for administrations during CytoSorb® use than for the adjacent peak levels. Finally, the meropenem peak level during the second period of CytoSorb® use was substantially lower than the peak level before use.

The observed substantially lower linezolid peak levels during CytoSorb® use might be due to adsorption by the cytokine filter. Indeed, different endogenous substances, apart from cytokines, are reported to be adsorbed by cytokine filters.6 Adsorption would also explain the lower peak level of meropenem during the second use of CytoSorb®. However, blood samples were not collected at optimal timepoints for meropenem; hence, the information for this antibiotic is limited. It should be mentioned that the high intra-individual variability observed for both antibiotics might also be due to the effects of critical illness.5,7 However, because of the possible adsorption of antibiotics by cytokine filters, therapeutic drug monitoring (TDM) might be especially important for patients using such systems. Indeed, first guidelines already recommended the use of TDM in critically ill patients.8,9 If TDM is not available, high loading doses or shorter intervals between antibiotic administrations could be used to achieve adequate antibiotic levels. The results suggest that further studies are needed to understand the impact of cytokine filters on the concentrations of different antimicrobials.

Funding
This study was supported by a Mérieux Research Grant (Institut Mérieux, Lyon, France).

Transparency declarations
None to declare.

We affirm that this manuscript is an honest, accurate and transparent account of the case being reported, and that no important aspects of the case have been omitted.

References

Interaction between voriconazole and flucloxacillin during treatment of disseminated Scedosporium apiospermum infection

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Keywords: triazoles, metabolism, S. apiospermum

Sir,

Voriconazole is a broad-spectrum triazole used in the treatment of many fungal infections including those caused by Scedosporium spp. Along with significant side effects, voriconazole has a variable metabolism and multiple drug interactions, requiring regular monitoring. We present a case of disseminated Scedosporium apiospermum infection in a patient who was treated with voriconazole, but was unable to achieve therapeutic levels, with a resultant clinical relapse while on flucloxacillin for a Staphylococcus aureus bloodstream infection.

The patient’s infection involved the skin, lungs and brain, and occurred against a background of recently commenced low-dose prednisolone for polymyalgia rheumatica. Skin biopsies isolated S. apiospermum and the patient was started on voriconazole, but was unable to achieve therapeutic levels, with a resultant clinical relapse while on flucloxacillin for a Staphylococcus aureus bloodstream infection.

While the patient had subtherapeutic voriconazole levels, they higher oral dosing, until the flucloxacillin was ceased (Figure 1).

The subsequent voriconazole levels fell to 1 mg/L, and remained subtherapeutic despite intravenous or increasingly higher oral dosing, until the flucloxacillin was ceased (Figure 1). While the patient had subtherapeutic voriconazole levels, they developed new skin lesions that were confirmed as S. apiospermum on a repeat biopsy, and the patient was restarted on terbinafine.
The activity of voriconazole against Scedosporium is well described, and it is considered to be first-line treatment for S. apiospermum infection.\textsuperscript{1,2} It inhibits fungal cytochrome P450, impairing the synthesis of ergosterol, but is also metabolized by hepatic cytochrome P450 enzymes CYP2C19, CYP3A4 and CYP2C9, with <2% being excreted unchanged in the urine. Its bioavailability is estimated to be >90% in healthy adults. Monitoring of drug levels is recommended due to a low therapeutic index, a significant interindividual variation in the expression and function of CYP2C19 and CYP3A4, and the highly variable non-linear kinetics of voriconazole.\textsuperscript{3 – 5}

Flucloxacillin, a semi-synthetic penicillin used for Gram-positive infections including those caused by S. aureus, is not a substrate or an inhibitor of cytochrome P450 enzymes. However, at high and/or multiple doses, flucloxacillin activates the pregnane X receptor (PXR) nuclear hormone receptor, with the potential to induce the expression of both CYP3A4 and CYP2C8/9 in a genotype-dependent manner.\textsuperscript{6,7} Levels of repaglinide (as a major substrate of CYP3A4 and used as a marker of PXR activity) reduce markedly following multiple doses of flucloxacillin.\textsuperscript{6} Interaction with cyclosporine (which is predominantly metabolized by CYP3A4) has also been observed, with levels falling by up to 55% in renal transplant patients receiving intravenous flucloxacillin, resulting in transplant rejection.\textsuperscript{8} The comparable antistaphylococcal penicillins dicloxacillin and nafcillin also activate PXR and increase CYP3A4 activity\textsuperscript{9} and potentially have similar clinical implications.

We propose that flucloxacillin-mediated PXR activation was the cause of this patient’s subtherapeutic voriconazole levels. To the best of our knowledge, this is the first documented interaction between these two medications. We recommend close surveillance when flucloxacillin (and potentially dicloxacillin and nafcillin) is used concurrently with voriconazole.

**Funding**

No specific funding received.

**Transparency declarations**

None to declare.

**References**

Systemic antimycotic and antifungal use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe

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Keywords: antimycotic use, antifungal agents, drug consumption, pharmacoepidemiology

Sir,
The WHO Regional Office for Europe and the Laboratory of Medical Microbiology of the University of Antwerp, Belgium, established a sustainable surveillance network to collect valid, representative and comparable antimicrobial consumption data in non-EU countries of the WHO European Region and Kosovo. Recently, the first results of this project discussing systemic antibiotic use were published.1

In this letter, we aim to report a cross-national comparison of the antimycotic and antifungal use rates in 2011 of 11 non-EU European countries and Kosovo and to compare these results with the EU countries involved in European Surveillance of Antimicrobial Consumption (ESAC, since 2011 ESAC-Net). All references, including those in the reference list, to ‘Kosovo’ mean ‘Kosovo [in accordance with UN Security Council resolution 1244 (1999)]’. The participating country representatives constructed an exhaustive valid national antimicrobial drug register and use file, including detailed information (unit strength, pack size, galenic form and route of administration) for all antimycotic and antifungal products and the number of corresponding packages available on the market (ambulatory and hospital care). As in the previously published data collected within the ESAC project,2,3 each medicinal product was classified according to the WHO Anatomical Therapeutic Chemical (ATC) coding system, i.e. antimycotics (ATC J02) and antifungals (ATC D01BA) for systemic use.4 The denominator data used were the total number of inhabitants per year of a country (mid-year population). The J02 and D01BA data expressed in DDD per 1000 inhabitants per day (DID) were compared with ESAC-Net data from 2011,5 and the data expressed in packages per 1000 inhabitants per day (PID) were compared with published ESAC data from 2009.6

A more detailed overview of the network, data availability, data suppliers, coverage, denominator data, data collection, validation and reporting is described elsewhere.1

Table 1 presents reliable total antimycotic and antifungal use data in DID for 12 countries, states or areas not belonging to ESAC-Net, i.e. 4 south-eastern European (SEE) countries (Bosnia and Herzegovina, Montenegro, Serbia and Turkey), 7 newly independent states (NIS) (Armenia, Azerbaijan, Republic of Belarus, Georgia, Kyrgyzstan, Republic of Moldova and Tajikistan) and Kosovo. Total antimycotic and antifungal use was low in DID in most countries and areas and ranged from 0.08 DID for Bosnia and Herzegovina and Kosovo to 2.33 DID for Turkey; proportional use differed widely between countries, states and areas. Terbinafine, overall the most frequently used antifungal in DID in ESAC-Net, was the most used substance in Turkey only. In Serbia, ketoconazole was the most used antifungal substance, while in the other nine countries and Kosovo fluconazole was mainly used.

Superficial mycotic skin infections represent the most frequent form of fungal infections with a prevalence of 20%–25% of the entire world population and are caused mainly by dermatophytes.8 According to most publications and treatment guidelines, the drug of choice for treating these infections is terbinafine.9 Furthermore, terbinafine is more cost-effective against dermatophytes compared with other antifungal agents.9 Whether the lower


J Antimicrob Chemother 2015
doi:10.1093/jac/dkv064
Advance Access publication 22 March 2015