

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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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 stix 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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literature.⁴⁻⁸ At least seven out of nine cases (including the present case) were patients of Afro-Caribbean origin^{4-6,8} (one case did not specify the ethnic origin⁷). In four cases there was a family history of diabetes.⁵⁻⁸ In two cases the patients were known to have established type II diabetes mellitus, well controlled on oral hypoglycaemic agents. After commencing clozapine their hyperglycaemia worsened, both requiring insulin treatment. In eight out of nine cases, including our own,^{4-6,8} the patients were taking other drugs concurrently and it is difficult to know whether those drug combinations may have impaired glucose metabolism. The fourth case⁷ involved a patient treated with clozapine as monotherapy and it is clear that clozapine alone was associated with the development of diabetic ketoacidosis.

In all the cases reported hyperglycaemia occurred early, about 4–8 weeks after the initiation of clozapine. In our case, it took 5 months before a diagnosis of ketoacidosis was made. However subsequent blood result showed a marked increase in HbA1c (11%), suggesting glucose tolerance had been impaired prior to presentation. In six out of nine cases discontinuation of clozapine led to the resolution of hyperglycaemia, though the time required for normoglycaemia to be achieved varied. In two cases the patients were continued on clozapine and still require treatment for raised sugars. In our case, 8 months after stopping clozapine, the patient still requires an oral hypoglycaemic agent. This suggests that clozapine may have unmasked latent diabetes.

Conclusion

Our case demonstrated that the drug clozapine may be associated with the development of diabetic ketoacidosis. It seems that people of Afro-Caribbean ethnic origin may be more susceptible to this side-effect. Little is known

Drugs known to cause hyperglycaemia/diabetes

Amoxapine, beta-blockers, calcium channel blockers, clonidine, corticosteroids, diazoxide, diuretics, isoniazid, oral contraceptives, phenothiazines, salbutamol, somatostatin, theophylline

Box 2

Learning points

- clozapine is an atypical antipsychotic drug used for the treatment of schizophrenia
- its side-effects, in particular agranulocytosis, restrict its use to patients unresponsive to or intolerant of conventional treatment
- diabetic ketoacidosis is associated with clozapine

Box 3

about the effect of clozapine on glucose metabolism and why black people should be at particular risk. Whether clozapine directly induces hyperglycaemia or merely acts as a trigger in people with a predisposition to diabetes remains unresolved. More research is needed to answer these questions. It is also important that physicians and psychiatrists are aware of the danger of diabetic ketoacidosis with clozapine therapy, especially in patients of Afro-Caribbean origin, those with a family history of diabetes and, of course, established diabetics. In these patients, blood glucose levels should be closely monitored.

Keywords: adverse drug reaction; clozapine; ketoacidosis; Afro-Caribbeans; diabetes

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