ACUTE INTRAVASCULAR HAEMOLYSIS ASSOCIATED WITH INTRAVENOUS ADMINISTRATION OF MEROPENEM IN A SIXTY FOUR YEAR OLD MAN

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ABSTRACT

We present the first reported case of severe intravascular haemolysis associated with the use of meropenem in a 64 year old man. The report highlights a further possible drug related cause of intravascular haemolysis. The patient, who had a background of dialysis dependent renal failure, epilepsy and learning difficulties, was admitted to the intensive care unit following laparotomy and large bowel resection. His background also included a reported childhood allergy to penicillin. Along with initial haemodynamic and ventilatory support he was treated with cefuroxime, metronidazole and gentamicin without incident. He went on to develop an abdominal collection, for which treatment included meropenem. Associated with the administration of meropenem was the development of severe intravascular haemolysis confirmed by laboratory analysis and microscopy, which resolved on cessation of meropenem therapy. We discuss the possible mechanisms involved in the development of drug induced haemolysis and suggest the most likely cause in this case.

Key Words: *meropenem, haemolysis*

Case Report

A 64-year old male with dialysis-dependent end stage renal failure, epilepsy and learning difficulties was admitted to our 30 bedded tertiary level Intensive Care Unit (approximately 1200 patients per annum) following laparotomy for imminent caecal perforation due to an acute ischaemic colitis.

He had a documented allergy to penicillin, which according to his family was manifest by a childhood rash. In the immediate post-operative period he required high levels of ventilatory and haemodynamic support in addition to renal replacement therapy. At this stage he received cefuroxime, gentamicin and metronidazole with no adverse reactions recorded. Over the first few days of his Intensive Care Unit admission his condition improved, allowing organ supportive therapy to be significantly weaned. However, on day 7 of admission he developed septic shock secondary to an intra-abdominal collection that required radiological drainage. The collection subsequently grew mixed gram negative organisms including *E.coli* (resistant to amoxicillin, cefuroxime and ciprofloxacin), *S. marascens*, *E. faecalis* and coliforms. At this stage he was commenced on meropenem 1g BD.

Following the initial dose of meropenem his haemoglobin concentration dropped from 8.1g/dL to 5.4g/dL over 12 hours. Biochemistry was consistent with haemolysis with levels of potassium, LDH and bilirubin above the measurable range in our laboratory. Haptoglobin levels were low at 0.1 g/L (0.3-2.0). A blood film demonstrated spherocytes and fragments in keeping with intravascular haemolysis. A direct antiglobulin test was negative. Coagulation tests were stable with platelets 221, fibrinogen 5.7 and INR 1.05. A subsequent assay for glucose-6-phosphate dehydrogenase was normal (15.2 U/gHb (6.8-20.6)). The patient was on continuous veno-venous haemofiltration at the time and it was noted that the haemofiltrate developed a red-brown discolouration. Subsequent tests demonstrated no red cells present in the filtrate. Haemoglobin concentration in the filtrate was not assessed.

The haemolysis was presumed due to a reaction to meropenem, which was ceased. Approximately 6 hours after the last dose of meropenem the haemolysis was no longer detectable biochemically, the blood film was reported as essentially normal, aside from some additional nucleated red cells, and the colour of the haemofiltrate returned to normal. No other aspects of management were altered during this period and although packed red blood cells were given, this followed the drop in haemoglobin. After resolution of all features of haemolysis, the patient spent a further 19 days on the intensive care unit before passing away as a result of overwhelming sepsis and multi-organ dysfunction syndrome.

DISCUSSION

Meropenem is a broad spectrum β-Lactam antibiotic, widely used in the treatment of both aerobic and anaerobic bacterial infections. Its broad range of activity, low incidence of side effects, minimal cross reactivity in penicillin allergic patients[1] and wide therapeutic range[2] make it a popular choice. Side effects are rare and usually minor in nature. Most common local effects are inflammation (1.9%), thrombophlebitis and pain at the injection site. Biochemical adverse events include mild derangement of hepatic enzymes and mild derangement of coagulation and renal function tests. Clinical adverse effects occur in less than 2% of patients and include diarrhoea, nausea, rash, headache and pruritis.[3-5] A search of both Medline and EMBASE revealed no reported incidents of haemolysis associated with meropenem use. In this case, the temporal relationship between the onset/offset of haemolysis and the commencement/cessation of meropenem is highly suggestive that meropenem was causative of the haemolysis.

Drug-induced haemolytic anaemia's commonly cause spherocytosis, as was present in this case.[6,7] In this critically ill patient there were other possible mechanisms that may have contributed. Sepsis can cause a mechanical haemolysis, usually through the development of disseminated intravascular coagulopathy[6]. However, the unchanged coagulation profile, fibrinogen level and platelet count suggest that this would be unlikely. Some infections (such as those by *Clostridium spp*.) can release toxins that act as haemolysins, although there was no evidence of *Clostridium spp*. found.[6] Furthermore, low grade haemolysis has been reported with extracorporeal membrane exposure including renal replacement therapy.[8] However, the haemolysis resolved despite continuation of haemofiltration making this unlikely. Inherited haemolytic anaemia's and autoimmune haemolytic anaemia's are unlikely given the rapid resolution and normal red cell morphology following cessation of meropenem.

Haemolysis occurring as a result of drug administration is well recognised and arises through one of two mechanisms.[6,7] Red cell autoantibodies can develop in response to some drugs, such as alpha-methyldopa. The antibodies are directed against red cell antigens and causes fixation of complement and red cell destruction by phagocytosis. Spherocytosis and haemolysis can occur. The direct antiglobulin test is usually positive. Resolution depends on clearance of the autoantibodies from the circulation and can take several weeks.

The majority of drug-induced haemolysis occurs with the drug acting as a hapten.[6,7] The drug binds to a red cell membrane glycoprotein and antibodies (either IgG or IgM) form that are directed against this complex. This results in complement mediated intravascular haemolysis.[7] The haemolytic reaction is dependent upon the presence of the drug. The direct antiglobulin test may be positive or negative depending on how tightly the drug is bound to the glycoprotein and whether the antibody is IgG or IgM. Spherocytosis occurs and haemolysis can be severe. Resolution is usually rapid after discontinuation of the causative agent. This is the most likely mechanism of haemolysis in the current case.

In summary, this is the first recorded incidence of haemolysis that is likely to be due to meropenem administration.

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