CASE STUDY

# SEVERE RHABDOMYOLYSIS FOLLOWING CO-ADMINISTRATION OF SIMVASTATIN AND FLUCONAZOLE IN AN HIV-POSITIVE MAN

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We report a case of rhabdomyolysis and acute renal failure in a 43-year-old man newly diagnosed with HIV and hepatitis B co-infection. Rhabdomyolysis was possibly induced by co-administration of simvastatin and fluconazole. Underlying hepatitis may have increased the risk of rhabdomyolysis by decreasing the metabolism of simvastatin. Few case reports link the development of rhabdomyolysis with the co-administration of these two drugs. This case calls for extra pharmacovigilance with proper patient education when prescribing drugs with potential for adverse interactions.

## CASE REPORT

A 43-year-old man presented to our genito-urinary clinic with a 3-month history of weight loss, poor appetite and recurrent genital ulcers. He had a past history of ischaemic heart disease and non-insulin-dependent diabetes mellitus. His medications included clopidrogel, gliclazide, metformin, atenolol, ramipril and simvastatin. On examination he was cachexic and had oral candidosis and penile ulcers typical of genital herpes (subsequently confirmed by a polymerase chain reaction test). Other findings were unremarkable. He tested positive for HIV antibodies.

The patient was prescribed fluconazole for the oral candidosis and co-trimoxazole for prophylaxis against pneumocystis pneumonia. A follow-up appointment was made for 2 weeks' time. However, 7 days later he was admitted complaining of muscle aches and difficulty in walking. His temperature was 39°C. He was unable to get up from a sitting position. There was no muscle tenderness, but he had significant weakness of hip flexors and extensors. Power distally was normal. Knee reflexes were normal and ankle reflexes were depressed. He had no bladder or bowel symptoms. The upper limbs and cranial nerves were normal. A urine specimen was dark and dipstick urinalysis showed 3+ red blood cells (RBCs) with no casts or proteins. The blood pressure was 140/70 mmHg. Urine microscopy and culture showed nil RBCs and no growth. Laboratory evaluation revealed sodium 125 mmol/l, potassium 6.0 mmol/l, urea 35.6 mmol/l, creatine 280 µmol/l, phosphate 0.77 mmol/l, calcium 2.42 mmol/l, magnesium 1.05 mmol/l, alanine transaminase 418 U/l, gammaglutaryl transferase l 743 U/l, alkaline phosphatase 460 U/l, albumin 25 g/dl, haemoglobin 10.9 g/dl, white blood cells $12.10\times10^9$, platelets $312\times10^9$, creatine kinase 18 123 U/l, lactate dehydrogenase 1 608 U/l (normal 220 - 450 U/l), HIV viral load 334 120 copies/ml, and CD4 count 28 cells/µl (3.3%). Hepatitis B surface antigen was positive. Ultrasound scans of the ureters and bladder were normal.

The patient was started on intravenous fluid therapy. Simvastatin, fluconazole and ramipril were discontinued. Within 3 weeks his muscle strength had improved with normalisation of the creatine kinase level and renal function. He continued to be pyrexial with no obvious focus of infection and rapidly went into respiratory failure requiring ventilatory support. A chest X-ray showed extensive alveolar opacification with confluent consolidation. He was treated for presumed pneumocystis pneumonia with high-dose co-trimoxazole. *Mycobacterium tuberculosis* was eventually cultured from a bronchial aspirate, a bone marrow aspirate and an early-morning urine specimen. He commenced quadruple therapy for tuberculosis followed by antiretrovirals (Truvada and efavirenz) 2 weeks later. He made a full recovery.

## DISCUSSION

Rhabdomyolysis is a musculoskeletal condition characterised by muscle weakness, an elevated creatine kinase level and myoglobinuria. The causes can be broadly classified into four categories, namely trauma related, excessive muscle activity, hereditary enzyme defects and medical causes. Medical causes include hypoxia, metabolic disorders, infections, temperature alterations and drugs.[1] Simvastatin is metabolised via the cytochrome P450 (CYP3A4) system. Concomitant administration of simvastatin and drugs that inhibit the CYP3A4 system can increase serum concentrations of simvastatin. Our patient developed rhabdomyolysis soon after commencing fluconazole. The underlying hepatitis coupled with the inhibitory effect of fluconazole on cytochrome CY3A4 may have led to increased serum levels of simvastatin leading to rhabdomyolysis. There are few case reports of rhabdomylysis developing after co-administration of simvastatin and fluconazole,[2] but rhabdomyolysis following primary HIV infection (PHI), infection with *M. tuberculosis* and treatment with high-dose co-trimoxazole has been reported.[3-5] Increasing life expectancy of HIV-positive patients will mean increasing co-morbidities requiring pharmacological treatment. Awareness of the potential adverse drug interaction between statins and the azoles, macrolides and antiretrovirals, especially in patients with underlying liver or renal disease, is important.


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# CASE STUDY

# MANAGEMENT OF RASH IN A PATIENT ON TB TREATMENT AND ANTIRETROVIRALS


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A 25-year-old man was diagnosed with tuberculosis (TB) on sputum testing. He had symptoms typical of TB – weight loss, night sweats and chronic cough. His baseline CD4+ count was 134/µl (12%). He was mildly anaemic, with a haemoglobin concentration of 11.3 g/l (normochromic and normocytic). Apart from mildly raised gamma-glytamyl transpeptidase (GGT) there were no other problems.

The patient was started on antiretrovirals (ARVs) (stavudine (d4T), lamivudine (3TC) and efavirenz (EFV)) only 11 days after the start of TB treatment. The ARVs were started at the same time as co-trimoxazole (Bactrim).

On day 24 of TB treatment, he presented for admission with the following:

- fever
- rash (macular papular) without involvement of mucous membranes
- cough as before
- increased GGT and alkaline phosphatase (now at three times the upper limit of normal) but normal transaminases.

## DIFFERENTIAL DIAGNOSIS

- TB immune reconstitution inflammatory syndrome (IRIS) – while the timing suggests this, the presence of a rash is unusual.
- Drug reaction – the patient had fever. If we believe this to be a drug reaction, we need to stop the offending drug.
- EFV – reactions to this drug tend to occur on the 11th to the 14th day: after start of treatment, so in terms of timing it is still a possible cause. It is common and occurs in about 17% of patients. Less than1% of patients have a sufficiently severe reaction to warrant stopping the drug (Stocrin package insert).

- Co-trimoxazole – a rash is reported in about 3.5% of patients and is most common in those who are HIV positive. Of all the drugs this is the least important, as there are alternative drugs that can be used for prophylaxis. While dapsone is inferior to Bactrim as prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP), it is still a viable option.
- TB treatment – rifampicin, isoniazid and pyrazinamide may cause a hypersentivity reaction with flu-like symptoms and uticaria. A rash from anti-TB treatment usually results from pyrazinamide, not rifampicin. If minor rashes and acneiform reactions to rifampicin occur, they are almost always self-limiting or can be treated symptomatically.

## MANAGEMENT

Co-trimxazole was stopped, ARVs were stopped, TB treatment was stopped, and the patient was given antihistamines and steroids (prednisone 20 mg twice a day). The rash and fever settled.

The idea of drug challenge is to identify the drug responsible for the reaction. Drug challenge starts with a small dose of with the TB drug *least* likely to be responsible for the reaction (a small dose is used because if a reaction occurs it will be less severe than the reaction to a full dose). The dose is gradually increased over 3 days.[1]

- INH: is this the drug least likely to be responsible, so this is where to start.
- The procedure is repeated, adding in one drug at a time. A reaction after adding a particular drug identifies that drug as the one responsible for the reaction. There is no evidence that this challenge process gives rise to drug resistance.
- If the drug responsible for the reaction is pyrazinamide, ethambutol or streptomycin, TB treatment is resumed without the offending drug. If possible, the offending drug is replaced with another drug. It may be necessary to extend the treatment regimen. This prolongs the total time of TB treatment, but decreases the risk of relapse.

The patient tolerated this process well and did not develop a rash again. We concluded that EFV was the most likely offender. He completed his TB treatment and was then started on a protease inhibitor (PI)-containing regimen. He is now well.

1. Treatment of TB, Guidelines for National Programs, WHO. http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf (accessed 11 September 2008).

# CASE STUDY – A SECOND OPINION ON MANAGEMENT

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Patients diagnosed with tuberculosis (TB) and then commenced on antiretroviral therapy (ART) are often on several drugs that can cause a hypersensitivity drug reaction. Such reactions may take the form of a drug rash (which may evolve to a Stevens-Johnson syndrome or toxic epidermal necrolysis), hepatitis, a drug fever or a combination of these. These reactions result in considerable morbidity directly and indirectly because they cause interruptions in optimal treatment for the TB and HIV.

Although recurrence of fever is a manifestation of TB IRIS, a maculopapular skin rash is not. In this case, the maculopapular rash represents a hypersensitivity drug reaction with associated fever. The patient described did not appear to have an associated drug-induced hepatitis, as this typically manifests with raised transaminases. His cholestatic liver function derangement was probably related to TB in the liver.

In this case the drugs that could have been responsible for the hypersensitivity reaction are co-trimoxazole, efavirenz (these are the two most likely culprits) and any of the TB medications (rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin can all result in hypersensitivity drug rashes). At our hospital we would follow similar principles of management to that followed by the author, but there are certain differences in our approach. While neither approach is necessarily more correct, a 'second opinion' on management of this case may be of interest to the reader.

The presence of fever in association with a drug rash means that the hypersensitivity reaction is severe and systemic. Administration of the drugs most likely to be the culprits must therefore be interrupted. In this case rather than interrupting all therapy we would interrupt only those medications that were the most probable culprits, as follows:

1. In terms of ART, we would stop efavirenz and continue the two nucleoside reverse transcriptase inhibitors (NRTIs), 3TC and D4T. It is possible to interrupt efavirenz (or nevirapine) for 5 - 7 days and continue the two NRTIs because of the long half-life of the non-nucleoside reverse transcriptase inhibitors (NNRTIs), which means that the patient is still effectively on three drugs for this period. Once the reaction has resolved (this usually occurs within this 5 - 7-day window) we would add Kaletra to the two NRTIs. (Kaletra would need to be increased to double dose once rifampicin was successfully reintroduced because of rifampicin's induction of lopinavir metabolism.)

2. We would interrupt all the TB treatment the patient was taking. If the patient was in the early stages of TB treatment, as in this case, we would put the patient on two or three alternative TB drugs that he was not on at the time of the reaction (e.g. streptomycin, ofloxacin, ethionamide) so as to continue TB treatment before rechallenge. Once the reaction had resolved, we would then use these drugs as a backbone upon which to rechallenge one first-line TB drug at a time at 3-day intervals starting with a low dose and increasing to full dose. We would use the following order: ethambutol, isoniazid, rifampicin, then pyrazinamide. The alternative TB drugs used as a backbone can be stopped if the first-line drugs are all successfully reintroduced.

When rechallenging after a skin reaction it is important to monitor the patient's temperature, observe his or her skin and ask about skin symptoms. Even *mild* skin symptoms such as burning or itching after a dose should alert the clinician that that drug should be avoided. The patient may be able to restart all TB medications in this situation, as co-trimoxazole and efavirenz are the most likely culprits. However, if a reaction occurs to one of the TB drugs on rechallenge, that drug will need to be avoided and TB treatment may need to be extended (e.g. to 9 months if pyrazinamide is omitted).

3. We would stop co-trimoxazole and not rechallenge it, given that it was being used as primary prophylaxis and the patient is now on ART which will restore protection against PCP with time.

Our approach in such a situation is therefore to interrupt the likely culprit drugs while continuing safer treatments for TB and HIV as the reaction settles and then rechallenge in a similar way to that described by the author. However, when a drug reaction is life threatening (e.g. severe hepatocellular injury with very high transaminases, hepatic encephalopathy or raised international normalised ratio (INR), or Stevens-Johnson syndrome) we would manage differently: ALL therapies the patient was taking at the time would be stopped in the acute situation.

For drug reactions we do not prescribe systemic corticosteroids. The evidence base for their use is controversial and contradictory. Some studies have demonstrated an increased risk of sepsis in patients with Stevens-Johnson syndrome, and as one cannot be sure that a skin rash will not evolve to this when a patient is first seen, we avoid them.


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