AMPATH LAB UPDATE

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Clinical Indications for Voriconazole Therapeutic Drug Monitoring

Voriconazole is considered to be the drug of choice for the treatment of invasive aspergillosis (evidence-based medicine A1 recommendation in European and IDSA guidelines). Immunocompromised patients, especially those with haematological malignancies (e.g. stem cell transplant patients) are at high risk for developing invasive fungal infections, such as aspergillosis and infections with *Fusarium* spp. The broad spectrum, including mould activity, as well as the availability of an oral form, makes voriconazole an ideal option for the prolonged treatment and secondary prophylaxis that is often required in these patients.

The pharmacokinetic and pharmacodynamic (PK/PD) variability of voriconazole makes it a difficult drug to dose. It has a narrow therapeutic index, meaning that there is a narrow margin between the levels needed for therapeutic activity and the levels at which toxicity occurs. To achieve potential efficacy, trough levels of between 1 and 5.5 mg/L are needed. In patients with severe infections e.g. multifocal or disseminated disease, CNS infection, or infection with a pathogen with elevated MICs, a trough level of 2-6 mg/L is recommended. The potential for toxicity, especially neurotoxicity, increases significantly at levels of ≥6 mg/L.

To further complicate the matter, intra- and inter-patient variability in levels of up to 10 times can occur. Reasons for this variability in levels include pharmacogenetics (e.g. CYP2C19 P450 mutations, where patients can be fast or slow metabolisers of voriconazole), significant drug interactions with commonly prescribed medication, and variability in absorption. All these factors can contribute to either increased toxicity or decreased efficacy of voriconazole. Pharmacogenetic testing, CYP2C19 Genotyping (Ampath test mnemonic CYP19), is available for patients on voriconazole if clinically indicated.

Therapeutic drug monitoring of voriconazole is essential in patients receiving the drug for the treatment of life-threatening infections.

Indications for therapeutic drug monitoring include the following patients:

- Patients with a poor clinical response, or suspected toxicity
- Patients treated for life-threatening forms of mycosis, such as invasive aspergillosis
- Patients experiencing sustained visual disturbances while on voriconazole therapy
- Patients receiving concurrent medications with potential drug interactions with voriconazole
- Patients undergoing hematopoietic stem cell transplantation, who receive voriconazole as either treatment or prophylaxis
- Paediatric patients who receive voriconazole, as levels are highly variable and fluctuate due to higher rates of drug elimination and the potential for underdosing

Blood should be collected for a serum trough level (collected 30 minutes before the next dose) 2–5 days after the initiation of therapy. The trough level should then be repeated after one week to confirm that the patient remains in the therapeutic range. Repeat monitoring is indicated until a steady-state level in the therapeutic range is confirmed, if there are any changes in the patient's clinical condition, concomitant medications are prescribed, or there is suspected toxicity.