Pharmacokinetics and Pharmacodynamics of a Novel Triazole, Isavuconazole: Mathematical Modeling, Importance of Tissue Concentrations, and Impact of Immune Status on Antifungal Effect

Peter A. Warn, Andrew Sharp, Arvind Parmar, Jayesh Majithiya, David W. Denning, and William W. Hope

School of Translational Medicine, 1.800 Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, United Kingdom

Received 3 December 2008/Returned for modification 24 March 2009/Accepted 12 May 2009

Isavuconazole is a triazole with broad-spectrum activity against medically important fungal pathogens. We investigated the pharmacokinetics and pharmacodynamics of isavuconazole in a murine model of disseminated candidiasis. We determined the pharmacokinetics in both plasma and kidney. The relationship between tissue concentrations and the resultant antifungal effect was described using a mathematical model. The pharmacodynamic parameter that optimally links drug exposure with the antifungal effect was determined using dose fractionation studies. The impact of the immune status of mice receiving isavuconazole was determined in persistently and temporarily neutropenic animals. The pharmacokinetics of 1.6 to 28 mg isavuconazole/kg of body weight were linear. Exposure-response relationships demonstrated near-maximal effect following the administration of >15 mg/kg. The mathematical model showed that exposures in the kidney were 5.77 times higher than those in plasma, and there was persistence of the drug at this site despite concentrations in plasma falling to undetectable levels. The in vitro and in vivo postantifungal effects were 2 to 5 and 8.41 h, respectively. The area under the concentration-time curve (AUC)/MIC ratio was the parameter that optimally linked drug exposure with the observed antifungal effect. The total drug AUC/MIC ratios associated with a 90% probability of survival in temporarily and persistently neutropenic mice were 270 and 670, respectively. Once corrected for protein binding, these values are similar to the magnitude of drug exposure associated with a high probability of a successful therapeutic outcome for other triazoles. This study provides the experimental foundation for the use of isavuconazole in patients with disseminated candidiasis.
stored at −80°C on Sabouraud dextrose agar (Oxoid, Basingstoke, United Kingdom) and incubated at 37°C for 48 h. Subsequently, the organism was subcultured in Sabouraud dextrose broth (Oxoid, Basingstoke, United Kingdom) and incubated at 37°C for 16 h on an orbital mixer. A fungal suspension was prepared by two washes in phosphate-buffered saline (PBS).

**In vitro susceptibility testing and determination of the postantifungal effect (PAFE).** Isavuconazole was provided as a pure powder by Basilea Pharmaceutica International Ltd. (Basel, Switzerland). The MIC was determined according to CLSI M27-A2 methodology (13). MICs were determined in duplicate on three separate occasions, and for the purposes of pharmacodynamics analysis, the modal value was used.

For the determination of the in vitro PAFE, the organism was grown overnight in Sabouraud dextrose broth, washed in PBS, and then resuspended in 250 ml of warmed RPMI 1640 supplemented with 2% glucose to achieve a final fungal density of 1 × 10^6 CFU/ml. The suspension was incubated at 37°C in a water bath for 30 min and then divided into 10-ml aliquots. Isavuconazole was added to tubes at 1/10 × 1/4 × 1/2 × 1 × 2 × 5 × 10 × 40 ×, and 100 × the MIC. Separate flasks containing the C. albicans suspension in drug-free medium served as the controls. The suspension was incubated for 3 h prior to being centrifuged and washed twice. Twenty-five milliliters of warm RPMI 1640 was then added, and quantitative subcultures were obtained immediately and hourly thereafter for 8 h and then at 14 and 24 h. Subcultures were incubated at 37°C for 48 h, and quantitative colony counts were determined. The PAFE was defined as the difference in the time required for treated fungi to increase in density by 1 log_{10} CFU/ml after drug removal relative to the time taken for untreated controls to grow 1 log_{10} CFU/ml.

**Murine models of disseminated candidiasis.** All experiments were performed under a United Kingdom Home Office project license PPL42/2356 and approved by The University of Manchester Ethics Committee. Male CD1 mice (Charles River Ltd., Kent, United Kingdom) weighing 22 to 24 g were used. The mice were housed in ventilated HEPA-filtered cages, and food and water were provided ad libitum.

A persistently neutropenic model was used for the majority of experiments, but a temporarne neutropenic model was also used in survival experiments (see below). All animals were housed in laminar flow (HEPA filters) cages. The inoculum was prepared in PBS of 200 mg/kg of body weight intraperitoneally on day −3 relative to infection. This resulted in profound neutropenia for 6 days (i.e., 3 days postinoculation). For the persistently neutropenic group, a second dose of cyclophosphamide was administered 5 days later (i.e., 48 h postinfection). Serial neutrophil counts were determined in both cohorts. For survival experiments, mice were treated for 5 days and then observed for 2 days. Mice surviving to the end of the experiment were sacrificed. The final fungal inoculum was prepared by dilution in PBS and verified by quantitative culture. Mice were infected i.v. via the lateral tail vein with 2 × 10^5 organisms in a 0.2-ml volume.

**Preparation of isavuconazole for in vivo use.** The prodrug, BAL8557, was obtained from the manufacturer (Basilea Pharmaceutica International Ltd., Basel, Switzerland) as pure powder and reconstituted in distilled water to produce a 10 mg/ml solution. This was further diluted in 5% glucose at 200 mg/kg of body weight intraperitoneally on day −3 relative to infection. This resulted in profound neutropenia for 6 days (i.e., 3 days postinoculation). For the persistently neutropenic group, a second dose of cyclophosphamide was administered 5 days later (i.e., 48 h postinfection). Serial neutrophil counts were determined in both cohorts. For survival experiments, mice were treated for 5 days and then observed for 2 days. Mice surviving to the end of the experiment were sacrificed. The final fungal inoculum was prepared by dilution in PBS and verified by quantitative culture. Mice were infected i.v. via the lateral tail vein with 2 × 10^5 organisms in a 0.2-ml volume.

**Pharmacokinetics of isavuconazole in infected immunosuppressed mice.** Both single- and multiple-dose pharmacokinetics of isavuconazole were determined in infected immunosuppressed mice. For single-dose studies, 1, 2, 5, 13, and 28 mg/kg of isavuconazole was administered s.c., and blood samples were obtained at 0.5, 1, 2, 4, 8, and 24 h posttreatment via cardiac puncture under isoflurane anesthesia. For multiple-dose pharmacokinetics, mice received 1.6 and 28 mg/kg every 24 h. Samples were obtained on day 5 to ensure that a steady state had been achieved. Blood and kidney samples were obtained at 96.5, 97.5, 100, and 104 h after initiation of therapy. Three mice were used for each dose-time point combination. Blood samples were centrifuged and then stabilized with 10 μL 2 M citric acid per ml plasma and stored at minus 80°C prior to analysis.

**Measurement of the active moiety, isavuconazole, in plasma and kidney.** Concentrations of isavuconazole in plasma and kidney were determined using a validated liquid chromatography-tandem mass spectrometry method as previously described (15, 16). Briefly, protein precipitation was achieved with the addition of 150 μl of acetonitrile/water (82) also containing 0.1% formic acid to 50 μl of plasma. Samples were centrifuged at 40,000 × g for 20 min, and 100 μl of the supernatant was mixed with 350 μl of 1 M ammonium acetate (pH 5). Samples were analyzed using a Shimadzu liquid chromatograph coupled with an ABI ScieQ QTrap 2000 mass spectrometer; a Phenomenex Synergi 4-μm Po-
TABLE 1. Means, medians, and standard deviations for parameter values from the mathematical model

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_e$ (h⁻¹)</td>
<td>26.50</td>
<td>26.97</td>
<td>1.40</td>
</tr>
<tr>
<td>$V_c$ (liter)</td>
<td>0.075</td>
<td>0.085</td>
<td>0.027</td>
</tr>
<tr>
<td>SCL (liter/h)</td>
<td>0.037</td>
<td>0.032</td>
<td>0.017</td>
</tr>
<tr>
<td>$K_{cp}$ (h⁻¹)</td>
<td>15.01</td>
<td>16.34</td>
<td>8.08</td>
</tr>
<tr>
<td>$K_{cp}$ (h⁻¹)</td>
<td>18.84</td>
<td>19.68</td>
<td>2.7</td>
</tr>
<tr>
<td>$K_{ck}$ (h⁻¹)</td>
<td>0.169</td>
<td>0.23</td>
<td>0.007</td>
</tr>
<tr>
<td>$K_{ck}$ (h⁻¹)</td>
<td>18.29</td>
<td>17.95</td>
<td>0.84</td>
</tr>
<tr>
<td>$V_{kidney}$ (liter)</td>
<td>0.00019</td>
<td>0.00019</td>
<td>0.00007</td>
</tr>
<tr>
<td>$K_{max}$ (log₁₀ CFU/g/h)</td>
<td>0.17</td>
<td>0.16</td>
<td>0.07</td>
</tr>
<tr>
<td>$C_{50}$ (mg/liter)</td>
<td>9.17</td>
<td>9.39</td>
<td>0.84</td>
</tr>
<tr>
<td>POPMAX (CFU/g)</td>
<td>39,443,500</td>
<td>35,591,644</td>
<td>66,770,500</td>
</tr>
<tr>
<td>Initial condition</td>
<td>1,684</td>
<td>2,217</td>
<td>800</td>
</tr>
</tbody>
</table>

* $K_e$ is the first-order rate connecting the s.c. injection site with the central compartment; $V_c$ and SCL are the volumes of distribution and clearance from the central compartment, respectively; $K_{cp}$ and $K_{ck}$ are the first-order rate constants connecting the central and peripheral compartments; $K_{ck}$ and $K_{ck}$ are the first-order rate constants connecting the central compartment and kidney; $V_{kidney}$ is the volume of the kidney; $K_{max}$ is the growth constant describing maximal growth; $C_{50}$ is the concentration of isavuconazole required to produce 50% effect on the maximal rate of growth; $H_{g}$ is the sigmoidicity constant for the drug effect on $C. albicans$ growth; POPMAX is the theoretical maximum $C. albicans$ burden in the kidney. The initial condition is the fungal burden at the time of systemic drug administration.

MIC (peak/MIC), and the fraction of the dosing interval in which total drug concentrations were more than the MIC ($T > MIC$); this was achieved using the median parameter values from the mathematical model and with the simulation module of ADAPT II (see below and Table 1). The AUC was determined by integration. An inhibitory sigmoid $E_{max}$ model was fitted to the AUC/MIC-effect, peak/MIC-effect, and $T > MIC$-effect relationships, and the extent to which these models accounted for the individual data sets was assessed using the coefficient of determination ($R^2$).

**RESULTS**

**Susceptibility testing and in vitro PAFE.** The MIC was 0.004 mg/liter. An in vitro PAFE for isavuconazole was not apparent at concentrations of ≤1× MIC. At concentrations of 2× MIC, the PAFE was 2 h, and at concentrations of 5×, 10×, 40×, and 100× MIC, the PAFE was 5 h.

**Pharmacokinetics.** The pharmacokinetics of BAL4815 following the administration of isavuconazole at 1.6, 5, and 13 mg/kg s.c. once to immunocompromised infected mice were linear (Fig. 1). After five doses of 1.6 and 28 mg/kg, the pharmacokinetics of isavuconazole were also linear. Concentrations of isavuconazole in the kidney were five to six times higher than those observed in plasma and underwent relatively rapid exponential decline (Fig. 1). Estimates of the pharmacokinetics parameters were obtained from the linked population pharmacokinetics model (see below) and are summarized in Table 1. The terminal half-life of isavuconazole in plasma was 3.41 h (calculated using the mathematical model discussed below).

**Exposure-response relationships.** The exposure-response relationship for isavuconazole is shown in Fig. 2. The fungal burden in the kidney at the time of treatment initiation was $2.44 ± 0.16 \log_{10} \text{CFU/g}$ and increased to 5.5 to 6 $\log_{10} \text{CFU/g}$ at the end of the study (i.e., 29 h postinoculation). The fit of the inhibitory sigmoid $E_{max}$ model to the data was acceptable, with a coefficient of determination of 0.84. The exposure-response relationship was relatively shallow, with near-maximal reduction in the fungal burden observed with dosages of >15 mg/kg.

**Time course of antifungal effect.** The fit of the linked mathematical model to the data was highly acceptable, with a coefficient of determination for the observed-predicted plasma drug concentrations, kidney drug concentrations, and kidney colony counts of 0.96, 0.98, and 0.96, respectively (Fig. 3). The mean and median estimates for the model parameter values and their standard deviations are summarized in Table 1. Both measures of central tendency adequately described the data, but the medians gave slightly better predictions for the plasma pharmacokinetics.

Model simulations (Fig. 4) following the administration of isavuconazole show the rapid clearance of drug from the plasma, the relatively higher concentrations achieved in the kidney, and the logarithmic growth of $Candida$ in the latter portion of the dosing interval. The ratio of the AUC in the plasma to the AUC in the kidney was 1:5.77, suggesting moderate accumulation of drug at the primary effect site. Simulations demonstrated progressive fungal growth when plasma and kidney concentrations fell below ~0.14 and 0.8 mg/liter, respectively, which are approximately 2 orders of magnitude higher than the MIC of 0.004 mg/liter. The mathematical model was used to determine the duration of the PAFE. The time taken for an increase of 1 $\log_{10}$ CFU/g kidney in the initial logarithmic growth phase of controls was 5.98 h (determined directly from the data), whereas the time taken for a 1 $\log_{10}$ CFU/g increase in the fungal burden in the kidneys of mice receiving isavuconazole once the plasma concentrations had dropped beneath the MIC was 14.39 h. Therefore, the in vivo PAFE was 8.41 h for this strain of $C. albicans$.

**Dose fractionation studies.** The total dosages of isavuconazole associated with 20, 40, 60, and 80% maximal effect were 3.3, 5.4, 8.1, and 13.5 mg/kg, respectively. The pharmacokinetic model was used to convert total dosages to AUC/MIC, peak/MIC, and $T > MIC$, and these estimates are summarized in Table 2. The regressions for the three variables versus effect are shown in Fig. 5 and demonstrate that the best fit of the inhibitory sigmoid $E_{max}$ model to the data was achieved using the AUC/MIC as the independent variable. An exposure-response relationship was not apparent for $T > MIC$ versus effect.

**Survival studies.** The Cox model suggested the significant impact of immune status and the AUC/MIC on survival ($P = 0.004$ and 0.002, respectively). As demonstrated in Fig. 6, temporarily neutropenic mice had a higher probability of survival without the administration of active drug, and 100% survival could be induced with smaller AUC/MIC exposures than was the case for persistently neutropenic animals. AUC/MICs of 270 and 670 were associated with a 90% probability of survival.
in temporarily and persistently neutropenic mice, respectively (Fig. 6).

**DISCUSSION**

Despite the advent of new drugs and a new antifungal drug class, the mortality from disseminated candidiasis remains 30 to 50% (7). Isavuconazole is a novel triazole with potential clinical utility for the treatment of invasive fungal infections. This study provides the experimental foundation for the optimal use of this agent for patients with disseminated candidiasis.

There was clearly a relationship between plasma concentrations and the observed effect; this was exploited in the dose fractionation studies to define the pharmacodynamic index that best accounted for the antifungal effect of isavuconazole. Importantly, however, attempts to mathematically (i.e., directly) link plasma concentrations with the antifungal effect in the kidney repeatedly failed because of the juxtaposition of
FIG. 3. (A) Observed-predicted plots after the Bayesian step for the concentrations of isavuconazole in plasma. (B) Concentrations of isavuconazole in the kidney. (C) Fungal density in the kidney.
FIG. 4. Simulations of the time course of isavuconazole in plasma (A) and kidney (B) and the growth of Candida in the kidney (C) in mice receiving 28 mg/kg isavuconazole as the active drug. The open squares represent raw data from individual mice (A and B) or the means of three or four mice (C) receiving 28 mg/kg isavuconazole as the active drug. The closed squares in panel C represent the fungal burden in vehicle-treated controls. The solid line represents the fit of the mathematical model to the pharmacokinetic and pharmacodynamic data.
rapid clearance of the drug from the central compartment and an antifungal effect that persisted beyond the time drug concentrations in plasma were undetectable. When kidney concentrations were modeled and the antifungal effect was linked to this compartment, a solution was obtained (see the appendix for details of the mathematical model). The triazoles are known to undergo extensive distribution to target tissues. Our data suggest that isavuconazole achieves 6-fold-higher exposures in the kidney than in plasma and that levels within the kidney persist long after levels in plasma become undetectable. Whether this also occurs in humans is not known, and the penetration of isavuconazole into other relevant tissue compartments, such as the epithelial lining fluid of the lung, has not been studied. We readily accept that tissue homogenates provide only a crude estimate of the concentration of drug at the effect site and that all organs have subcompartments that have different properties in terms of fungal pathogenesis and drug penetration. Nevertheless, this study demonstrates that homogenates represent a useful, albeit imperfect, surrogate for tissue concentrations and that they may aid in further understanding antifungal effect.

The triazoles are widely regarded as having a fungistatic mode of action against Candida spp., and our data are entirely consistent with this notion. Both fluconazole and posaconazole do not induce overt fungal killing in experimental models of disseminated candidiasis but retard fungal growth (1, 4). Due to the relatively short terminal plasma half-life and short PAFE of isavuconazole, we observed progressive fungal growth in the latter portion of the dosing interval as both plasma and kidney levels of drug declined beneath a threshold. Importantly, this threshold was not the MIC of isavuconazole but rather a concentration approximately 2 orders of magnitude higher. This is probably a reflection of the relatively high levels of protein binding exhibited by the compound, since only a small fraction of the total measured drug is free to engage with its microbiological target.

The classically designed dose fractionation studies clearly suggest that the AUC/MIC is the variable that best links isavuconazole exposure with the observed effect, and this is consistent with findings for other triazoles (1–4, 12). The mathematical model, however, suggests that the progressive growth seen in the latter portion of the dosing interval can be prevented by fractionated dosing to ensure that levels in plasma (or tissue) remain above a threshold. This was especially apparent in this study because of the short half-life of isavuconazol

### TABLE 2. Estimates for the various pharmacodynamics variables for dosage fractionation regimens

<table>
<thead>
<tr>
<th>Dose of isavuconazole</th>
<th>AUC/MIC</th>
<th>Peak/MIC</th>
<th>Fraction of dosing interval more than MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.27 once</td>
<td>387.75</td>
<td>128.75</td>
<td>0.62</td>
</tr>
<tr>
<td>1.63 b.i.d</td>
<td>384.25</td>
<td>64.5</td>
<td>1</td>
</tr>
<tr>
<td>0.82 q.i.d</td>
<td>372.25</td>
<td>32.25</td>
<td>1</td>
</tr>
<tr>
<td>5.35 once</td>
<td>630</td>
<td>209.25</td>
<td>0.68</td>
</tr>
<tr>
<td>2.67 b.i.d</td>
<td>633.75</td>
<td>106.25</td>
<td>1</td>
</tr>
<tr>
<td>1.34 q.i.d</td>
<td>614.25</td>
<td>48.25</td>
<td>1</td>
</tr>
<tr>
<td>8.12 once</td>
<td>969.5</td>
<td>322.5</td>
<td>0.73</td>
</tr>
<tr>
<td>4.06 b.i.d</td>
<td>960.25</td>
<td>161</td>
<td>1</td>
</tr>
<tr>
<td>2.03 q.i.d</td>
<td>930.5</td>
<td>80</td>
<td>1</td>
</tr>
<tr>
<td>13.48 once</td>
<td>1599.75</td>
<td>532.5</td>
<td>0.79</td>
</tr>
<tr>
<td>6.74 b.i.d</td>
<td>1584.5</td>
<td>265</td>
<td>1</td>
</tr>
<tr>
<td>3.37 q.i.d</td>
<td>1544.75</td>
<td>128.75</td>
<td>1</td>
</tr>
</tbody>
</table>

*Total active drug equivalent (mg/kg) administered s.c. b.i.d., twice a day; q.i.d., four times a day.
*b The MIC was 0.004 mg/liter.
*c The initial peak concentration is shown.

### FIG. 5. Regressions from the dose fractionation experiments.

(A) Total drug peak concentration/MIC versus effect. (B) Total drug AUC/MIC versus effect. (C) Fraction of the dosing interval in which total drug concentrations are more than the MIC. The data are means ± standard deviations for six mice. The solid line is the fit of the inhibitory sigmoid $E_{\text{max}}$ model to the data.
azole (3.41 h) in relation to the extended dosing interval (24 h).

This is unlikely to be clinically relevant given the much longer terminal half-life in humans. The in vivo PAFEs for fluconazole and posaconazole have been estimated to be 4 to 21 and 24 h, respectively, and this prolonged effect has been used to account for the observation that the AUC/MIC appears consistently as the dynamically linked variable for the triazoles. A number of factors may contribute to the in vivo PAFE, including sub-MIC effects, the time for organisms to recover from impaired ergosterol synthesis, and the persistence of the drug at the effect site (4). The mathematical model suggests that the prolonged mean residence time of isavuconazole in the kidney is an important determinant of the PAFE, and the same may also be true for other triazoles.

Several experimental studies suggest that immune function has a critical bearing on the antifungal drug effect (8, 9). This study highlights striking differences in the probabilities of survival for persistently and temporarily neutropenic mice receiving the same dosages of isavuconazole. While this is well known and intuitively obvious to many clinicians, there are important implications for the broad application of pharmacodynamics targets outside the setting in which they have been derived. The survival study and the Cox model suggest that a total drug AUC/MIC of 670, which is associated with 90% probability of survival after 5 days of therapy, is a potential pharmacodynamic target for isavuconazole for disseminated candidiasis in neutropenic hosts. Ideally this finding should be confirmed with several other strains. Interestingly, this value produces a submaximal decrement in the fungal burden when assessed using log_{10} CFU/g (Fig. 5). This is consistent with previous work that suggests that relatively small decrements in the fungal burden produce prolongation of survival (10). If a correction is made for protein binding, then the magnitude of this target is comparable to those identified for other triazoles. A lower drug exposure target may be appropriate for non-neutropenic hosts.

APPENDIX

The murine pharmacokinetics of isavuconazole and the antifungal effect induced by the administration of the prodrug to persistently neutropenic mice were described using the following five simultaneous inhomogeneous differential equations:

\[
\frac{dX(1)}{dt} = B(1) - K_e \times X(1)
\]

\[
\frac{dX(2)}{dt} = -K_p \times X(2) - K_{ak} \times X(2) + K_{ec} \times X(3) + K_{ac} \times X(4)
\]

\[
\frac{dX(3)}{dt} = -K_{ap} \times X(2) - K_{ec} \times X(3)
\]

\[
\frac{dX(4)}{dt} = -K_{ak} \times X(2) - K_{ac} \times X(4)
\]

\[
\frac{dX(5)}{dt} = K_{g_{max}} \left(1 - \frac{X(5)}{V_{POMAX}}\right) \times X(5)
\]

\[
\times \left(1 - \frac{\frac{X(4)}{V_{kidney}}}{C_{g_{max}} + \frac{X(4)}{V_{kidney}}}\right)
\]

Equations 1, 2, 3, and 4 describe the pharmacokinetics of isavuconazole and its distribution to the kidney, which is the primary effect site. Compartments 1, 2, 3, and 4 represent the subcutaneous injection site, central compartment, peripheral compartment and kidney, respectively. X(1), X(2), X(3), and X(4) represent the amount of the drug (in milligrams) in these respective compartments. The prodrug was administered subcutaneously into compartment 1 as a bolus [B(1)], from where it equilibrated with the central compartment (compartment 2) and degraded completely to the active moiety isavuconazole. Drug in the central compartment equilibrated with the rest of the body (compartment 3) and the kidney (compartment 4), which has volume V_{kidney} (in liters). There was first-order elimination from the central compartment (SCL, in liters/h), which has volume V_{g} (in liters). K represents the various first-order intercompartmental rate constants.

Equation 5 describes the rate of change of the number of Candida organisms within the kidneys as influenced by the growth of Candida and the concentrations of isavuconazole in the kidney. X(5) represents the number of Candida organisms in the kidney. The term 5a describes the capacity-limited growth of C. albicans within the kidney and contains the parameters K_{g_{max}} and POMAX, which represent the maximum growth rate constant and the maximum theoretical fungal density achievable in the kidney, respectively. As the number of organisms within the kidney approaches POMAX, the rate of Candida growth slows and approaches zero. The term 5b in equation 5 provides a way of allowing isavuconazole to exert a fungistatic as opposed to a fungicidal effect (i.e., growth suppression rather than explicit killing). In the absence of drug, this term defaults to 1, and Candida grows in an unrestrained manner. Following a progressively higher concentration of isavuconazole, the growth rate of Candida is constrained to approach zero. C_{g_{max}} is the concentration of isavuconazole at which the effect on growth is half-maximal, and H_s is the associated slope function.

ACKNOWLEDGMENTS

This study was supported by the Fungal Research Trust and Basilea Pharmaceutical International Ltd.

REFERENCES


