Case report

Rifampicin induced shock during re-exposure for treatment of latent tuberculosis

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SUMMARY
We present a case of a young Asian female with rheumatoid arthritis who received latent tuberculosis infection (LTBI) treatment prior to treatment with a biologic agent, and developed shock with resistant hypotension on re-exposure to rifampicin. We discuss the epidemiology, pathophysiology and management of rifampicin induced shock, concluding that clinicians should be aware of this rare, but potential adverse effect, and be aware that adverse reactions to rifampicin are more frequent during re-exposure or longer dosing interval regimes. The evidence for desensitisation following such a reaction is lacking and this approach is not currently recommended. We would suggest close collaboration between specialties prescribing immunosuppression and the tuberculosis team when LTBI treatment is required after a reaction, with patient involvement to discuss the risks and benefits of treatment options.

BACKGROUND
Rifampicin induced shock is extremely uncommon with few cases in the literature. It is usually described following intermittent doses or re-exposure. It is an important complication that physicians should be aware of when prescribing anti-tuberculosis (TB) medications, or working in healthcare centres where those receiving treatment might present.

CASE PRESENTATION
A 25-year-old Asian female with seropositive rheumatoid arthritis who had failed trials of methotrexate and hydroxychloroquine (stopped due to chest pain and shortness of breath) and sulfasalazine (stopped due to rash), and in whom a trial of the anti-tumour necrosis factor drug etanercept was being considered, was referred for latent tuberculosis infection (LTBI) screening in keeping with current guidelines.[1] She had no significant medical history and a family history significant only for a paternal aunt with rheumatoid arthritis.

Investigation revealed a positive interferon-gamma release assay (T-SPOT.*TB*, Oxford Immunotec Limited, Milton, UK) and normal chest radiograph, with no symptoms of active TB disease. Rifinah (Sanofi, Italy), a combination of rifampicin and isoniazid, was initiated for LTBI treatment but was poorly tolerated due to nausea, anorexia and weight loss, and was stopped after 2 weeks. The patient was systemically well at this time, and blood

tests unremarkable. Fifteen days later, a trial of rifampicin monotherapy was initiated. Ten minutes after the first dose the patient began to experience diarrhoea, recurrent vomiting, fever and blurred vision.

On presentation to the emergency department she was hypotensive (blood pressure 103/68 mm Hg), tachycardic (heart rate 146) and febrile (temperature 38.1°C). Her respiratory rate and oxygen saturations were both normal at 16% and 100%, respectively. Physical examination was unremarkable and abdomen was soft.

INVESTIGATIONS
Venous blood gas showed an elevated lactate of 4.6 mmol/L, with pH 7.35, PaO_2 of carbon dioxide 4.6 kPa and bicarbonate 19.3 mmol/L. Full blood count showed an initial leukopaenia (white cell count 2.7×10^9/L), which was unusual for her with a previously normal value. This rose to 9.3×10^9/L with a neutrophilia of 8.9×10^9/L within 9 hours. There was no eosinophilia (0.1×10^9/L). Other baseline bloods including haemoglobin, platelets, electrolytes, renal and liver function tests, coagulation screen, troponin and C-reactive protein were all within normal ranges. Her amylase was mildly elevated at 141 U/L. Her chest X-ray was clear. A CT scan of her abdomen and pelvis was completed and showed thickening and enhancement of the left hemicolon and rectum only.

Cultures of her blood, stool and urine were negative. Repeat blood tests demonstrated a spike in troponin, which rose to 92 ng/L at 9 hours. She developed a transaminitis with peak alanine aminotransferase of 185 U/L 6 days after admission. This was likely to have been secondary to an ischaemic insult; virology, blood screen and ultrasound were normal and her blood markers gradually improved. A flexible sigmoidoscopy performed following the CT scan showed a normal rectum and distal sigmoid colon, with biopsy showing minimal non-specific findings of increase in chronic inflammatory cells.

TREATMENT
The patient was empirically treated for septic shock with intravenous fluids and broad spectrum intravenous antibiotic cover (ceftriaxone, amikacin and metronidazole). The severe hypotension failed to respond to aggressive fluid resuscitation, reaching a nadir of 81/45 mm Hg, and she was admitted to the Intensive Care Unit where she received

inotropic support with norepinephrine. She had a good response to norepinephrine and was weaned after 24 hours. No steroids were given. A tryptase level taken over 24 hours after her initial reaction was normal at 6.9 ug/L.

OUTCOME AND FOLLOW-UP

The temporal association between drug administration and the onset of symptoms, and the lack of any other clear cause of deterioration was suggestive of rifampicin induced shock. No further rifampicin was administered. Discussions with the patient, rheumatology team and TB multi-disciplinary team (MDT) resulted in a decision to recommend the use of low TB risk biologics with increased vigilance for the development of TB in place of LTBI therapy.

DISCUSSION

Epidemiology of rifampicin induced shock

Rifampicin is generally a well-tolerated drug, and is widely used in the treatment of gram positive bacterial infections, non-tuberculous mycobacterial infections and TB. Common side effects include orange discolouration of body fluids, gastrointestinal symptoms (nausea, anorexia, abdominal pain, diarrhoea) and flu-like syndromes.[2 3] Hypersensitivity reactions to rifampicin are rare, and may include fever, rash, flu-like syndrome, acute kidney injury, haemolytic anaemia, thrombocytopenia, disseminated intravascular coagulopathy and anaphylaxis.[4] Hypotension secondary to rifampicin is very uncommon, occurring in around 0.01% of patients.[4]

Adverse drug reactions are seen more frequently with intermittent dosing of rifampicin, with effects increasingly pronounced with higher doses given at longer intervals, potentially due to the production of rifampicin induced antibodies.[5–7] There are also case studies describing severe hypersensitivity reactions following re-exposure after many years.[8 9] Adverse reactions are also more frequent in HIV positive patients, potentially due to a shift in CD4 cell types from type 1 to type 2 T helper cells and increased secretion of Interleukin-4 and overproduction of IgE.[10]

Clinical presentation of rifampicin induced shock

Within the literature, there a number of case reports of rifampicin induced shock.[11–17] A review of reported cases from 1966 to 1999 by Martinez et al found that most presented with prodromes (usually rash) prior to the reaction, and that 75% experienced the reaction within minutes of exposure.[8] Symptoms included severe hypotension with fever, exanthema, dyspnoea, abdominal pain and vomiting, with variable organ involvement.[8 11–17]

Mechanisms

Various mechanisms for rifampicin induced shock have been posited, including types 1–4 hypersensitivity reactions.[13] Many authors support a dominant IgE mediated type I hypersensitivity reaction as the likely underlying mechanism,[8 12 15] while others have suggested combined hypersensitivity pathways.[9 18 19] Rifampicin may also have a direct vasodilatory effect via upregulation of inducible nitric oxide synthase mRNA transcription, previously demonstrated in vitro,[20] and effects on the histaminergic systems involved in vascular tension control.[21]

Diagnosis

The diagnosis of rifampicin induced shock is primarily clinical. Initial bloods should include full blood count, renal function, liver function and coagulation screen to pick up hypersensitivity-mediated adverse reactions as outlined above. For suspected anaphylactic reactions, the National Institute for Health and Care Excellence (NICE) also recommends taking serum mast cell tryptase levels as soon as possible after emergency treatment is started, with a second sample ideally within 1–2 hours from onset of symptoms (no later than 4 hours).[22] As an indicator of mast cell degranulation, elevated tryptase levels have a 72% sensitivity and 72% specificity for anaphylaxis, rising to 85% and 92% in the presence of hypotension.[23] However, tryptase levels peak approximately 1 hour after the reaction and it has a short plasma half-life of only 2 hours, such that the test is of limited value when delayed.[24]

Tests that can be used after the acute episode to confirm the presence of rifampicin hypersensitivity include intradermal skin prick testing, radioallergosorbent testing, and in vitro assessment of T-cell responses to rifampicin (lymphocyte transformation test).[9 25 26]

Management

In the acute phase of rifampicin induced shock, the drug should be discontinued.[26] Further management options depend on the severity of symptoms, and may include vasopressors, antihistamines, steroids and fluid resuscitation.[27] Future use of rifampicin should be avoided. Some case studies outline successful desensitisation to rifampicin, but these have been almost entirely carried out in patients who had experienced cutaneous adverse reactions and we are not aware of any trials of desensitisation following an anaphylactic-type reaction.[25 28–32] Chien et al investigated the safety of rifabutin use in 221 adults who had experienced rifampicin related adverse effects (not including shock) and reported a success rate of 72%, with 21% experiencing mild adverse reactions to rifabutin and 7% having severe reactions.[33]

Outcomes in this case

In the case described, the rapid onset of severe hypotension following repeated exposure to rifampicin was consistent with rifampicin induced shock syndrome. A delay in measuring tryptase levels means that the normal level identified is of little value.

In this case, a patient centred, MDT discussion took place to decide on future treatment options for her rheumatoid arthritis. The patient did not want to try an alternative treatment for her latent TB given the severity of her reaction to rifampicin, and did

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Learning points

- ► Patients being started on rifampicin should be asked about previous exposure and previous adverse reactions.
- ► Clinicians should be aware of the small but important risk of severe adverse reactions, on rifampicin re-exposure. This is particularly relevant for those working in emergency services and infectious disease/respiratory/tuberculosis (TB) treatment programmes.
- ► The evidence for desensitisation following severe adverse reactions to rifampicin is lacking and this approach is not currently recommended. We would suggest close collaboration between specialties prescribing immunosuppression and TB multi-disciplinary teams when latent TB infection treatment is required after rifampicin reactions, with patient involvement to discuss the risks and benefits of treatment options.

not want to try biologic therapy due to the risk of reactivation of her TB. Looking back in her history, it was thought that the chest pain she experienced while taking methotrexate before may have been due to reflux, and so a decision was made to re-trial methotrexate at a low dose alongside a proton-pump inhibitor.

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