

# Pharmacogenetic Testing

Pharmacogenetic testing aims to identify patients who are more likely to respond, or to develop an adverse effect to a prescribed or self-administered drug.

### Clinical case study

An epileptic patient, stable on the anti-epileptic drug carbamazepine, also receives the antacid omeprazole for severe gastro-oesophageal reflux. He has oesophageal candidiasis and an oral azole antifungal agent is thought appropriate. Which one would you recommend? (1)

### The pharmacological and pharmacogenomic basis

- Ketoconazole is no longer recommended for acute candidiasis because of its potential hepatotoxicity. Both ketoconazole and itraconazole absorption are also interfered with by changes in gastric pH which would be expected with omeprazole.
- The azoles also show differential effects on the drug-metabolising enzymes CYP3A4, CYP2C9 and CYP2C19.
- Carbamazepine induces CYP3A4 and inhibits CYP2C19. Carbamazepine is also metabolised by CYP3A4, which is inhibited by various azole antifungals to varying extents (see Table).
- Omeprazole is metabolised by CYP2C19.
- Therefore genotyping should be useful for guiding therapy in this case.
- Carriers of HLA-B\*1502 (an immune system gene variant) are at increased risk of Stevens-Johnson Syndrome, a potentially lethal adverse effect, when given carbamazepine.

### Why is CYP450 genotyping not used in daily clinical practice?

- The magnitude of effects of any induction or inhibition of CYP450 enzymes is difficult to quantify in the presence of multiple interactions.
- In practice it is easier to avoid prescribing drugs, known to be metabolised by specific enzymes, when a potential interaction exists. For example, it might be more appropriate to avoid co-prescription of interacting drugs, or to monitor blood levels, rather than to rely on genotyping. Given that epilepsy is more difficult to control, a change of antacid agent is preferable.
- The same applies to the choice of azole antifungal. While dose-reduction may minimise the risk of adverse effects of drug-drug interactions, this needs to be counter-balanced against possible therapeutic failure.
- Even when a theoretically better choice of drug is made, close clinical monitoring is necessary. Therefore genotyping may not contribute much more for the additional costs and effort involved. In other words, the clinical utility and cost-effectiveness of genotyping are not compelling in this case.
- HLA-B\*1502 is not an issue here as the patient is stabilised on carbamazepine.

Azole antifungal	CYP3A4	CYP2C9	CYP2C19
Fluconazole	Weak inhibitor	Potent inhibitor	Potent inhibitor
Itraconazole	Substrate and inhibitor		
Ketoconazole	Substrate and inhibitor		
Voriconazole	Substrate (minor) and inhibitor	Substrate and inhibitor	Substrate and inhibitor

Fig. 1 Table

### Further reading

- (1) Baxter K, Marshall A. (2008) Drug interactions that can occur with azole antifungals. *Pharmaceutical Journal* 280:280.
- (2) Chung W-H, Hung S-I, Hong H-S et al. (2004) A marker of Stevens-Johnson syndrome. *Nature* 428:486.