Poster

[P27-2] P27-2: Anti-infective drugs (7): Antifungals

Chair: Yoh Takekuma, Japan

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[P27-2-8] Computerised optimal fluconazole dose selection improves early target attainment in critically ill patients

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Background

Patients with critical illness are known to have highly variable antimicrobial pharmacokinetics resulting in unpredictable exposures. Though therapeutic drug monitoring (TDM) is a proposed solution, access to pharmacology laboratory services is often limited and results that can meaningfully impact prescribing decisions for most drugs are rarely available at the outset of therapy. We postulated that a computerised optimal dose selection approach would result in drug exposures at least as good as a TDM-based approach and that both would be superior to standard intravenous (IV) dosing for the bis-triazole antifungal agent fluconazole.

Methods

A previously validated population pharmacokinetic model was used to simulate (i) standard dosing (400mg/day) with and without a loading dose (800 mg), (ii) standard dosing with loading dose followed by intensive sampling for determination of TDM dose adjustment and (iii) computerised optimal dose selection (without TDM) based on a simulated population of 1000 patients. All simulations were conducted in R using the *mrgsolve* package. Utilising the Shiny web application framework for R, an app was designed to potentially facilitate clinical implementation of this strategy.

Results

Standard fluconazole dosing led to substantial underexposure patients with organism Minimum Inhibitory Concentrations (MICs) of 2 mg/L, at 48h and 168h respectively; whilst incorporation of a loading dose improved early exposure, a proportion of patients remained sub-therapeutic at later timepoints indicating dose indivdualisation strategies are required. Whilst TDM provides an opportunity to facilitate this, early attainment of treatment targets remains poor. Our computerised dose selection strategy was highly effective with nearly all patients (99%) with organism MICs 2 mg/L meeting targets at 24h of therapy with less overexposure compared to standard dosing.

Conclusions

A simulated computerised optimal dose selection approach resulted in desired fluconazole exposures for nearly the entire population from the outset of therapy. We have designed a simple interface that could allow implemention and validation in a clinical setting without extensive pharmacometric expertise. Our proposed strategy has the potential to allow fluconazole dose individualisation in critical illness from the outset of therapy in the absence of TDM and may improve patient outcomes in severe fungal infections.