Specimen details and interpretation of results
The posaconazole 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 posaconazole. The target level is > 0.7 mg/L for prophylaxis and > 1.25 mg/L for treatment (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 posaconazole to be determined accurately even in the presence of other drugs, including other antifungal agents. 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 [1]. We participate in the European EQA scheme run by KKGT in Holland.

The need for therapeutic monitoring of posaconazole
Posaconazole is an antifungal drug licensed for prophylaxis in neutropenic patients undergoing chemotherapy for acute myeloid leukaemia or myelodysplastic syndromes or those who patients who have received a haematopoietic stem cell transplant and are receiving immunosuppressive regimens for graft versus host disease. It is also licensed for treatment of invasive aspergillosis in patients who are intolerant or refractory to amphotericin B or itraconazole [2].

Posaconazole is only available as an oral formulation and its bioavailability is affected by various dietary and gastric factors, with significant improvements in oral bioavailability when taken with food (168% c.f. fasted state) and especially if the food is high in fat (290% c.f. fasted state) [3]. Doses upto 800mg/d result in dose-proportional pharmacokinetics, but absorption is saturated at 800mg/d [4]. Absorption of posaconazole is further improved by splitting the dose (200mg QDS c.f. 400mg BD), administration with either an acidic beverage or a nutritional supplement [5;6]. Concomitant administration of cimetidine [2] or omeprazole [7] both decrease posaconazole serum trough levels, probably due to reduced gastric acidity and it is thought that other H₂ receptor agonists or proton pump inhibitors will have similar effects on absorption [8].

Posaconazole, in contrast to voriconazole, has limited interactions with the cytochrome P450 system. It does not inhibit CYP1A2, 2C8/9, 2D6 or 2E1, but does inhibit 3A4 [9]. Posaconazole is metabolised via UDP glucuronidation and is a substrate for P-glycoprotein [10], and hence serum levels may be affected by inhibitors or inducers of these pathways, including erythromycin, rifabutin or ciclosporin [2].

The outcome of therapy with posaconazole appears to relate to the levels which are achieved in patients during treatment. In a salvage study for invasive aspergillosis, the response rate increased with increasing serum levels and in patients with average serum levels of 0.13, 0.41, 0.7 and 1.25 mg/L, the response rates were 24, 53, 53 and 75% respectively [11]. In an analysis of two studies of posaconazole for prophylactic use, levels above 0.7mg/L demonstrated reduced clinical failure [12].
Certain patient groups are known to have lower exposure to posaconazole. A study of 98 patients with persistent febrile neutropenia or refractory fungal infections demonstrated that exposure to posaconazole was 52% lower in those who had received allogeneic bone marrow transplants, compared with non-BMT patients, an effect which may be due to concomitant medications or mucositis [13].

Posaconazole is associated with a range of toxicities, but as yet there is no data to suggest that these are related to serum levels.

Currently there is no consensus as to how often, when or in whom posaconazole therapeutic monitoring should be carried out. In a recent single centre study, low serum levels were associated with diarrhoea or mucositis [14] and in another report from a referral centre carrying out posaconazole levels, 70% of samples did not reach a level of 0.7mg/L [15], suggesting that absorption is a serious problem for many patients. Properly controlled trials are required to address the frequency of monitoring, but until then it may be pertinent to measure posaconazole levels in patients who i) have progressive disease whilst on therapy, ii) experience episodes of diarrhoea or mucositis, iii) receive concomitant medications with known drug interactions, or iv) where drug compliance is uncertain[16].

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

Reference List