

ARTICLE

Drug interactions: principles and practice



SELF-TEST QUESTIONS

True or false?

5. Drugs with high oral bioavailability are often affected by pharmacokinetic drug interactions.
6. Fluvoxamine is a strong inhibitor of cytochrome P450 2C19.

Answers on page 103

cause significant harm. Knowing a few drugs well and making judicious use of available information is more effective for managing drug interactions than relying solely on electronic decision support. ◀

Conflict of interest: Dr Polasek has consulted for Genelex Corporation on the GeneMedRX Drug Interaction Checker. Dr Snyder, Dr Doogue: none declared.

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Drug interactions

Fatal rhabdomyolysis following voriconazole and simvastatin

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Case

An 85-year-old woman presented with an acute onset of generalised weakness and functional decline. The patient had a history of insulin-requiring diabetes, hypercholesterolaemia, hypertension, glaucoma and chronic kidney disease. She also had longstanding fungal keratitis (>60 days) which had been unsuccessfully treated with topical therapy.

The patient's chronic conditions were managed with multiple medications, including simvastatin 20 mg daily. She had started oral voriconazole, 200 mg twice a day, 32 days before her admission.

The patient was observed in hospital for a few weeks. She was examined by two ophthalmology senior house officers and an infectious diseases physician before a general physician made the diagnosis of rhabdomyolysis.

Blood tests showed a creatine kinase of 23 200 U/L (normal range 34-145), aspartate transaminase 1030 U/L (<31), alanine transaminase 393 U/L (<34) and creatinine 255 micromol/L (<110). Sodium,

potassium, prothrombin time and full blood count were normal.

The rhabdomyolysis was suspected to be the result of a drug interaction between simvastatin and voriconazole.¹ Both drugs were ceased on day 20 of the patient's admission and her blood tests improved. Unfortunately, the woman's clinical symptoms did not resolve and she died of respiratory failure secondary to respiratory muscle weakness 10 days after the concurrent therapy was stopped.

Comment

Simvastatin is a substrate of cytochrome P450 3A4² and voriconazole is a known inhibitor of this enzyme.² However, their interaction is not documented specifically in key reference sources such as the Australian Medicines Handbook or in the product information, although class interactions are detailed.² It is listed as an interaction in dispensing software.³ Throughout the admission, the patient's medication was reviewed by three different clinical pharmacists.

They conducted a thorough medication history, reconciled this with her current medication chart and signed for pharmaceutical review without noticing the interaction.

A contributing factor to the interaction being overlooked was that there were multiple medication charts in use. As the woman was on simvastatin from home, it was not individually dispensed for her or entered on her previous discharge prescription. Simvastatin and voriconazole were therefore on different charts and the hospital pharmacy was only asked to supply voriconazole. Dispensing software would therefore not detect an interaction. A pharmacist could have independently identified the interaction on review of all charts, if they had been presented together.

The patient was on a low dose of simvastatin. As the risk of myopathy is linked to higher doses,² the clinicians may not have considered that there was a risk of a significant interaction. However, the woman was elderly with impaired renal function and multiple comorbidities, so she was at increased risk of adverse effects. Assessment of her drugs in relation to her condition did not result in any preventive actions such as reducing the dose of simvastatin, ceasing it altogether or ensuring monitoring for any signs of myopathy or altered blood test results.

Voriconazole requires multiple approvals for use in our hospital. The pharmacists stated that they focused primarily on the processes of approval and medication reconciliation. They did not consider whether the drug choice was appropriate or whether the patient's therapy needed reviewing in light of the new medicine. They described medication reconciliation as 'matching up' the patient's previous and current medications. The lack of a focus on anticipating, mitigating or preventing drug-drug, drug-patient and drug-disease processes resulted in none of the pharmacists identifying the potential drug interaction.

Conclusion

The interaction between voriconazole and simvastatin is not adequately described in commonly available references. The clinical significance of this interaction may be increased when individual patient factors are taken into account. Clinicians should be vigilant for this interaction and the need to consider individual risk factors when reviewing patients. A focus on tasks and processes in hospitals runs the risk of removing the patient as the focus of care. ◀

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