Beta-blocker toxicity — the role of glucagon

Report of 2 cases

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Summary

We describe 2 cases of acute overdosage with β-adrenergic receptor blocking agents. Both patients presented with profound bradycardia and cardiogenic shock. The effectiveness of intravenous glucagon administration is demonstrated in the first case. We suggest that glucagon should be used more readily in cases of circulatory failure due to β-blocker poisoning than has hitherto been the case.

Case reports

Case 1

A confused and disorientated 28-year-old man presented at the medical emergency ward, having ingested approximately 3 g propranolol. On arrival the patient was cold and clammy with cyanosed arms and legs, was hypotensive (systolic blood pressure (BP) 40 mmHg) and had a marked sinus bradycardia (heart rate (HR) 40/min). No other arrhythmias were noted. Early resuscitative measures included gastric lavage, boluses of intravenous atropine (0,04 mg/kg) and a continuous infusion of isoprenaline (starting dose 0,55 μg/kg/min; normal inotropic dose 0,05 μg/kg/min). Response to these measures was disappointing and the patient was transferred to the intensive care unit, at which point the systolic BP was 60 mmHg and the HR 55/min. Continuous cardiac monitoring was initiated but there was no need for ventilatory support. Isoprenaline administration as a continuous infusion was stepped up from the initial dose of 0,55 μg/kg/min to 1,1 μg/kg/min. The systolic BP increased to 70 mmHg and the HR to 72/min. On the second day a single bolus injection of glucagon (10 mg intravenously) at first caused no change in the patient's condition, but a second dose 30 minutes after the first caused a dramatic rise in BP (110/70 mmHg) and HR (96/min), and considerably improved peripheral perfusion. Isoprenaline administration was gradually tapered off during the next 12 hours, and the patient's condition remained stable. The patient was discharged from the intensive care unit to the medical ward 3 days after admission.

Case 2

A 71-year-old woman with a 2-month history of hypertension was treated with, among other drugs, propranolol. Three days before admission the patient reportedly took more than the prescribed dose and presented with dyspnoea, fatigue, excessive sweating and increasing swelling of both ankles. On admission she was pale, lethargic, cyanosed and in overt biventricular failure. The BP on admission was 90/60 mmHg and the patient was tachypnoeic (respiratory rate 35/min). The ECG revealed a sinus bradycardia (HR 40/min) with a QTc interval within the normal range. Bilateral basal crepitations and mild wheezing were present. Atropine failed to increase the HR and decreased cardiac output. The patient's cardiac failure responded to a continuous infusion of low-dose isoprenaline (0,02 μg/kg/min) and vigorous diuresis with furosemide and amophylline. The HR at the time of discharge was 80/min and the BP 115/70 mmHg.

Discussion

Acute overdosage with β-adrenergic blocking drugs has been reported relatively infrequently considering their current widespread use for the treatment of hypertension, dysrhythmias and angina pectoris. Although this group of drugs contains many members, only a few (propranolol, atenolol, metoprolol, oxprenolol, practolol, sotalol) have to date been involved in poisoning episodes. Variations in the pharmacological properties of the different β-blockers affect their therapeutic action and predictable effects, but we do not know how important these individual features are in serious cases of overdosage. The response to β-blocker overdosage is extremely variable — patients have tolerated up to 4 g propranolol daily and deliberate overdosage with both practolol and propranolol without serious adverse effects; conversely, circulatory collapse may occur in patients with pre-existing cardiac failure when sympathetic drive is inhibited by even a small dose of β-adrenoceptor antagonist.

The clinical features of β-blocker overdosage include bradycardia, cardiogenic shock, hypotension, convulsions, respiratory depression and coma. Death is usually due to asystole. The ECG may show atrioventricular or intraventricular conduction defects. However, not all seriously ill patients have a bradycardia, and sinus tachycardia and tachyarrhythmias have been reported with practolol and sotalol overdose respectively. In 2 cases of self-administered sotalol overdosage ventricular fibrillation and ventricular tachycardia were described by Elonen et al. The striking feature in both these cases was severe prolongation of the Q-T interval to almost twice normal. This is not surprising when one considers that sotalol is a class 3 anti-arrhythmic agent (Vaughn-Williams classification) and has a quinidine-like action. In fact, in the second of Elonen et al.'s cases the ventricular tachycardia showed features a little suggestive of torsade de pointes-type ventricular tachycardia, and as expected in this condition the first patient responded to

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dopamine infusion and cardiac pacing, and the second to isoprenaline.

Therapeutic options in the treatment of severe toxicity are limited and include intravenous atropine, β-stimulants, intravenous glucagon and transvenous electrical pacing. Intravenous atropine 2-3 mg (0.04 mg/kg) in divided doses should be given to reduce unopposed vagal activity. Of the β-stimulants, isoprenaline has been the most widely used, but the dose needed to reverse β-blockade is extremely variable. This has been convincingly demonstrated in our patients — despite doubling an already extremely high infusion rate of isoprenaline (from 0.55 µg/kg/min to 1.1 µg/kg/min) in the first patient, the condition remained refractory and unresponsive, an experience that parallels that of Lagerfelt and Matell.7 Another disadvantage is that isoprenaline has vasodilator properties and may thus reduce diastolic BP. The newer β-stimulants, dopamine and dobutamine, may overcome the problems of isoprenaline, but experience with these agents in β-blocker toxicity is limited.

Much controversy has been generated about the role of glucagon as an inotropic agent. Impressive and dramatic responses, similar to that demonstrated in our first patient, have been reported by Kosinski and Malindzak8 and by Ward and Jones.9 In Illingworth's case10 the patient required a further infusion of glucagon over the next 12 hours to maintain the improvement in HR and BP. Goenen et al.11 note that glucagon may be preferable in the presence of tachycardia, arrhythmia or β-blockade. However, Hamer et al.12 found no convincing inotropic response in the diseased heart and argued that the regional redistribution of blood flow produced by the drug must considerably limit its therapeutic value in cardiology. It may be that the myocardium in Hamer's patients was relatively unresponsive to glucagon because of the long-standing left ventricular stress leading to failure (as opposed to acute cardiac failure in overwhelming β-blockade), and that the increase in the force of contraction was secondary to the increase in ventricular volume acting through the Frank-Starling mechanism.

Heralded as a potentially useful inotropic agent, glucagon was first introduced into clinical practice in 1968.13 It is a naturally occurring amino-acid compound liberated in small amounts from pancreatic alpha cells. Its primary action is to stimulate glycogenolysis and gluconeogenesis endogenously since it is directly delivered to the liver. Its chief systemic action as an inotropic agent rests in its ability to increase cyclic adenosine monophosphate (cAMP) by stimulation of adenyl cyclase, simulating the action of catecholamines (Fig. 1). Its effects are not blocked by β-receptor blocking drugs, and, unlike other positive inotropic agents, glucagon has the advantage of not increasing cardiac irritability. In addition, its use does not preclude the use of lignocaine or electrical cardioversion, should the need arise, which is of particular importance in myocardial infarction. Although its action is rapid, its haemodynamic effects are short-lived, probably due to the extremely rapid destruction of the drug by the liver. In severe β-blocker poisoning the response to glucagon may be transient, and an infusion of 4 mg/h should be given and reduced gradually as the patient improves. Glick14 and Lvoff and Wilken15 have reviewed the use of glucagon and discussed its role in heart failure. Several points can be emphasized from these reports.

Firstly, one of the principal drawbacks of glucagon administration is that it produces severe nausea and vomiting and hyperglycaemia. However, administration of an anti-emetic overcomes these effects so that the drug may be continued.

The hyperglycaemia rarely exceeds 10 mmol/L.16 Secondly, although some patients in severe cardiac failure respond to glucagon, the response is unpredictable. Thirdly, its antagonistic action in myocardial failure in patients who have β-blocker poisoning may be superior to that of β-stimulants because it bypasses the β-receptor (Fig. 1). Fourthly, in some patients who have developed functional bundle-branch blocks after myocardial infarction, administration of glucagon may induce normal conduction.

In conclusion, we believe an early recourse to glucagon administration would be wise in profound β-blockade, if therapy with atropine and isoprenaline fails. Transvenous pacing may be useful if drugs do not increase the HR.

REFERENCES


FURTHER READING