Pharmacodynamics of Voriconazole in Children: Further Steps Along the Path to True Individualized Therapy

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Abstract

Voriconazole is the agent of choice for the treatment of invasive aspergillosis in children of at least 2 years of age. The galactomannan index is a routinely used diagnostic marker for invasive aspergillosis and can be useful for following the clinical response to antifungal treatment. The aim of this study is to develop a pharmacokinetic-pharmacodynamic (PK-PD) mathematical model that links the pharmacokinetics of voriconazole with the galactomannan readout in children. Twelve children receiving voriconazole for treatment of proven, probable and possible invasive fungal infections were studied. A previously published population PK model was used as the Bayesian prior. The PK-PD model was used to estimate the average AUC in each patient and the resultant galactomannan-time profile. The relationship between the ratio of the area under the concentration-time curve (AUC) to the concentration of voriconazole that induced half maximal killing (AUC:EC50) with the terminal galactomannan level was determined. The voriconazole concentration-time and galactomannan-time profiles were both highly variable. Despite this variability, the fit of the PK-PD model was good, enabling both the PK and PD to be described in individual children. (AUC:EC50)/15.4 predicted terminal galactomannan (P=0.003) and a ratio >6 suggested a lower terminal galactomannan level (P=0.07). The construction of linked PK-PD models is the first step in developing control software that enables not only individualized voriconazole dosages, but individualized concentration targets to achieve suppression of galactomannan levels in a timely and optimally precise manner. Controlling a galactomannan level is a first critical step to maximizing clinical response and survival.
Introduction

Voriconazole is an extended-spectrum triazole antifungal agent with activity against *Aspergillus* spp., *Candida* spp., *Cryptococcus neoformans*, *Fusarium* spp., and *Scedosporium apiospermum* (1). Voriconazole is licensed for use in children > 12 (United States) or > 2 (Europe) years of age with invasive aspergillosis (IA), fluconazole-resistant invasive *Candida* infections, infections caused by *Scedosporium* spp. and *Fusarium* spp., and in non-neutropenic children with candidemia (2). In all patient age groups, voriconazole is a first-line agent for the treatment of IA (2, 3). The inter- and intra-individual variability in drug exposure is high and some of this variability can be attributed to CYP2C19 genotype (4), impaired liver function (5), age (6), inflammation (7), and CYP2C19/CYP3A-interacting co-medication (8). This coupled with a reasonably detailed understanding of the relationship between drug exposure and the probability of both therapeutic response and toxicity has led to a recommendation to use therapeutic drug monitoring (TDM) as an adjunct to routine clinical use of voriconazole (9). We have recently developed software for dosage individualization in both adults and children (10, 11). The underlying algorithms can be used to achieve desired serum drug concentration targets in both adults and children in an optimally precise manner.

In clinical settings, galactomannan index is increasingly used as a biomarker for the diagnosis of invasive aspergillosis. According to the EORTC/MSG diagnostic criteria for invasive fungal diseases, galactomannan can be used as a microbiological criterion to establish a diagnosis of invasive aspergillosis (12). Galactomannan is a large molecular weight polysaccharide cell wall fungal antigen that is released into the bloodstream during hyphal growth and angioinvasion (13). Routine sequential monitoring of serum galactomannan levels can be used for the early detection of invasive aspergillosis (14).
There is now increasing interest in using galactomannan to follow the response to antifungal therapy (15). Such a strategy is supported by the observation that patients with unremittingly high circulating antigen levels tend to have a poor clinical outcome. The availability of a biomarker with both diagnostic and prognostic significance is relatively unique in infectious diseases. An understanding of galactomannan kinetics and its response to antifungal drug concentrations provides the possibility to provide true individualized antifungal therapy.

Here, we developed a linked pharmacokinetic-pharmacodynamic (PK-PD) mathematical model to describe the serum pharmacokinetics of voriconazole and the pharmacodynamics quantified in terms of the circulating galactomannan levels. Since much of the pharmacokinetic and pharmacodynamic data was necessarily sparse, we buttressed the pharmacokinetics by using richer data obtained from the early phases of drug development. Such an approach enabled us to ensure robust estimates of the PK, which would have otherwise been extremely difficult or resulted in biased parameter estimates.

The development of a linked PK-PD model is a further step in the provision of true individualized therapy where a drug is administered to control a biomarker that is itself intricately linked to therapeutic responses and optimal clinical outcomes.
Patients and methods

Patients.

All patients aged <18 years receiving voriconazole with at least one voriconazole serum concentration and galactomannan level measured within the 9-year period from January 2005 to March 2014 were eligible for inclusion in this study. The medical, pharmacy and laboratory records at the University Medical Center Groningen were reviewed. Demographic, microbiological and clinical data were collected using standardized case report forms. The voriconazole treatment regimen and serum concentrations of voriconazole were also collected. Information that could potentially influence the voriconazole serum concentrations were identified and reviewed for potential inclusion of these serum concentrations into the population PK-PD model. The EORTC/MSG criteria (12) were used to determine the probability of invasive fungal disease to each patient at the start of voriconazole therapy. The Medical Ethical review board of the University Medical Center Groningen (metc 2013-491) waived the requirement to obtain informed consent from individual patients.

Therapeutic Drug Monitoring

All patients at the University Medical Center Groningen that were treated with voriconazole underwent therapeutic drug monitoring. The first sample was typically taken after 2 days and results were reported the same day. The therapeutic trough concentration targets were >1 mg/L and <6 mg/L. Concentrations outside these values prompted a change in dosage. There was no algorithm for dosage adjustment, but typically the dose of voriconazole was increased or decreased by 30-50% and concentrations were re-measured.
after several days. Galactomannan was not used to make decisions about dosage adjustment.

Voriconazole assay.

The voriconazole serum concentrations were determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method (16). All measurements were performed on a Thermo Fisher (San Jose, USA) triple quadrupole LC–MS/MS with a Finnigan™ Surveyor® LC pump and a Finnigan™ Surveyor® autosampler, which was set at a temperature of 20 °C. The Finnigan™ TSQ® Quantum Discovery mass selective detector was operating in electrospray positive ionization mode and performed selected reaction monitoring. The ion source spray voltage was set at 3500 V, the sheath and auxiliary gas pressure at 35 Arbitrary units (Arb.) and 5 Arb., respectively and the capillary temperature at 350 °C. Cyanoimipramine was used as internal standard. Analyses were performed on a 50 mm × 2.1 mm C18 5-μm analytic column (HyPURITY AQUASTAR, Interscience Breda, The Netherlands). The column temperature was set on 20°C. The mobile phase consisted of an aqueous buffer (containing ammonium acetate 10 g/L, acetic acid 35 mg/L and trifluoroacetic anhydride 2mL/L water), water and acetonitrile. Chromatographic separation was performed using a gradient with a flow of 0.3 mL/min and a run time of 3.6 minutes. Sample preparation was performed by protein precipitation and found suitable, resulting in linear calibration curves in the range of 0.1 - 10 mg/L. The peak height ratios of voriconazole and internal standard were used to calculate concentrations. This method was validated in accordance with the Guidance for Industry Bioanalytical Method Validation of the Food and Drug Administration. The validation showed an overall bias ranged from 0.1-2.3%, a within run CV ranged from 1.9-7.8% and a between run CV ranged from 0.0-3.1%.
Galactomannan assay.

The samples for the determination of galactomannan index were measured using Platelia Aspergillus EIA kit (Bio-Rad Laboratories) as described by the manufacturer. A cut-off value for positivity in serum of >0.5 was used.

Pharmacokinetic-pharmacodynamic modeling.

The pharmacokinetic (i.e. serum voriconazole concentrations) and pharmacodynamic (i.e. galactomannan values) data from the 12 children were necessarily sparse—they were collected as part of routine clinical care rather than as part of a prospective clinical trial. In addition, these sparse pharmacokinetic and pharmacodynamic data were not necessarily optimally informative. Fitting any pharmacokinetic model to a limited, sparse and non-optimally informative dataset is either not possible or will lead to biased parameter estimates. We circumvented this problem using a two-step process. In the first step, each of the 12 new patients had their PK estimated using a previously described population PK model where the PK model served as the Bayesian prior (11). In the second step, the Bayesian posterior estimates for each patient’s PK parameters were fixed and the pharmacodynamic parameters were then estimated by fitting the pharmacodynamic component of the model to each patient’s galactomannan data. The population program Pmetrics was used for all modeling (17).

The structural pharmacokinetic mathematical model consisted of three differential equations that described the rate of change of the amount of voriconazole within each compartment. A fourth equation described the rate of change of galactomannan in the serum. These four inhomogeneous ordinary differential equations are as follows:
\[
\frac{dX_1}{dt} = -K_a \cdot X_1
\]  

(1)

\[
\frac{dX_2}{dt} = K_a \cdot X_1 + RateIV - \frac{V_{max}}{K_m \cdot V + X_2} \cdot X_2 - K_{cp} \cdot X_2 + K_{pc} \cdot X_3
\]  

(2)

\[
\frac{dX_3}{dt} = K_{cp} \cdot X_2 - K_{pc} \cdot X_3
\]  

(3)

\[
\frac{dX_4}{dt} = KGM_{prod} \cdot \left[1 - \left(\frac{X_4}{V_{P0_{max}}}\right)\right] \cdot \left(1 - \frac{X_4^H}{EC_{50} + X_4^H}\right) \cdot X_4
\]  

(4a)

\[
-KGM_{elim} \cdot X_4
\]  

(4b)

Where: \(X_1, X_2, \) and \(X_3\) are the amounts (in milligrams) in the gut, central compartment, and peripheral compartment, respectively and \(\frac{dX_n}{dt}\) is the instantaneous rate of change in the amount of drug in compartment \(n=1, 2\) or \(3; K_a\) is the first-order rate constant of drug absorption after an oral bolus dose from the gut compartment (#1) to the central serum compartment (#2); \(RateIV\) is the rate of intravenous voriconazole infusion; \(V_{max}\) is the maximum rate of the enzyme activity in metabolism of voriconazole (mg/h) and it was allometrically scaled for body weight (kg) using the equation \(V_{max} = V_{max0} \cdot kg^{0.75} ; K_m\) is the concentration of voriconazole in the central compartment at which voriconazole clearance is half-maximal; \(V\) is volume of the central compartment (liters) and it was also allometrically scaled as \(V = V_{0} \cdot wt; K_{cp}\) and \(K_{pc}\) are the first-order rate constants connecting the central compartment and peripheral compartment (#3); \(X_4\) is the concentration of galactomannan in the serum; \(KGM_{prod}\) is the maximal production rate of galactomannan in the central compartment; \(POP_{max}\) is the maximal achievable galactomannan value; \(KGM_{elim}\) is the maximal rate of elimination of galactomannan from the central compartment; \(H\) controls the...
steepness of the relationship between drug concentration and reduction in galactomannan production in the central compartment; and EC50 is the concentration of voriconazole at which half-maximal reduction in galactomannan production is achieved. The oral bioavailability of voriconazole, $F$, was included because patients received voriconazole both orally and intravenously. In Pmetrics, $F$ is a multiplier on oral doses, and it is not included within the differential equations.

Equations 1, 2 and 3 describe the rate of change of voriconazole in the gut, central serum and peripheral tissue kinetic compartments, respectively. Equation 4 describes the rate of change of galactomannan in the central serum kinetic compartment, and we divide this equation into two separate terms for clarity. First, 4a describes the production of galactomannan, which is limited by a maximum value and also by voriconazole concentrations in a sigmoidal function, such that when concentrations are infinite, production is zero; second, 4b describes the sum of all physiologic galactomannan elimination mechanisms. A baseline galactomannan value within compartment 4 on the day of the first voriconazole dose was also estimated within Pmetrics, with a possible range of 0.1 to 12, reflective of clinically observed extremes. The fit of the mathematical model to the data was assessed using visual inspection and linear regression of the observed-versus-predicted values both before and after the Bayesian step.

**Exposure response relationships**

The relationship between a traditional pharmacodynamic measures of drug exposure such as the ratio of the area under the concentration time curve (AUC):minimum inhibitory concentration (MIC) and therapeutic response is often not possible to determine for invasive
aspergillosis because the invading pathogen is usually not recovered. Therefore, we used a new concept in these analyses. The AUC:EC₅₀ is the ratio of the voriconazole daily AUC to the EC₅₀, which is the posterior Bayesian estimate of the \textit{(in vivo)} concentration of voriconazole required to induce half maximal reduction in galactomannan levels in each individual patient. Thus, the EC₅₀ is analogous to the more traditional \textit{in vitro} estimate of drug potency, which is the MIC, but instead reflects an \textit{in vivo} estimate of potency that can be derived from the change in galactomannan and voriconazole drug concentrations. The average daily AUC was calculated by estimating the total fitted AUC for each patient and dividing by the number of 24-hour treatment intervals. The average AUC circumvents the problem of defining which AUC is important for treatment effect (e.g. the AUC following the first dose or after a week of dosing). The relationship between the AUC:EC₅₀ and the final galactomannan or survival was explored.
RESULTS

Demographics

The demographic data for the study population are summarized in Table 1. Fifty percent of patients had either AML or ALL. The total mortality rate of the patient population was distressingly high: 10 (83.3%) of the 12 children died. For 4 of the 12 patients Aspergillus spp. was recovered and three of the four patients died from invasive aspergillosis. In the remaining patients a diagnosis of probable invasive aspergillosis was established using galactomannan.

TDM data for voriconazole and galactomannan

There were a total of 261 and 33 measurements available for voriconazole concentrations and galactomannan levels from the 12 children, respectively. The concentration-time profiles for these respective readouts are shown in Figure 1.

Population PK-PD model

The fit of the population PK-PD model to the data was acceptable despite the extreme pharmacokinetic and pharmacodynamic variability that is evident in Figure 1. The Bayesian posterior estimates for the pharmacokinetics and pharmacodynamics are shown in Figure 2 in Panel A and B, respectively. The pharmacodynamics (i.e. galactomannan) were not well described using either the mean or median values for the parameters from the population model (data not shown). There simply was not a single set of parameter values that could be identified that was adequate to describe the time course of galactomannan in
every patient. In contrast, however, the time course of galactomannan in each individual
patient was readily described with a high degree of precision using the Bayesian posterior
estimates for each patient. The heterogeneity of the different trajectories of galactomannan
in individual patients is evident in Figures 1 and 3. Of note, the initial condition (i.e. the
galactomannan level at the commencement of treatment) was strikingly different between
patients, potentially reflecting differences in underlying fungal burden. Furthermore, the
time course of galactomannan in response to voriconazole therapy was also highly variable
and ranged from a prompt decrease through to persistent antigenemia with no apparent
therapeutic response.

Relationship between AUC:EC50 and terminal galactomannan or survival.
The relationship between AUC:EC50 and terminal galactomannan is shown in Figure 4.
Using a simple non-linear relationship, terminal galactomannan was strongly predicted by
(AUC:EC50)/15.4 (p=0.003). As a possible breakpoint, patients with an AUC:EC50 > 6 tended
to have a more consistently lower terminal galactomannan level (P=0.07). In contrast,
AUC:EC50 was not associated with survival. The mean in those who died was 6.1 vs. 7.6 in
those who survived (P=0.76).
Much has been written about the use of therapeutic drug monitoring as an indispensible adjunct to the use of voriconazole for the treatment of invasive aspergillosis and other invasive fungal diseases (9). There is a strong and growing evidence base to support such an assertion. Patients with serum concentrations < 1 mg/L appear to have poorer clinical outcomes and higher mortality compared with patients with concentrations > 1 mg/L (18). Similarly, patients with trough concentrations > 5 to 6 mg/L have a higher probability of having hepatotoxicity and confusion (18, 19). The case for routine TDM is further enhanced by the extreme pharmacokinetic variability that is characteristic of voriconazole and clearly evident in this study. The question raised by this study and these analyses is whether TDM and dosage adjustment to achieve desired serum drug concentrations is the ultimate solution for using voriconazole and whether it constitutes “true individualized therapy”.

The current strategy for TDM of voriconazole (or any other antimicrobial) is quite inconsistent with respect to individualization. The case for quantifying and controlling individual pharmacokinetic variability through dose modification is made time and again by many people (including us). We have gone as far as use the information stored within population pharmacokinetic models to construct software that can be used for dosage individualization of voriconazole in adults and children (10, 11). Importantly, the use of such software demands that the clinician define a drug concentration target that is deemed as having a high probability of therapeutic success and a low probability of toxicity. All the therapeutic targets that are used and cited in various guidelines are derived from large populations of patients, which are in effect “average” values. Such an approach is counter to all notions of individualized therapy, and in fact is "one-size fits all" target selection. A
significant advance that is enabled by the use of biomarkers such as galactomannan is the prospect of achieving true individualized target concentrations based on measured pharmacodynamics. Some patients will need more drug exposure, while others will need less. A different way of expressing this idea is that both the pharmacokinetics and pharmacodynamics are different from patient to patient, but need to be optimized for an individual. *A priori* the trajectory of the voriconazole concentration-time profile or the galactomannan in an individual patient is unknowable. Variability in both pharmacokinetics and pharmacodynamics contributes to both good and poor clinical outcomes, and the achievement of optimal clinical outcomes requires control of both.

Figure 3 is particularly illustrative of the many challenges facing clinicians that are treating children with invasive fungal diseases. Firstly, the pharmacokinetics of voriconazole are highly variable, as previously described by us and many others. Second, and perhaps more importantly is the observation that the pharmacodynamics are also highly variable.

There is no way of predicting which path (galactomannan trajectory) an individual patient will follow once voriconazole is started. Results from phase II and III clinical studies (20, 21) suggest that on average a satisfactory clinical response will be obtained when a fixed dosing strategy is used, but that does not provide any guarantee that the patient has been dosed such that the likelihood of response is above average. Galactomannan provides a real-time indication of the patient’s individual response to voriconazole and whether a therapeutic response is being achieved or not. It is possible to react to changes in galactomannan directly rather than just the voriconazole concentration. Consider the differences in galactomannan responses between Patient ID 177 and Patient ID 180 in Figure 3. Both patients achieve comparable voriconazole serum concentrations in the first days of therapy, but their pharmacodynamics are completely different for reasons that may not be
immediately obvious. Patient ID 177 appears not to be responding to voriconazole and should have the dose increased, changed to an alternative agent, or a second antifungal agent added. Instead, the dosage was reduced probably because the upper TDM target was exceeded (again, this value is derived from a population of patients). However, the population value may not have been appropriate for that patient. This suboptimal regimen resulted in sustained galactomannan antigenemia and the patient ultimately died. In contrast, Patient ID 180 achieved a sustained response in their galactomannan trajectory (despite having voriconazole concentrations ordinarily considered to be associated with a higher probability of toxicity) and ultimately survived.

We do not claim this is an ideal dataset. The data are sparse and not collected at optimally informative times. Fitting was difficult and required a pre-existing population PK model that could be used as a Bayesian prior. Despite some limitations, it is remarkable that the PK-PD mathematical model fits any of the data given it is collected in routine clinical settings. Importantly, however, there is only an acceptable fit of the model to the data after the Bayesian step. In this regard, fitting models to galactomannan data is similar to fitting mathematical models to drug resistant data where population fits are often notoriously bad. The reason for this is obvious following a brief inspection of the raw data in Figure 1, Panel B. The galactomannan data are non-monotonic. Some profiles rise unexpectedly, while others fall. Such heterogeneity in response makes it nearly impossible to derive a single set of parameter values that account for all the data in a reasonably unbiased yet satisfactorily precise manner. We could have performed Monte Carlo simulation on the Bayesian posterior estimates to explore the impact of both pharmacokinetic and pharmacodynamic variability on the therapeutic outcome, but ultimately decided that this would have produced unreliable results given the paucity of data (some patients only have one or two
observations), but this could easily be done in the future with larger and more comprehensive datasets.

The AUC:EC\textsubscript{50} is a pharmacodynamic index that may be helpful in future studies of invasive aspergillosis. While the EC\textsubscript{50} requires at least one measured voriconazole and galactomannan in a patient and requires some PK-PD modeling expertise, it captures and quantifies much of the pharmacodynamic variability that is evident in this study. Thus the AUC:EC\textsubscript{50} provides an understanding of the therapeutic response in terms of drug exposure (AUC) as well as the pharmacodynamics. A high estimate for EC\textsubscript{50} may be caused by factors such as high fungal burden, the presence of antifungal resistance mechanisms, a delay in the initiation of antifungal therapy, infection with sanctuary sites and profound immunosuppression. In this way, we view it as potentially superior to the \textit{in vitro} MIC, which does not account for the clinical therapeutic environment within a patient. The AUC:EC\textsubscript{50} is a fully individualized \textit{in vivo} estimate of drug potency, and it significantly predicted terminal galactomannan levels, even in this small study. It did not predict survival, but the majority of this cohort died from a range of causes including the underlying disease. Furthermore, terminal galactomannan is likely a more objective reflection of \textit{in vivo} voriconazole efficacy than survival, which is multi-factorial, especially in these kinds of patients with complex underlying medical problems.

The next steps are clear. Larger, richer datasets that contain richer and optimally informative sampling for both voriconazole and galactomannan will enable the construction of more robust pharmacokinetic-pharmacodynamic mathematical models. These models will form the basis of dual output stochastic controllers where a clinician has the option to individualize dosing to control the serum drug concentrations, the circulating biomarker or both. Such an advance represents a further critical step towards the provision of true
individualized therapy, which is surely the ultimate goal of all clinicians treating any patient with a life-threatening invasive fungal infection. Such an approach is one key advance for better care of immunocompromised patients who usually have multiple comorbidities. Moreover, as circulating biomarkers are developed for other diseases this approach can be applied to a wider range of infections.
References


Table 1: Patients demographics and characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
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<tbody>
<tr>
<td>Gender (male)</td>
<td>8 (58.3)%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>6 (5 - 10)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>22.4 (18.8 - 33)</td>
</tr>
<tr>
<td><strong>Underlying disease</strong></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>5 (41.7)%</td>
</tr>
<tr>
<td>AML</td>
<td>1 (8.3)%</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>3 (25)%</td>
</tr>
<tr>
<td>Other malignancies a</td>
<td>3 (25)%</td>
</tr>
<tr>
<td><strong>EORTC classification b</strong></td>
<td></td>
</tr>
<tr>
<td>Proven</td>
<td>2 (16.7)%</td>
</tr>
<tr>
<td>Probable</td>
<td>6 (50)%</td>
</tr>
<tr>
<td>Possible</td>
<td>4 (33.3)%</td>
</tr>
<tr>
<td><strong>Voriconazole administration</strong></td>
<td></td>
</tr>
<tr>
<td>Intravenous (mg/kg per dose)</td>
<td>6.1 (4.7 – 6.9)</td>
</tr>
<tr>
<td>Oral (mg/kg per dose)</td>
<td>10.2 (6.8 – 10.8)</td>
</tr>
<tr>
<td>Voriconazole trough concentration (mg/L)</td>
<td>4.1 (1.6 – 6.1)</td>
</tr>
<tr>
<td><strong>Galactomannan index</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.3 (0.5 – 8.1)</td>
</tr>
</tbody>
</table>

Note. AML: acute myelogenous leukemia, ALL: acute lymphoblastic leukemia.

Data are presented as median (interquartile range), unless specified otherwise.

1 Number of patients (%).

a Other malignancies included non-Hodgkin lymphoma, immunodeficiency, osteosarcoma, Hodgkin lymphoma, rhabdomyosarcoma.

b Based on the opinion of the attending physician of the Children Oncology ward at the beginning of the admission. Patients classified as having possible invasive aspergillosis refers to the fact that GM was initially negative when voriconazole was commenced, but later became positive, at which time the diagnostic classification was upgraded to probable.
Figure 1: Voriconazole concentration-time profile of 12 pediatric patients (Panel A) and the galactomannan-time profile (Panel B) for 12 patients who had concomitantly collected galactomannan and serum voriconazole concentration data. Note: the sampling of voriconazole and galactomannan were not linked. Hence, voriconazole serum concentration data were available after galactomannan sampling had stopped.
Figure 2. The observed-predicted values after the Bayesian step for voriconazole serum concentrations (left panel) and for galactomannan (right panel). The solid line is the linear regression of the observed-predicted concentrations and the estimates for the intercept.
Figure 3. Serum voriconazole concentration-time profiles (solid black line) and serum galactomannan-time profiles (grey line) from the 12 children with concomitant PK and PD data. The raw data for voriconazole is shown (black circles) and galactomannan (grey circles). In each case, the model fit is from the Bayesian posterior estimate. Only patients 159 and 180 survived.
Figure 4. Relationship of voriconazole average daily AUC to EC50 ratio and final galactomannan (i.e. last measured galactomannan) in the 12 children. Panel A: Terminal Galactomannan=(AUC:EC50)/15.4 (p=0.003). Panel B: AUC:EC50 > 6 suggested a more consistently lower terminal galactomannan (P=0.07).