Isavuconazole levels in non-immunocompromised patients treated for chronic pulmonary aspergillosis

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Background:

Chronic pulmonary aspergillosis (CPA) is an uncommon and problematic disease, found in immunocompetent patients with prior or current lung disease, thought to affect some 240,000 people in Europe. Long-term oral azole antifungal therapy is usually required for treatment. Careful monitoring of azole serum concentrations is recommended to assure therapeutic levels, and to avoid possible toxicities and complications associated with drug interactions. Isavuconazole has good activity against Aspergillus. Isavuconazole has several attributes (good bioavailability, reduced toxicity) that could make it a useful new treatment option for CPA. To gain an understanding of the pharmacokinetics of isavuconazole in patients treated for CPA at the UK National Aspergillosis Centre (NAC) a bioassay was developed at the Mycology Reference Centre Manchester. This was modeled on a validated assay for posaconazole which is based on an agar diffusion method with Candida kefyr as the indicator organism. At the NAC, standard dosing is used and the first sample for therapeutic drug monitoring is normally taken at 2-4 weeks after initiation of therapy and every 3 to 6 months thereafter (first patient commenced isavuconazole treatment in Dec 2015). All levels were clinically reported. Dose modifications were made in a few patients whose levels were <1.0, or >6.0 mg/L with side effects.
Material/methods:
A data-base search was performed for a 12-month period (Dec 2015-Dec 2016). This identified 85 serum levels from 25 patients treated for CPA with isavuconazole at the NAC.

Results:
The median number of levels per patient was four (range 1-8). Eight levels were pre-dose, seven were post-dose and 70 were random. The mean level (all patients, all samples) was 2.83 mg/L. The mean post-dose level was 4.78 mg/L and the mean pre-dose level was 3.87 mg/L. Of the random levels, 43% of samples had been taken within 30 days from the first sample, 10% within 31-60 days, 14% within 61-90 days, 14% within 91-150 days and 10% >150 days. Samples taken within 0-30 days (2-8 weeks from initiation of therapy) had a mean level of 4.42 mg/l (range 0.028->7.5 mg/L). The following month the mean level was 2.97 mg/L (0.4-5.51). At 2-3 months the mean was 3.49 mg/L (1.56-4.71), at 4-6 months 3.53 mg/L (2.06-6.32), and from 6 months onwards the mean level was 3.14 mg/L (2.0-4.19). 70% of levels decreased after the first sample. None of the pre-dose levels were matched with a post-dose level.

Conclusions:
Isavuconazole levels in patients treated for CPA showed wide variation during the first 1-2 months of therapy. After this, the variation in levels decreased. In most patients, after the initial fall in concentration during the first two months, the levels stabilised.