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Inotropic effect of prenalterol in amitriptyline poisoning

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Abstract. A case of severe amitriptyline poisoning with grade IV coma, seizures, bradycardia and hypotension who did not respond to dopamine was successfully treated with prenalterol, a new cardioselective β-agonist. The case is discussed with respect to plasma concentrations of dopamine, prenalterol and amitriptyline. Prenalterol, hydrocortisone and insulin may be useful as inotropic agents in tricyclic poisoning where dopamine fails to provide an adequate response.

Key words: Amitriptyline – Hydrocortisone – Insulin – Prenalterol – Cardiac failure

Although most cases of tricyclic antidepressant poisoning are adequately managed with supportive care, severe overdose produces central nervous and cardiac effects with coma, hypotension, reduced cardiac output and arrhythmias. Techniques aimed at increasing elimination – such as forced diuresis, dialysis and haemoperfusion [1] – are of little value. Treatment therefore rests on ameliorating the toxic effects of the drug. We report a case of amitriptyline poisoning successfully treated with prenalterol, (a cardioselective β-adrenoceptor agonist), insulin and hydrocortisone where dopamine failed to produce an adequate inotropic response.

Case report

A 77-year-old male on maintenance therapy for asthma and high blood pressure was admitted after taking amitriptyline in a self-poisoning attempt. On admission the patient was in grade IV coma with general seizures. Body temperature 35.4 °C. After 7.5 mg diazepam i.v. the systolic blood pressure fell from 80 to 40 mm Hg. The ECG showed a prolonged P-R and QRS interval with sinus rhythm and a heart rate of 100 bpm, falling to 50 bpm. At this point the central venous pressure was 7.5 cm H_2O. After intubation, gastric lavage was performed and terminated with 10 g of activated charcoal. The patient was then placed on a ventilator and slightly hyperventilated. Because of the poor response to crystalloid solutions a dopamine infusion was started one hour after admission, initially at 5 increasing to 10 μg/kg/min. After a further hour blood pressure remained at 50 mm Hg although the heart rate had increased to 100 bpm. An isoprenaline infusion was also run but three hours after admission the blood pressure was still 50 mm Hg and heart rate 95 bpm. At this point prenalterol was given (10 mg bolus dose i.v.) and a drip with 50 mg prenalterol in 500 ml 5.5% glucose started at 50 ml/h (approx 1.4 μg/kg/min). The isoprenaline and dopamine infusions were stopped. The systolic blood pressure increased to 130 mm Hg and the heart rate fell to 80 bpm. Within an hour urine production had recommenced. The CVP increased from 5 to 8 cm H_2O. Twelve hours after admission the systolic blood pressure again fell to 50 mm Hg. A bolus dose of 5 mg prenalterol i.v. did not immediately increase blood pressure, and a dopamine drip was restarted with little effect and again stopped after 3 h. One g hydrocortisone and 12 IU rapid onset insulin were given i.v. followed by 0.5 mg digoxin. Although the CVP remained stable at 9 cm H_2O, after 30 min the blood pressure returned to 130/70. The patients cardiovascular status thereafter remained stable, although the patient had repeated seizures requiring diazepam. The prenalterol drip was discontinued after a total of 40 h, and the patient extubated on the third day after admission. The patient made a complete recovery.

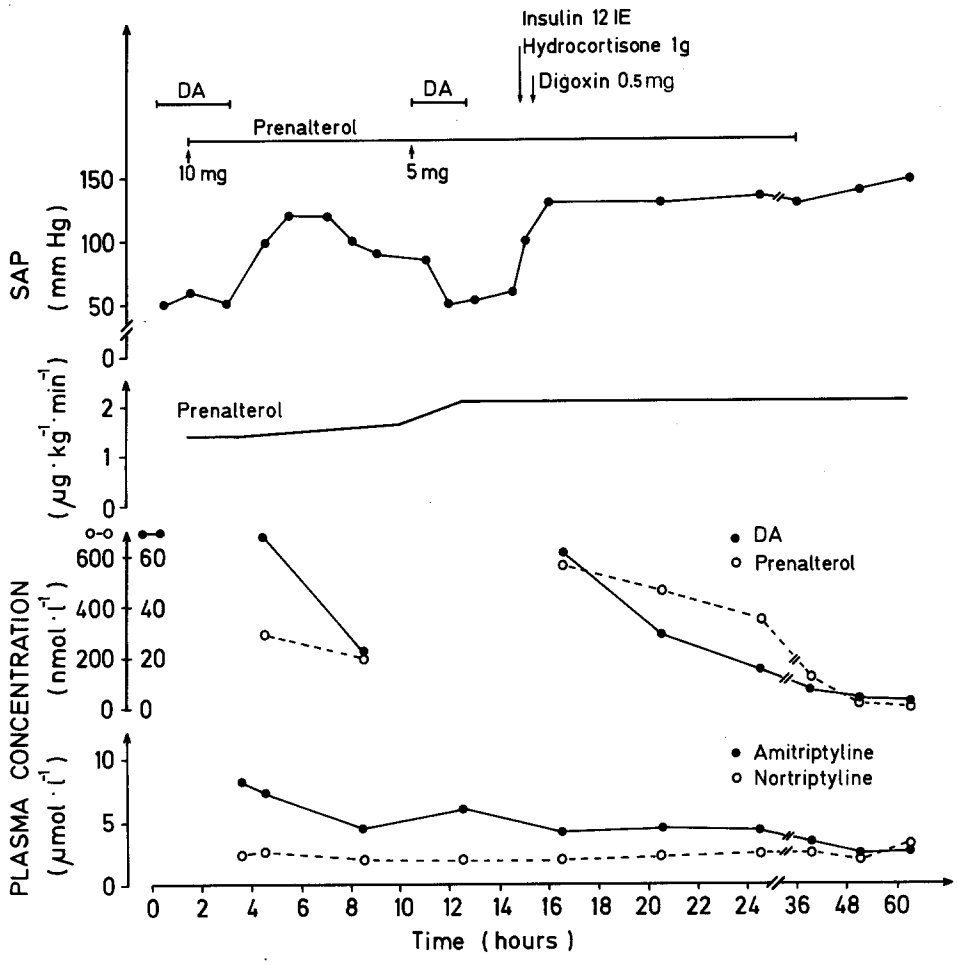

Fig. 1. Infusions (———) and bolus doses of drugs given, (DA = dopamine) systolic arterial blood pressure (SAP), prenalterol infusion rate, and plasma concentrations of dopamine (●–●) and prenalterol (○–○) in nmol · l^{-1}, amitriptyline (●–●) and nortriptyline (○–○) in μmol · l^{-1} in a case of amitriptyline poisoning

Analysis

Dopamine was analysed using a radioenzymatic assay; prenalterol by gas chromatography and mass spectrometry; and amitriptyline with a gas chromatographic method. The results of these analyses are shown in Figure 1.

Discussion

This 77-year-old man presented with severe amitriptyline poisoning with a high initial plasma amitriptyline concentration. Low cardiac output failure developed without the concurrent appearance of arrhythmias, suggesting that contractility rather than rhythm disturbances was the major problem. Dopamine is well established as a drug with positive inotropic and chronotropic actions in man and has been clinically used in tricyclic poisoning [2]. However, although an infusion of 15 μg/kg/min producing plasma concentrations of about 70 mmol/l was given, the inotropic response was inadequate. Since the vasodilatory effect of isoprenaline due to β_2-stimulation is well known, it is not surprising that isoprenaline also failed to produce an adequate inotropic effect. Prenalterol is a cardioselective β-agonist which, in the dog, has been shown to have an inotropic effect in amitriptyline poisoning at plasma concentrations of 100–200 mmol/l [3]. There are no previous reports of the use of prenalterol in tricyclic poisoning in man. In this patient a bolus of 10 mg i.v. produced an inotropic response with a slight fall in heart rate at a plasma concentration of almost 300 nmol/l. After this both dopamine and prenalterol concentrations fell, suggesting that the prenalterol dose in the drip was not sufficient to maintain an adequate inotropic effect, and again the blood pressure fell. It is difficult to ascribe the increase in blood pressure after 15 h to prenalterol alone, since a pronounced pressor response was seen 30 min after a bolus dose of insulin together with 1 g hydrocortisone. In addition, digitalis and dopamine were given concurrently. The role of corticosteroids and insulin in shock is at present not clear, although experimental evidence supports

the use of large doses of corticosteroids [4]. Similarly, insulin may be of value in cardiac failure [5]. Insulin in combination with glucose may favour potassium reentery into hypopolarized myocardial fibres and restore them into a normal state of polarization. However, with the return in systolic blood pressure to 130 mm Hg, the measured prenalterol concentrations were very high. After this point therapeutic concentrations of prenalterol were maintained until the infusion was discontinued.

Dopamine and prenalterol did not provoke arrhythmias – and in this respect appear to be safe to use in patients predisposed to a myriad of cardiac disturbances. Prenalterol appears to be a useful inotropic drug in severe amitriptyline overdose with bradycardia and may be of particular value where dopamine therapy is inadequate. The combination of high doses of a corticosteroid and rapid onset insulin may possibly enhance an inotropic effect.

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