Adverse drug reactions of the month

Plasma expanders used to treat or prevent hypotension can themselves cause hypotension

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The usual cause of hypotension in the surgical patient is hypovolaemia. This is often treated with plasma expanders. However, reactions to plasma expanders may themselves cause hypotension. Failure to recognise this situation could have disastrous consequences.

Case report

A 74-year-old man was undergoing an elective open repair of an infrarenal abdominal aortic aneurysm. His medical history was unremarkable apart from mild left ventricular heart failure for which he was on enalapril 5 mg and frusemide 40 mg daily. His resting electrocardiogram (ECG) was normal. He was not known to have any allergies. Induction and maintenance of anaesthesia was with the following combinations of drugs: fentanyl, midazolam, etomidate, vecuronium, nitrous oxide and isoflurane. The operation was proceeding without complication and with minimal blood loss. Prior to releasing the aortic clamp at completion of the top and bottom anastomosis and 90 minutes since the start of the operation, the patient was given a unit of the colloidal plasma volume expander Gelofusine. Within 5 minutes of starting the infusion his blood pressure dropped from 100/55 mmHg to 70/45 mmHg. There was no surgical bleeding and no ischaemic changes on the ECG monitor. By pulse oximetry there was no drop in oxygenation. In order to correct the hypotension a further 500 ml of Gelofusine was rapidly infused. This was followed by a further drop in blood pressure to 50/30 mmHg. With this almost instantaneous drop in blood pressure the diagnosis of Gelofusine allergy was considered. The patient was treated with adrenaline and cross-matched blood was thereafter used as volume replacement. With transfusion of blood, the blood pressure slowly normalised and the patient's condition improved. The operation was completed without further complications and the patient was transferred to the intensive care unit. On arrival, he was haemodynamically stable but was noted to have a swollen face. A small test dose of Gelofusine (100 ml) given in the intensive care unit reproduced the transient hypotension, with an immediate drop in systolic pressure from 120 to 80 mmHg which responded to the plasma expander Hespan. Subsequent progress was unremarkable and the case has been reported to the Committee on Safety of Medicines (CSM) via the yellow card scheme.

Summary points

- plasma expanders used to treat hypotension can themselves cause hypotension due to allergic or anaphylactoid reactions
- treatment of such reactions should be the same as any other allergic reaction except that an alternative plasma expander should be used
- such adverse reactions should be reported to the CSM via the yellow card system

Discussion

Gelofusine is a colloidal plasma volume expander used in the treatment of hypovolaemia. It is prepared from bovine collagen. As with other colloidal plasma expanders, mild urticarial reactions have been reported.¹ Severe anaphylactoid reactions following the use of Gelofusine occur with a reported incidence of between 0.066 and 0.345% of patients.² They are more common in those with a known drug allergy and in male patients. The CSM received two reports of allergic reactions (non-fatal), and 11 anaphylactic reactions (one fatal), in the UK between 1981 and 1995, although they are probably under-reported. The mechanism may be due to non-immune complement C3 activation triggered by colloid particles in the gelatine formulation or by combination with components in the patient's blood.³

Synthetic colloid volume expanders are commonly used in the treatment of hypotensive patients. The commonest cause of hypotension in a surgical patient is hypovolaemia. Blood loss was minimal in this case and therefore an alternative explanation was required. The swollen face was consistent with an allergic hypothesis. There have been case reports of reaction between angiotensin-converting enzyme (ACE) inhibitors and plasma expanders, particularly stable plasma protein solution, but no such reports have been found related to Gelofusine.⁴

Such allergic reactions, if suspected should be treated in the usual way with adrenaline, an antihistamine, steroids, and volume expansion using alternative non-collagen-derived plasma expanders, crystalloid solutions or blood. Although anaphylactic reactions to plasma expanders are rare, they can be life-threatening, particularly if infusion of plasma expanders is

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continued in the mistaken belief that shock is due to hypovolaemia. Anaesthetists and surgeons need to be aware that such allergic reactions can occur.

Keywords: plasma expanders; allergic reactions; hypotension; adverse drug reaction; Gelofusine

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- 2 Laxenaire MC, Charpentier C, Feldman L. [Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, mechanisms. A French multicentre prospective study](French). *Ann Fr Anesth Reanim* 1994;13:301-10.

- 3 Watkins J, Wild G, Appleyard TN, Hardy G. Complement activation by polystarch and gelatin volume expanders. *Lancet* 1990;335:233.
- 4 Young K. Hypotension from the interaction of ACE inhibitors with stable plasma protein solution. (letter) *Anaesthesia* 1993;48:356.

Diabetic ketoacidosis and clozapine

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Clozapine is an antipsychotic drug used for the management of schizophrenia. Due to its side-effects, it is reserved for patients unresponsive to, or intolerant of the conventional antipsychotic drugs.¹ Cases of hyperglycaemia have been reported as a rare complication of clozapine. We report a case of diabetic ketoacidosis associated with the use of clozapine.

Case report

A 30-year-old Afro-Caribbean man with paranoid schizophrenia was admitted under the care of the medical team with severe vomiting for 2-3 days. He had a history of mild asthma and hidradenitis suppurativa but no previous or family history of diabetes. He had been treated previously by the psychiatrists but had not responded to conventional doses of neuroleptics. Therefore, five months prior to this admission, he had been started on clozapine. The dose was built up gradually over the subsequent weeks to 150 mg bid. His only other treatment was minocycline for hidradenitis suppurativa.

On examination he was apyrexial and clinically dehydrated but otherwise normal, with a normal full blood count. Urea and electrolytes revealed sodium to be low at 124 mmol/l, potassium 3.8 mmol/l, urea and creatinine raised at 8.0 mmol/l and 152 µmol/l, respectively, amylase normal and glucose raised at 24.9 mmol/l. Urinalysis revealed copious ketones and arterial blood gases showed pH 7.27, pCO₂ 3.2 kPa, pO₂ 13.4 kPa and bicarbonate 11.2 mmol/l. Chest X-ray and electrocardiogram were normal and toxic screen for salicylate and paracetamol was negative. A diagnosis of diabetic ketoacidosis was made and the patient was treated with a sliding scale regime of insulin, and intravenous fluid rehydration with potassium supplements.

Over the next 24 hours his blood sugar stabilised and his urea and electrolytes improved. Unfortunately the patient's psychiatric condition complicated his management. He had no insight into his illness, and would not accept his insulin injections or BM sticks monitoring. After liaising with his psychiatrists it was

Side-effects of clozapine

Drowsiness, sedation, headache, dry mouth, hypersalivation, convulsions, neuroleptic malignant syndrome, tachycardia, postural hypotension, arrhythmias, pericarditis, myocarditis, cholestasis, pancreatitis, agranulocytosis.

Box 1

decided that clozapine should be stopped in view of its association with hyperglycaemia. Clozapine was substituted by olanzapine, another of the newer agents for the treatment of schizophrenia. We also sought advice from a consultant diabetic physician, who suggested maximum doses of an oral hypoglycaemic agent. The patient was controlled on gliclazide 160 mg bid. Over the next two weeks his blood sugar remained stable at around 7-11 mmol/l and he was discharged back to the psychiatrists. He remains on gliclazide 80 mg bid 8 months after his initial presentation.

Discussion

Clozapine is used for people with schizophrenia who have had an inadequate response to at least two standard neuroleptics (Guide to the clozapine patient monitoring service, Sandoz Pharmaceuticals). It has an unusual neuropharmacological profile, with a low affinity for dopamine D₂ receptors (unlike other antipsychotic drugs), but a high affinity for D₄ and 5-HT₂ receptors.² It has good efficacy and causes fewer extrapyramidal side-effects than the conventional neuroleptics. About 30% of patients respond after 6 weeks, 49% by 6 months and 61% by a year (Information fact sheet on clozaril, Sandoz Pharmaceuticals). However, its side-effects (box 1) prevent it being used as a first-line treatment. The major complication is agranulocytosis which occurs in 0.8% of treated patients.³ Thus, initiation of the drug must be in hospital with close monitoring of the blood counts.

There are eight other cases of hyperglycaemia associated with clozapine reported in the

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