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# Rhabdomyolysis and elevated liver function tests—what's the underlying cause?

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## Case

A 71-year-old man with a past history of carcinoma of the prostate was admitted in August 2011, feeling unwell and with new-onset weakness of the quadriceps muscles for the past 2 days. He had initially received a diagnosis of adenocarcinoma of the prostate in May 2011 and he had been treated with cyproterone acetate 300 mg since June 2011. He had also been on aspirin 75 mg and simvastatin 40 mg unchanged for the past 2 years.

On admission, here, he appeared unwell but normotensive and afebrile. He had weakness of his lower limbs (power 2/5) with normal reflexes. Serum creatinine was 338 μmol/L and liver function tests were also markedly abnormal [alanine transaminase 887 U/L (normal < 41 U/L), γ-glutamyltransferase 111 U/L (normal < 41 U/L)]. Previous serum creatinine results and liver function were all normal. Urine dipstick was positive for blood but urine microscopy was negative. Ultrasound showed normal sized kidneys and normal liver parenchyma. The creatine kinase was 78820 U/L. A complete virology and immunology screen, including Jo-1 antibodies, was negative.

## Question

What is the most likely cause of the rhabdomyolysis and why are the liver function tests elevated?

## Answer

The most likely cause of the rhabdomyolysis is the interaction between cyproterone acetate and simvastatin via cytochrome P450 3A4 [1]. Hepatotoxicity is also a well-described side effect of cyproterone acetate [2].

## Discussion

Rhabdomyolysis is a syndrome characterized by muscle necrosis and the release of intracellular constituents into the circulation [3]. A variety of mechanisms lead to rhabdomyolysis and drugs are often implicated (Table 1) [3].

HMG-CoA reductase inhibitors (statins) are associated with a range of clinical syndromes, ranging from myalgias to myositis to overt rhabdomyolysis [4]. The mechanisms of statin-induced myopathy are still not well understood. Statins inhibit the conversion of HMG-CoA to mevalonic acid and also reduce the synthesis of coenzyme Q10. Both pathways may affect membrane integrity and/or mitochondrial calcium signalling and so cause myopathy in susceptible individuals [4].

Cyproterone acetate is a steroidal anti-androgen used in the treatment of prostate cancer in Europe (it is not currently approved for this indication in the USA). Cyproterone acetate and simvastatin are both metabolized by the cytochrome P450 isoenzyme CYP3A4 (Figure 1) and cases similar to ours have been described before. Hepatotoxicity due to cyproterone is also well characterized [2]. Interpretation of liver function tests in rhabdomyolysis needs to take into account that aspartate aminotransferase is also released from damaged muscle, whereas elevation of ALT to the degree seen in our case is not seen in rhabdomyolysis [5]. In our patient, renal and liver function returned to baseline with fluid resuscitation and after simvastatin and cyproterone acetate had been stopped. This, as well as the time course of events and the absence of other identifiable causes of rhabdomyolysis, gave us further confidence in the interpretation. Nephrologists are traditionally well aware of interactions via CYP3A4 since cyclosporine also interacts with simvastatin via this mechanism, leading to severe myopathy in susceptible patients.

## References

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**Table 1.** Causes of rhabdomyolysis[a]

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|---|
| Trauma and muscle compression (crush injury, electric shock, seizures, torture, conga drumming; compartment syndrome and ischaemia; extensive vascular or trauma surgery; coma and immobility) |
| Extremes of temperature (burns and hypothermia) |
| Metabolic myopathies (carnitine palmitoyltransferase deficiency, McArdle disease, many others [3]) |
| Drugs |
| Metabolic effects (anticholinergics and antidepressants, antihistamines, azathioprine, barbiturates, benzodiazepines, bezafibrate, carbon monoxide, clofibrate, cytotoxics, ethanol, ethylene glycol, fenfluramine, gemfibrozil, glutethamide, interferon, methanol, naltrexone, opiates, propofol, oxprenolol, labetolol, paracetamol, podophyllin, statins, zidovudine, streptokinase, alteplase) |
| Hypokalaemia (amphotericin, licorice, diuretics, others) |
| Autoimmune (cyclosporine, non-steroidals, penicillamine, others) |
| Membrane effect (carbon tetrachloride, colchicine, fugu poison, herbicides, snake bites, many others) |
| Agitation (hemlock, ketamine, Lysergic acid diethylamide, others) |
| Neuroleptic malignant syndrome |
| Serotonergic syndrome (amphetamines, ecstasy, serotonine reuptake inhibitors) |
| Infections (Viruses: influenza A and B, coxsackievirus, Epstein-Barr, herpes simples, parainfluenza, adenovirus, echovirus, HIV, cytomegalovirus. Bacteria: bacterial pyomyositis. Others: human granulocytic anaplamosis, falciparum malaria) |
| Electrolyte disorders (hypokalaemia, hypophosphataemia) |
| Endocrine disorders (hyperosmolality nonketotic hyperglycaemia) |
| Inflammatory myopathies (polymyositis, dermatomyositis, paraneoplastic necrotizing myopathy) |

[a]From [3], modified.

**Fig. 1.** CYP3A4. The cytochrome P450 proteins are mono-oxygenases, which are localized in the endoplasmatic reticulum. CYP3A4 consists of several β-sheet elements and many α helices with a haem group at the centre, the active site of the enzyme (image in the public domain at Protein Data Bank, http://www.rcsb.org/pdb/explore/explore.do?structureId=1W0E, accessed 22 September 2011).

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