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Itraconazole pharmacokinetics and how this affects its use in the prophylactic treatment of aspergillosis.

Produced the Medicines Optimisation Team
Greater Manchester Commissioning Support Unit

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Author: Stephen Woods BPharm, MRPharmS

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Introduction

GMCSU Medicines Optimisation team were asked to look into the issue with regard to the National Centre for Aspergillosis (NCA) requesting the prescribing of itraconazole by the brand Sporanox® for patients in whom they initiated treatment. This raised concerns with GP practices due to the price differential. Itraconazole generic costs £1.15 per day and Sporanox® costs £3.67 per day at the NCA recommended dose of 200mg twice a day.

The NCA claims that there is a difference in bioequivalence between the itraconazole 100mg capsules made by the various generic and brand manufacturers. Switching between available itraconazole products is allegedly sufficient to affect patient outcomes. It was also suggested that changing Sporanox® to generic itraconazole capsules versions resulted in failure of treatment.

The NCA reports that in cases where patients referred to them are already treated with itraconazole, and who happen to be on one of the generics, no switch to Sporanox® will be made.

Background

Aspergillus is an ubiquitous fungus, found in soil, water, the air and rotting vegetation. The vast majority of clinical disease is associated with *Aspergillus fumigatus*, although other species such as *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger*, may occasionally be isolated from clinical samples.

Aspergillosis symptoms can be defined as invasive, saprophytic or allergic. Invasive diseases caused by *Aspergillus* species include infections of lower respiratory tract, sinuses and skin. The central nervous and cardiovascular systems and other tissues may become infected as a result of haematogenous dissemination or direct extension from contiguous foci of infection. Saprophytic involvement includes *Aspergillus* otomycosis and pulmonary aspergilloma. Allergic conditions encompass allergic *Aspergillus* sinusitis and allergic bronchopulmonary aspergillosis. Itraconazole is treatment of choice for aspergillosis due to relative cost effectiveness.

Itraconazole pharmacokinetics

Itraconazole is a triazole derivative and shares structural similarities (a five-membered ring and a complex side chain) to the azole group (imidazoles and triazoles). Itraconazole has a broad spectrum of fungistatic activity.

Itraconazole, like all triazoles, has three nitrogen atoms in its azole ring which are thought to improve tissue penetration, prolong half-life and increase specificity for fungal enzymes. Itraconazole is a very weak base (pKa = 3.7), is ionized at a low pH such as found in gastric secretion, and is highly lipophilic being practically insoluble in water and in dilute acidic solutions.

Evidence review

Studies in healthy volunteers looking at absorption of itraconazole oral capsules demonstrated an absorption improvement after food intake (Prentice & Glasmacher 2005). Thomas et al (2008) also found that absorption of the oral capsule formulation was improved when taken with food or an acidic cola beverage. These studies also showed that there was marked inter-subject variation in plasma concentrations. Itraconazole also demonstrates a number of interactions with various drugs resulting in an increase or decrease in itraconazole plasma concentrations, or an increase in the plasma concentration of the interacting drug (Jansen-Cilag Ltd 2013).

Different formulations (including pelleted form) of itraconazole capsule were tested for variability in absorption and plasma concentration (De Beule & Van Gestel 2001). This is not thought to be problematic for superficial fungal infections, because itraconazole accumulates at the site of infection and high plasma concentrations are unnecessary. However, for more serious systemic fungal infections consistent plasma concentrations are critical. This variability of absorption from the different capsule formulations was thought to have potential negative impact on therapeutic outcomes.

According to Prentice & Glasmacher (2005) the most significant result of a pharmacokinetic or pharmacodynamics animal study showed a strong inverse relationship between plasma concentrations of itraconazole and the pulmonary burden of *Aspergillus fumigatus* following therapy for experimental infection ($r = 0.87$, $P < 0.001$).

Association between plasma levels and clinical outcome is not clearly defined, a level above 250ng/ml, after steady state plasma concentrations are achieved, is seen as desirable (Cystic Fibrosis Trust 2009) (Prentice & Glasmacher 2005). However according to Hurlé et al (2006), current data concerning itraconazole are insufficient to define a therapeutic window for this drug, although a value of 500 ng/mL for C_{min}[1] has been accepted as the efficacy breakpoint for this drug. The authors review the pharmacological aspects of greatest relevance in relation to the monitoring of itraconazole serum levels.

A double-blind cross-over study of acidified polyethylene glycol and pelleted forms of the itraconazole capsules (200mg daily) in patients receiving remission induction therapy for acute myeloblastic leukaemia (Prentice & Glasmacher 2005) showed that a significant number of patients had levels below 250 ng/mL and that there was wide inter- and intra-patient variation in levels with both preparations. This study also showed that the day 14 median mean peak concentration (C_{max}) was approximately half of that obtained with half the dose used in normal volunteers, even with good compliance, and compliance was in fact variable.

The hydroypropyl –ß-cyclodextrin (HPCD) solution of itraconazole provides a more uniform oral bioavailability that is further enhanced in the fasting state. Prentice and Glasmacher (2005) state that even bioavailability is only achievable if the drug (HPCD) is given intravenously. It was also shown that the solution achieves greater plasma levels than the capsule. They also suggest that owing to the inter-patient variation of bioavailability and metabolism (which is characteristic to all azoles), it is impossible to predict levels in individual patients and that routine sampling is needed to monitor plasma drug levels.

[1] Minimum serum concentrations (C_{min}) selected as the sampling time for monitoring itraconazole levels. Blood was withdrawn immediately before administration of the next dose.

Fagiolino et al (2007) provide further evidence to the complex issues around the bioavailability of itraconazole. A study, which involved itraconazole in administration to 24 healthy volunteers (12 men and 12 women) suggest the impact of gender on drug plasma levels. They concluded that in women bioavailability of itraconazole was smaller and the area under the curve (AUC) more variable than in men. Low bioavailability appeared to relate to the higher stomach pH observed in women and the effect of the menstrual cycle on both pH and CYP3A4 expression.

Variability of bioavailability between makes of itraconazole

The branded Sporanox® 100mg capsules produced by Jansen-Cilag Ltd is the UK licensed product alongside 6 variations of Sporanox 100mg capsules indicated as parallel imports from within the EU and generic capsules.

The NHS Dictionary of Medicines and Devices (dm+d) database lists 13 product suppliers for generic versions of itraconazole 100mg capsules (this includes some parallel imports of the Sporanox® brand where the name differs in the originating country).

There is only one document available on the Medicines and Healthcare products Regulatory Agency (MHRA) website which presents bioequivalence data for itraconazole and its active metabolite hydroxyl-itraconazole.

Public Assessment Report Decentralised Procedure, Itraconazole 100mg capsules (2009) for marketing authorisation holder Pharmakal Ltd.(website accessed on 22/04/2013).

Itraconazole

Test Name	Parameter	Geo Mean Ratio (test/reference)	Lower 90% LL	Upper 90% LL
Classic 90% CI	AUC0-t	92.759	81.885	105.077
Classic 90% CI	AUC0-inf	92.818	82.404	104.549
Classic 90% CI	Cmax	96.142	85.905	107.598

-Hydroxyl-itraconazole

Test Name	Parameter	Geo Mean Ratio (test/reference)	Lower 90% LL	Upper 90% LL
Classic 90% CI	AUC0-t	92.075	81.406	104.142
Classic 90% CI	AUC0-inf	92.269	81.866	103.994
Classic 90% CI	Cmax	94.544	85.910	104.046

Logarithmic transformation (Ln-transformed) values of the pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} have been used to calculate the Least Square Means for the test and reference product (Sporanox®) in line with procedures recommended by the Food and Drug Administration (FDA, 2001). Geometric mean ratio of test and reference for each parameter with 90% confidence interval (CI) has then been tabulated.

The bioequivalence study submitted by the applicant was performed according to the respective Note for Guidance and Good Clinical Practice requirements. Replicate study design was used, which according to the MHRA (2009) is acceptable for highly variable drugs; as where the statistical methods used to handle the incorporation of within-subject variance component in the bioequivalence conclusions.

The 90% confidence intervals for the ln-transformed AUC and C_{max} for itraconazole and its active metabolite lay within the acceptance criteria of 80%-125%. The MHRA (2009) stated that bioequivalence was demonstrated after a single dose (100mg) administration of two formulations of itraconazole. This allowed difference in bioequivalence is based on international consensus that differences of less than 20% are not clinically significant.

No bioequivalence data could be found for other generic itraconazole 100mg capsules detailed on the MHRA website, although it can be assumed that they have met the EU bioequivalence requirements for generic medicinal products and the 90% confidence intervals for both the mean AUC and C_{max} lies within the interval of 80% to 125% of the reference product.

The European Medicines Agency is currently producing product-specific guidance on the demonstration of bioequivalence; however, itraconazole was not included in the first wave of sixteen products and there was no indication it was planned for the next wave.

The only available paper that comments on difference in bioavailability between the itraconazole capsules produced by different manufacturers was published as a letter to editor (Pasqualotto & Denning, 2007). The authors describe a case study of three patients, who were switched from originator brand Sporanox® capsules to itraconazole capsules marketed by Sandoz Ltd (no longer marketed in the UK). Reduction of plasma levels of itraconazole and changes in patients' clinical conditions were reported.

Pasqualotto & Denning (2007) argue that this drop in itraconazole blood levels was due to the switch to the Sandoz generic, however, there is no discussion of other potential causes being investigated or considered. Only one patient on re-starting the Sporanox® brand managed to achieve itraconazole levels within the expected range (6.1 to 21.3 mg/mL). One of the two patients that didn't achieve expected itraconazole blood levels after 5 months of re-treatment with Sporanox® had a sputum culture revealing *A. fumigatus* resistant to itraconazole; where previous multiple specimens had been culture-negative for years prior to this. For this patient there is no mention as to when the last sputum culture was carried out and this is therefore not conclusively due to the switch to generic. The conclusion reached by Pasqualotto & Denning (2007) appears unfounded and the evidence is of low quality.

Discussion

Itraconazole bioavailability is affected by a variety of factors, which potentially include differences due to the manufacturing process, although all UK licensed generics will meet the bioequivalence criteria set by the MHRA.

No evidence is currently available to prove that switching between itraconazole from different manufacturers can cause differences in bioavailability and that those differences would contribute to changes in itraconazole blood levels and subsequently worsening of patients' clinical condition. Additionally, the MHRA (2014) report that they have received no reports indicating a variation in bioavailability or bioequivalence between itraconazole containing products.

The MHRA (2014) also stated:

"The MHRA has received a total of 12 UK spontaneous 'suspected' adverse drug reaction (ADR) reports describing a lack of drug effect with itraconazole containing products. These reports were however related to the underlying condition and pathogen resistance which is an issue not directly related to product substitution or quality. A lack of drug effect would not be surprising if the pathogen is resistant at the start, or develops resistance during treatment; additionally pathogen resistance could be an issue whether using a generic or innovator itraconazole product."

The marked inter and intra subject variation in plasma concentrations achieved with itraconazole 100mg capsules can be explained by pharmacokinetics properties such as poor aqueous solubility, the presystemic first-pass effect with the involvement of transporters such as P-glycoprotein, the high extent of metabolism mediated by the CYP450 system and a high probability of pharmacological interactions.

There is only anecdotal evidence of altered treatment outcomes associated with switching between generic versions of itraconazole 100mg capsules and the brand Sporanox®.

It needs to be noted that there is evidence that moving from a branded drug to a generic version can result in non-adherence by individuals, which can worsen the therapeutic outcome. It is also established that effective communication of medication switches to patients can mitigate this problem. (Horne, R., 2005) (Pharmacy in Practice, 2010).

Conclusion

There is no evidence to indicate that patients should be maintained on a specific make of itraconazole 100mg capsules. However, they should have regular monitoring to ensure they remain in the therapeutic range, due to pharmacokinetic issues listed above.

If patients are switched from the Sporanox® brand to a generic version of itraconazole 100mg capsules they must be counselled carefully to ensure they remain compliant with treatment. It may be advisable to monitor blood levels within 2 to 4 weeks of the switch taking place.

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