine and did not exhibit anticholinergic findings or QRS widening, it is unlikely that her cardiovascular compromise was induced by the tricyclic agent.

Management

Glucagon has long been the treatment of choice for massive β-blocker overdose. The activation of glucagon receptors, through G-protein-mediated mechanisms, stimulates adenyl cyclase and increases intracellular cyclic adenosine monophosphate independent of β_1-adrenergic receptors.[19] Other treatments for β-blocker overdose include β_1-agonists, atropine, phosphodiasterase inhibitors (e.g., aminophylline, amrinone and milrinone), cardiac pacing and hemodialysis. Hemodialysis should be reserved for removal of renally excreted β-blockers that are minimally protein bound in patients who are refractory to pharmacologic therapy.[9]

Two prior case reports[10,15] describe successful treatment of serious β-blocker overdose with calcium chloride. In the first case,[15] a 22-year-old woman ingested a large amount of propranolol as well as a smaller amount of metoclopramide and alcohol. Upon arrival in the ED she was given epinephrine, atropine, lidocaine and sodium bicarbonate; then cardioversion was performed for ventricular tachycardia. After defibrillation she developed electromechanical dissociation (EMD) with wide-complex sinus rhythm. At this time, 1 g of calcium chloride was administered and, within 30 seconds, the patient's QRS complexes normalized and she regained palpable pulses with a blood pressure of 80/40 mm Hg. Five and 10 minutes later, she slipped back into EMD, but both episodes were successfully treated with repeat doses of calcium chloride. After the second recurrence, a calcium chloride infusion was initiated and titrated according to blood pressure and ECG pattern. The infusion was stopped after 60 minutes, at which point electrolytes, blood glucose and plasma osmolality were normal. The serum calcium level was 3.29 mmol/L (normal 2.12–2.62 mmol/L). The patient was subsequently transferred to the intensive care unit and discharged home 48 hours after admission with no neurologic sequelae.

The second case[10] involved a 20-year-old woman who ingested 1800 to 2500 mg of atenolol, as well as 500 mg of hydrochlorothiazide, 240 mg of fluoxetine and 40 mL of chlordesmetildiazepam. On arrival in the ED, the physical findings were normal, blood pressure was 70/60 mm Hg, and her ECG was within normal limits, but 16 hours later, systolic blood pressure had dropped to 40 mm Hg and pulse rate to 38 beats/min. The ECG showed a junctional rhythm with left bundle branch block and a prolonged QTc interval. At that time the serum atenolol concentration was 32 000 ng/mL. Epinephrine, magnesium sulfate, potassium chloride, and glucagon infusions were started, and a temporary transvenous pacemaker was inserted. Her condition transiently improved, but 48 hours after the overdose her heart rate dropped to 45 beats/min and she became pulseless. Epinephrine and calcium chloride (1 mg of each) were administered through the central line, and pulses rapidly returned. She then slipped back into EMD and was treated successfully with 1 g of calcium chloride followed by a calcium chloride infusion. On day 12 she was discharged with no cardiac, neurological or renal sequelae.

Treatment guidelines

The Resuscitation Council of the United Kingdom[28] and the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiac care[29] both recommend the use of calcium in EMD associated with hyperkalemia, hypocalcemia and calcium antagonist overdose. It should be noted that the protocols for advanced cardiac life support do not directly govern the treatment of drug poisonings, but rather give algorithms for the treatment of hypotension, a known toxic effect of β-blockers.

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Conclusion

β_1-Adrenergic blocking agents are potentially lethal in overdose situations. In these cases physicians should enlist the help of the local poison control centre and should consider treatment with β_1-agonists, atropine, glucagon, phosphodiasterase inhibitors, cardiac pacing and hemodialysis. The case reports presented suggest that calcium chloride is an effective therapy and should be considered in cases of significant β-blocker intoxication.

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Correspondence to: Dr. Scott Anderson, EMA Office, London Health Sciences Centre, 375 South St., London ON N6A 4G5; fax 519 667-6769, sanderso@julian.uwo.ca