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| **TITLE OF CASE** |
| Rifampicin induced shock during re-exposure for treatment of latent tuberculosis |
| **SUMMARY** |
| We present a case of a young Asian female with Rheumatoid arthritis who received latent tuberculosis infection treatment (LTBI) 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 medications, or working in health care 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 (TNF) drug etanercept was being considered, was referred for latent tuberculosis infection (LTBI) screening in keeping with current guidelines1. She had no other past medical history and a family history significant only for a paternal aunt with rheumatoid arthritis.Investigation revealed a positive T-spot (Oxford Immunotec Limited, United Kingdom) and normal chest radiograph, with no symptoms of active tuberculosis 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 mmHg), tachycardic (heart rate 146) and febrile (temperature 38.1 degrees Celsius). 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, partial pressure of carbon dioxide 4.6 kPa, and bicarbonate 19.3 mmol/L. Full blood count showed an initial leukopaenia (white cell count 2.7 109/L), which was unusual for her with a previously normal value. This rose to 9.3 109/L with a neutrophilia of 8.9 109/L within 9 hours. There was no eosinophilia (0.1 109/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 computed topography (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 six 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 nonspecific findings of increase in chronic inflammatory cells. |

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| **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 mmHg, and she was admitted to the Intensive Care Unit where she received inotropic support with noradrenaline. She had a good response to noradrenaline 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.

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| **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 tuberculosis 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.

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| **DISCUSSION**  |

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| 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 tuberculosis. Common side effects include orange discolouration of body fluids, gastrointestinal symptoms (nausea, anorexia, abdominal pain, diarrhoea), and flu-like syndromes2,3. Hypersensitivity reactions to rifampicin are rare, and may include fever, rash, flu-like syndrome, acute kidney injury, haemolytic anaemia, thrombocytopenia, disseminated intravascular coagulopathy and anaphylaxis4. Hypotension secondary to rifampicin is very uncommon, occurring in around 0.01% of patients4. 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 antibodies5,7. There are also case studies describing severe hypersensitivity reactions following re-exposure after many years8,9. Adverse reactions are also more frequent in human immunodeficiency virus (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 Immunoglobulin E10.Clinical presentation of rifampicin induced shock:Within the literature, there a number of case reports of rifampicin induced shock11-17. A review of reported cases from 1966-1999 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 exposure8. Symptoms included severe hypotension with fever, exanthema, dyspnoea, abdominal pain and vomiting, with variable organ involvement8,11-17.Mechanisms:Various mechanisms for rifampicin induced shock have been posited, including type 1-4 hypersensitivity reactions13. Many authors support a dominant IgE mediated type I hypersensitivity reaction as the likely underlying mechanism8,12,15, whilst others have suggested combined hypersensitivity pathways9,18,19.Rifampicin may also have a direct vasodilatory effect via upregulation of inducible nitric oxide synthase mRNA transcription, previously demonstrated in vitro20, and effects on the histaminergic systems involved in vascular tension control21. 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, 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 hypotension23. However, tryptase levels peak approximately one 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 delayed24.Tests that can be used after the acute episode to confirm the presence of rifampicin hypersensitivity include intradermal skin prick testing, radioallergosorbent testing (RAST), and in vitro assessment of T-cell responses to rifampicin (lymphocyte transformation test [LTT])9,25,26. Management:In the acute phase of rifampicin induced shock, the drug should be discontinued26. Further management options depend on the severity of symptoms, and may include vasopressors, antihistamines, steroids, and fluid resuscitation27. 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 reaction25,29-32. Chien et al investigated the safety of rifabutin use in 221 adults who had experienced rifampcin 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 reactions33.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 tuberculosis given the severity of her reaction to rifampicin, and did not want to try biologic therapy due to the risk of reactivation of her tuberculosis. 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.**LEARNING POINTS/TAKE HOME MESSAGES**  |

1. Patients being started on rifampicin should be asked about previous exposure and previous adverse reactions

2. 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 treatment programmes.

3. 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 MDTs when LTBI treatment is required after rifampicin reactions, with patient involvement to discuss the risks and benefits of treatment options.

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| **PATIENT’S PERSPECTIVE** |
| ***TIP:*** *This is an important section and gives the patient/next of kin the opportunity to comment on their experience. This enhances the case report and is strongly encouraged.* |

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