

Adverse drug reaction

Haemolytic anaemia due to metformin

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Metformin is widely used in type 2 diabetes mellitus patients. Lowered levels of vitamin B12 and folate due to impaired gastrointestinal absorption have been documented with long-term metformin therapy,¹ but clinically these effects are insignificant and do not cause anaemia. We report a patient with haemolytic anaemia caused by metformin.

Case report

A 51-year-old woman presented at our hospital on 30 July 1998 with a history of osmotic symptoms of one month duration. On physical examination she was obese (body mass index 31.5). Investigations revealed fasting plasma glucose levels of 15 mmol/l (normal 4.2-6.1 mmol/l) without ketonuria.

A clinical diagnosis of type 2 diabetes mellitus was made. Dietary modification was advised and metformin treatment started (850 mg bid). Nine days after starting treatment, she experienced easy fatigability and developed jaundice. There was no history of fever, drug ingestion, alcohol intake, liver disease or blood transfusion. Clinically, she had pallor and scleral icterus. There was no other clinical abnormality.

Detailed investigations for jaundice were carried out 3 days after its onset. The haemoglobin concentration was 9.1 g/dl (12-16 g/dl), haematocrit 0.30 (0.37-0.48), and mean corpuscular volume 102 fl (86-98 fl). The reticulocyte count was raised at 0.045% (0.006-0.022%); platelet and leucocyte counts were normal. Peripheral blood smear showed polychromatophilia. There were no haemoparasites. Plasma lactate dehydrogenase level was raised at 300 IU/l (100-190 IU/l), and serum haptoglobin level was low at 0.2 g/l (0.5-2.2 g/l). Red cell glucose-6-phosphate dehydrogenase (G-6-PD) activity was normal. Direct Coombs test was positive with anti-C3 but not with anti-IgG. Serum total bilirubin was 112 µmol/l (5.1-17 µmol/l) and unconjugated bilirubin level 85 µmol/l (3.4-12 µmol/l). Serum aminotransferase levels were normal; tests for hepatitis B surface antigen, IgM antibodies to hepatitis B core antigen, antibodies to hepatitis C virus and IgM antibodies to hepatitis A virus were negative. On ultrasonography, the liver and spleen were normal.

Metformin was stopped on clinical suspicion of haemolytic anaemia. The patient was followed up over the next 6 weeks. Jaundice regressed and serum bilirubin values returned to normal. The possibility of Gilbert's syndrome was excluded by observing a lack of

increase in serum bilirubin during a 48-hour fast. Euglycaemia was achieved on diet restriction and exercise. At the end of 6 weeks, her plasma fasting glucose was 6 mmol/l, haematocrit 0.38, reticulocytes 0.021% and red cell G-6-PD activity was normal.

With the patient's informed consent and approval from the ethics committee, the patient was rechallenged with 500 mg of metformin daily. She developed easy fatigability and scleral icterus on the third day. The serum total bilirubin concentration increased to 59 µmol/l, with an unconjugated fraction of 42 µmol/l. Haematological investigations again revealed features of haemolytic anaemia. Metformin was discontinued on the fourth day of rechallenge, following which the serum bilirubin level returned to normal over a period of 12 days.

Discussion

We feel that this patient had metformin-induced haemolysis leading to jaundice and hyperbilirubinaemia. Once an adverse drug reaction is suspected, discontinuance of the suspected drug followed by disappearance of the reaction is presumptive evidence of a drug-induced illness. Confirmatory evidence may be sought by cautiously re-introducing the drug and watching for re-appearance of reaction. A rechallenge with the patient's informed consent and approval from the ethics committee led to prompt re-appearance of jaundice and haemolytic anaemia. Although it is difficult to ascribe causality, as manifestations of drug-induced diseases frequently resemble those of other diseases, and a given set of manifestations may be produced by different and dissimilar drugs,² the temporal relation of metformin intake with the appearance of haemolytic anaemia and jaundice, and the rapid re-appearance of jaundice on rechallenge strongly support a causal relation.

Drugs directly implicated in immunohaemolytic anaemia can be divided into two types, on the basis of mechanisms of their action³: drugs such as alpha methyl dopa, that induce a disorder identical in every respect to the warm-antibody immunohaemolytic anaemia, and drugs that can become associated as haptens with the erythrocyte surface and induce the formation of an antibody directed against the erythrocyte-drug complex. The association between drug and membrane protein may be relatively tight, as in the case of penicillin, or relatively loose, as in the case of quinidine and most other drugs.

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In the first type of drugs, the autoimmune disorder is due to alteration of protein(s) of the Rhesus complex such that the protein(s) becomes immunogenic; the resulting antibodies cross react with the normal Rhesus protein. Red cells are coated with IgG but not C3. A positive direct Coombs test is observed in approximately 10% of these patients. As the antibody does not react with the drug, indirect Coombs' test is positive even when the drug is not added to the test. A small minority of these patients develop spherocytosis and haemolysis, which may be severe. Haemolysis decreases over a period of several weeks after cessation of drug therapy, although the direct Coombs' test may remain positive for more than a year.³

In most other cases, when a drug induces an immune haemolytic reaction, the antibody is directed against the combination of the drug and the membrane glycoprotein to which it is attached. The drug adheres relatively firmly to the erythrocyte surface. The haemolytic reaction *in vivo* is dependent on the presence of the drug and ceases shortly after the drug is discontinued. Since the antibody is usually IgG, spherocytosis and splenic destruction may occur. Complement is not usually fixed and haemolysis *in vivo* is not very severe. Penicillin and its congeners may lead to this type of reaction if the drug is given in very high doses.³

Other drugs (eg, quinine, quinidine, sulfonamides, sulfonylureas, phenacetin, stibophen, and dipyrone) do not adhere as tightly to the red cell membrane glycoproteins. The antibodies which they generate are able to fix complement, and these complexes remain on the red cell surface. The direct Coombs' test is positive with anti-C3 but not anti-IgG. The antibody is detected in the indirect Coombs' test only when the drug is added to the incubation mix-

Drugs causing immunohaemolytic anaemia

- aminosalicylic acid
- penicillins
- cephalosporins
- phenacetin
- chlorpromazine
- procainamide
- dapsone
- quinidine
- insulin
- rifampin
- isoniazid
- sulfonamides
- levodopa
- methyldopa
- melphalan
- mefenamic acid

ture. Haemolysis may be quite severe, sometimes resulting in intravascular haemolysis. Resolution is usually prompt after the drug is discontinued.³ This seems to be the most likely mechanism of haemolysis in our patient, since the direct Coombs' test was positive with anti-C3 but not anti-IgG.

A literature search revealed only one other report of a similar side-effect due to metformin.⁴ There have been no other reports to drug regulatory agencies or to the World Health Organisation Adverse Drug Reaction Monitoring Centre. Physicians should take note of this adverse effect of metformin, since this drug is used extensively.

Keywords: metformin; haemolysis; jaundice; anaemia; adverse drug reaction

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