Voriconazole therapeutic monitoring

Specimen details and interpretation of results
The voriconazole assay is carried out using liquid chromatography-tandem mass spectrometry and is run twice weekly (usually Monday and Thursday). Samples for the assay should be plain serum and taken immediately prior to a dose of voriconazole. The range reported for the assay is for pre-dose/trough specimens and so results do not apply for samples taken at any time other than immediately before the dose. The recommended therapeutic range is 2 – 5.5mg/L (see discussion below for more details). Results will be telephoned through to requesting laboratories as long as a contact telephone number and name are provided. Please note, results are normally sent out by post and so lack of contact details on the request form will delay the time for the result to be received.

Validation of the assay
The assay is carried out by liquid chromatography-tandem mass spectrometry which allows levels of voriconazole to be determined accurately even in the presence of other drugs, including other antifungal agents. This method has been shown to be faster and more selective than other methods of analysis. The method used at the Mycology Reference Centre in Leeds has been fully validated according to the guidelines for “Bioanalytical Method Validation” published by the FDA. We participate in the European EQA scheme run by KKGT in Holland.

The need for therapeutic monitoring of voriconazole
Voriconazole is an antifungal drug used in the treatment of various fungal infections and is the treatment of choice for invasive aspergillosis. It is available in both oral and IV formulations, with good oral bioavailability (>90%). Voriconazole is metabolised by the cytochrome P450 (CYP) enzymes, particularly CYP2C19 and to a lesser extent CYP 2C9 and CYP 3A4. These enzymes are also involved in the metabolism of a wide range of other drugs and hence the potential for drug interactions is significant. The result of these interactions may be either to increase or decrease the metabolism (and hence serum level) of voriconazole or to increase or decrease the metabolism of the other drug. Because of this, use of concomitant medications may adversely affect the level of voriconazole obtained during treatment. Drugs which have the most dramatic effect on voriconazole levels include rifampicin, carbamazepine, phenobarbital, efavirenz and ritonavir, all of which are contraindicated for concomitant use with voriconazole.

In addition to this, the CYP enzymes show genetic polymorphisms. This is particularly pronounced for the 2C19 enzyme, for which 26 allelic variants have been described. These allelic variants give rise to three main phenotypes: i) homozygous extensive metabolisers; ii) heterozygous poor metabolisers; and iii) homozygous poor metabolisers. In Caucasian European populations the poor metaboliser phenotype is mainly associated with the 2C19*2 allele, whilst in Asian populations, the presence of 2C19*3 can further contribute to this phenotype. The incidence of poor metabolisers is 2-6% of Caucasian populations and 15-30% of Asian populations. Levels of voriconazole in poor metabolisers can be up to 4 times higher than those in extensive metabolisers. Recently, a rapid metaboliser 2C19 phenotype (2C19*17) has been described and in patients with this phenotype, levels of voriconazole are significantly lower than either the extensive metabolisers or poor metabolisers. Genetic polymorphisms in CYP2C19 contribute 49% of the variance in clearance of voriconazole.

The therapeutic window for voriconazole is relatively narrow. If levels are too low, clinical efficacy is correspondingly lower and at high levels toxicity is seen. The exact figures for the lower and upper limit for serum levels are the matter of some discussion and
controversy and the ranges used will vary between laboratories. A study of 52 patients with invasive fungal disease, demonstrated that lack of clinical response occurred more frequently in patients with trough levels <1mg/L than those with trough levels > 1mg/L\textsuperscript{13}. This difference was statistically significant (p=0.02) and when the voriconazole dose was increased in the patients with low levels, all of them responded. Another study showed that favourable clinical outcome correlated with trough levels above 2.05mg/L in 28 patients, most of whom had invasive aspergillosis\textsuperscript{14}. Most recently, a study of 25 patients showed that those with serum trough levels above 2.2 mg/L had significantly better outcomes and lower fungal infection related mortality than those with lower trough levels (p=0.003)\textsuperscript{15}.

Voriconazole is associated with a range of toxicities and side effects, including deranged liver function, visual disturbances and neurotoxicity\textsuperscript{4}. Some studies have demonstrated that occurrence of toxicity is related to the peak serum trough level. Data shows that there is a correlation between peak serum trough levels and visual disturbances. The incidence of visual disturbances at trough levels <3 mg/L is 10-20%, rising to 25% at levels of 3-4 mg/L and up to 40% where levels are 9 mg/L\textsuperscript{1}. Serum trough levels do not appear to correlate with hepatotoxicity, with similar numbers of patients affected whether their trough level was above or below 5.5mg/L\textsuperscript{13}.

Currently there is no consensus as to how often, when or in whom voriconazole therapeutic monitoring should be carried out. Whilst some authors suggest routine monitoring for all patients as soon as steady state is reached\textsuperscript{15}, others have suggested monitoring levels only in patients when interacting concomitant medications are introduced or stopped, when there is any suspicion of toxicity or treatment failure\textsuperscript{1}. Properly controlled trials are required to address this issue, but until then it may be pertinent to measure voriconazole trough levels in patients who i) have progressive disease whilst on therapy, ii) exhibit signs or symptoms of toxicity, iii) receive concomitant medications with known drug interactions, or iv) where drug compliance is uncertain\textsuperscript{16}.

If you wish to discuss the assay or aspects of voriconazole levels, please contact Dr Ruth Ashbee in the Mycology Reference Centre on 0113 3926787.

References
5. Voriconazole SPC.
9. FDA. Antiviral Drugs Advisory Committee: Briefing document for Voriconazole (Oral and intravenous formulations) 2001