Pharmacodynamics of isavuconazole in a Dynamic In vitro Model of Invasive Pulmonary Aspergillosis

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DYNAMIC MODEL OF THE HUMAN ALVEOLUS

MATHMATICAL MODELLING

ABSTRACT

Background: Invasive pulmonary aspergillosis is a life-threatening infection. Triazole resistance to isolates of Aspergillus fumigatus is of increasing clinical concern. Isavuconazole is a novel triazole agent in phase III clinical development. PK-PD analyses may provide decision support for safe and effective antifungal regimens and is an important component of setting in vitro susceptibility breakpoints

Methods: A Dynamic in vitro model of the human alveolus was used to describe the pharmacokinetics and pharmacodynamics of isavuconazole against two wild-type and two previously defined azole resistant isolates of A. fumigatus. A human-like concentration time profile for isavuconazole was generated. Minimum inhibitory concentrations were determined using CLSI and EUCAST methodologies. Galactomannan was used as a biomarker of fungal density. AUC-MIC target values were calculated using a population based mathematical model.

Results: Isolates with higher MICs required a higher AUC in order to achieve maximal suppression of galactomannan. The AUC-MIC target necessary to achieve 90% probability of galactomannan suppression was 11.40 for EUCAST methodology.

Conclusions: Data generated in this study may be bridged to humans to define susceptibility breakpoints for isavuconazole against A. fumigatus when clinical data is available.

BACKGROUND

The emergence of triazole resistance in Aspergillus fumigatus is of increasing clinical concern. An understanding of the pharmacokinetics and pharmacodynamics (PKPD) of antifungal agents against Aspergillus spp may assist clinicians in optimising the use of antifungal agents to improve clinical outcomes. Isavuconazole is a novel antifungal triazole agent in the latter phases of development. Isavuconazole exhibits potent antifungal activity in vitro against the majority of Aspergillus fumigatus isolates. PKPD data obtained from studies of isavuconazole in mice may be difficult to bridge to humans because of substantial inter-species differences in clearance. Here, we use a previously described and validated dynamic in vitro model of the human alveolus, which enables human-like pharmacokinetics of isavuconazole to be simulated.

METHODS

ORGANISM AND PREPARATION OF INOCULUM

Isolates of A. fumigatus were recovered from 480°C stocks and sub-cultured onto potato dextrose agar for 5 days. Colonies were then washed with PBS and filtered. A conidial suspension of 1.5 x 10⁶ was prepared using a haemocytometer and was confirmed by quantitative culture.

CONSTRUCTION OF CELLULAR BILAYER

A previously defined cell culture model of the human alveolus using 12-well cell culture plate inserts was used. The cellular bilayer consisted of human pulmonary arterial endothelial cells (HPAECs) and human alveolar epithelial cells (A549).

ISAUVACONAZOLE PK-PD

The PK and PD of isavuconazole against A. fumigatus isolates were determined in four individual circuits. Isavuconazole dosages of 8mg, 0.1mg, 0.5mg, 0.5mg and 1.5mg were administered to the central compartment of each corresponding circuit. These dosages were used for all strains. Samples for both PK and PD were taken every 6 hours between 6-54 hours post inoculation. Isavuconazole concentrations in media were measured using high performance liquid chromatography (HPLC) with a Shimadzu Prominence (Shimadzu). Galactomannan (GM) was used as a quantitative biomarker in order to evaluate the antifungal efficacy of isavuconazole. Galactomannan levels were measured using a double-sandwich enzyme linked immunosorbent assay.

RESULTS

Isavuconazole causes a concentration-dependent reduction in galactomannan concentrations that are liberated from A. fumigatus.

The MIC and the genotype account for a considerable portion of pharmacodynamic differences that are observed between strains.

An AUC/MIC target of 11.40 is associated with near maximal antifungal activity in this model of early invasive pulmonary aspergillosis.

These results should be considered in conjunction with results from other pharmacodynamic models and data from other investigators/laboratories.

Data generated in this study may be bridged to humans to define susceptibility breakpoints for isavuconazole against A. fumigatus when clinical data is available.

REFERENCES


Figure 4: Pharmacokinetics and pharmacodynamics of isavuconazole against 1H1426. The model maximum inhibitory concentration (MIC) of isavuconazole is 4 mg/L.

Figure 5: Pharmacokinetics and pharmacodynamics of isavuconazole against the 1H1534. The model maximum inhibitory concentration (MIC) of isavuconazole is 8 mg/L.

Figure 6 (left): The relationship between the AUC/MIC ratio (observed using EUCAST) and CLSI methodology (b) and the probability of galactomannan suppression. An AUC/MIC of 11.40 is associated with a 90% probability of galactomannan suppression.

Table 1: Minimum inhibitory concentrations were determined in 10 independent experiments. Means depicted have doi: 10.1016/S0370-1616(12)01882-2