Antifungal therapy: drug–drug interactions at your fingertips

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The Information Age has revolutionized the ability of healthcare professionals (HCPs) to oversee a substantial body of clinically relevant information literally at one’s fingertips. In the field of clinical pharmacology, this may be particularly useful for managing drug–drug interactions (DDIs). A thorough understanding of the underlying mechanisms of DDIs allows the HCP to predict such interactions and avoid those of greatest clinical significance. Specifically, successful treatment with antifungal agents is complicated by the high potential to interact with other concomitant medications. We describe here the development of a real-time knowledge base of DDIs with antifungal agents, providing expert recommendations to HCPs on how to handle DDIs with these drugs. This new resource will facilitate rapid identification, quantification and classification of these DDIs by clinicians with varying levels of experience and resources worldwide, ultimately improving patient safety and strengthening health systems.

Introduction

Invasive fungal diseases (IFDs) are an important cause of morbidity and mortality in immunocompromised and otherwise debilitated patients. Although prophylactic or therapeutic use of antifungal drugs has substantially improved the outcome of IFDs, effective treatment can be complicated by drug–drug interactions (DDIs). Specifically, the antifungal class of azoles causes a high degree of significant DDIs, impacting the pharmacokinetics (PK) of either azoles, concomitant medications or both.1,2 This could result in either supratherapeutic plasma concentrations with subsequent risk of toxicity or subtherapeutic plasma concentrations potentially leading to therapeutic failure. Echinocandins, lipid and other formulations of amphotericin B and flucytosine are also involved in DDIs.3–5 Although these interactions are mostly of limited clinical importance compared with the azoles. Nevertheless, these interactions should be taken into account for clinical management in specific settings.

Despite widespread efforts to monitor for DDIs with antifungal agents, it is almost impossible for the clinician to be conversant with all possible DDIs and assess their potential consequence for an individual patient. In 2009, we published a review to provide recommendations on the clinical management of nearly 200 such DDIs.6 The complexity of the DDIs we described prompted us to develop a new approach for managing antifungal drug interactions.

A new approach in identifying DDIs with antifungal agents

The list of potential DDIs involving antifungal agents continues to grow as more evidence becomes available, so the literature requires constant re-evaluation of the clinical management of these DDIs. Drug interaction databases are a solution, but are not without disadvantages. Access to commercial databases (e.g. Lexi-Interact™) might be hindered due to the high costs associated with its use (membership fee), especially in resource-limited settings. Other databases such as DrugBank are freely available and afford up-to-date information,6 but they seldom offer a general approach to identifying DDIs or provide advice on specific clinical management. In our opinion, an ideal resource should not only provide a comprehensive, up-to-date overview of DDIs with antifungal agents, but should also describe the underlying mechanism and scientific evidence as well as offer tailor-made clinical advice on how to manage these interactions.

The clinical value of tailor-made web sites that provide information on managing DDIs in HIV-infected patients treated with antiretroviral drugs has been clearly demonstrated.7 Among these web sites, pharmacists ranked the HIV Drug Interactions database of the University of Liverpool8 among the highest by quality and usefulness.9 Given that antifungal drugs have similar potential for complicated DDIs as do antiretroviral drugs10 and the clear unmet need for a similar initiative based on the questions we received after publishing our review,6 we decided to adopt a similar approach for antifungal drugs entitled Fungal Pharmacology (http://www.fungalpharmacology.com).11

How we developed Fungal Pharmacology

Several years ago, we initiated the development of Fungal Pharmacology with the aim of providing up-to-date, easily accessible information on DDIs between antifungal agents and other prescription drugs, over-the-counter medicines and natural products. The intended users included hospital and general...
medical practitioners, hospital and community pharmacists, clinical pharmacologists, medical microbiologists, infectious diseases physicians and nursing staff. To promote its use, especially in resource-limited settings, we wanted Fungal Pharmacology to be completely free of charge. Mobile devices have also become commonplace in healthcare settings, so our goal was to also make the DDI application available to devices using Apple® and Android® operating systems. DDIs could be retrieved by entering a single drug or a class of drugs. Alternate therapeutic options with drugs from the same class would also be listed with their relevant severity. A data-sharing function was also added to enable clinicians to share relevant information with other colleagues. A detailed overview of the development process is shown in Figure 1.

A PhD student was appointed to gather all the primary information on DDIs acting under supervision. An international panel of hospital pharmacists, clinical pharmacologists, clinicians and microbiologists with extensive knowledge on the treatment of IFDs was convened to help design the web site and app. A communications agency and web designer were then employed to develop a facility for storing information and the initial version of the web site and app. By employing a usability test constructed by our web designer, the web site's content, navigation, interaction, layout and system functionality were evaluated by a user panel of clinicians and hospital pharmacists.

After an initial review and trial, the test panel offered suggestions for improvements and additional requirements (e.g. both a choice in alphabetical and severity listing of DDIs). Completion of

Figure 1. Development process and project timeline for Fungal Pharmacology.
data entry and composing clinical advice was achieved by continuous data integrity checks by our user panel. Every single DDI and clinical advice was peer-reviewed by our expert panel before the web site and app went live at the end of 2014. The interface of the web site is illustrated in Figure 2.

We included all currently licensed antifungal drugs for treatment of IFDs including azoles (fluconazole, itraconazole, posaconazole and voriconazole), echinocandins (anidulafungin, caspofungin and micafungin), lipid and other formulations of amphotericin B and flucytosine. Information was obtained from multiple sources including primary literature, product information, Micromedex®, Stockley’s Drug Interactions, Lexi-Interact™ and G-Standard (medicines standard in Dutch healthcare). Possible theoretical interactions were described referring to the pharmacological mechanism. For example, we extrapolated DDIs with ketoconazole to the azoles fluconazole, itraconazole, voriconazole and posaconazole based on their CYP3A4 inhibition potential. Besides drugs selected based on reported DDIs, an additional 100 drugs (not necessarily interacting drugs) were added to the database based on their frequent use in daily practice. Generic drug names were reported (using both the International Nonproprietary Name and United States Adopted Name, e.g. paracetamol/acetaminophen), which were categorized according to the WHO Anatomical Therapeutical Chemical (ATC) classification system. Severity of the DDI was classified using the Grading of Recommendations Assessment, Development and Evaluation approach. This approach was also used to evaluate the quality of available evidence, which led to an adapted algorithm also used by the HIV Drug Interactions database (offering four levels of evidence quality: high, moderate, low and very low (see Table S1, available as Supplementary data at JAC Online) Both grading of quality of evidence and strength of recommendation were compared with the grading in multiple sources described above, which was then peer-reviewed by the expert panel. In case of discrepant data described in the literature or product information (Summary of Product Characteristics (Europe) and US prescribing information (USA)), these differences were described in the clinical advice. Final recommendations and approval were done by the expert panel. Additional information on QT interval prolongation of both interacting drugs was retrieved.

Figure 2. Composite screen shot representing the structure of Fungal Pharmacology (displaying a drug–drug interaction between itraconazole and immunostimulants/suppressants, i.e. ciclosporin).
from the CredibleMeds® QT drugs list (available at https://www.crediblemeds.org/). Automatic searches and new record alerts using search engines (PubMed/EmBase) were undertaken weekly to ensure all information on DDIs with antifungal drugs was up to date. With this, Fungal Pharmacology is, to our knowledge, the first web-based resource for keeping abreast of DDIs with antifungal drugs in such great detail.

To further provide a better understanding of the underlying mechanisms of DDIs, detailed information on the PK of antifungal drugs is provided on the web site. Reports of new abstracts from major conferences and articles are presented in a news bulletin. More general information, recent notifications and changes in the product information by licensing agencies such as the EMA and US FDA are also shown.

Unfortunately, our approach only allows for paired DDIs rather than predicting tertiary interactions (groups of three or more drugs). In order to enhance our database with the ability to predict multiway interactions, this would require a tailor-made network inference algorithm,17 which cannot be readily applied to our web site.

Future directions
In the light of new information available and new drugs on the market, we implemented a quality control system for data on new and already-existing DDIs. In biweekly meetings, new key data from published papers, abstracts and product information are reviewed by one pharmacist and this information is assessed by an additional three assessors. Final comments and suggestions are then added to Fungal Pharmacology. Additionally, we address the feedback from our users in order to maintain quality and keep bias as low as possible. Collaborations are also being sought with Dutch healthcare organizations, such as the Dutch Medicines Evaluation Board, to provide additional sources of data input.

Knowledge bases such as Fungal Pharmacology should not be used as a standalone solution, but rather should aid clinical decisions and support electronic health records by incorporating therapeutic drug monitoring data, patient demographics, laboratory tests (e.g. liver function tests and glomerular filtration rate values) and clinical information such as side effects, laboratory abnormalities and ECG read-outs. In this way, the clinical advice on the DDI with antifungal drugs could be even more patient specific, anticipating altered PK parameters in the target population.

Conclusions
Healthcare professionals involved in the prevention and treatment of life-threatening IFDs now have a comprehensive tool at their disposal for managing >1000 clinically important DDIs with antifungal agents. Together with in-depth advice on the clinical management of these interactions, Fungal Pharmacology can greatly assist in maximizing the chance of clinical and microbiological success while minimizing the risk of treatment-related side effects due to DDIs.

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Transparency declarations
None to declare.

Supplementary data
Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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