Optimisation of fluconazole therapy for the treatment of invasive candidiasis in preterm infants

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ABSTRACT

Introduction Fluconazole is an important antifungal in the prevention and treatment of invasive Candida infections in neonates, even though its use in preterm infants is still off-label. Here, we performed a population pharmacokinetic study on fluconazole in preterm neonates in order to optimise dosing through the identified predictive patient characteristics.

Methods Fluconazole concentrations obtained from preterm infants from two studies were pooled and analysed using NONMEM V.7.3. The developed model was used to evaluate current dosing practice. A therapeutic dosing strategy aiming to reach a minimum target exposure of 400 and 200 mg×hour/L per 24 hours for fluconazole-susceptible C. albicans meningitis and other systemic infections, respectively, was developed.

Results In 41 preterm neonates with median (range) gestational age 25.3 (24.0–35.1) weeks and median postnatal age (PNA) at treatment initiation 1.4 (0.2–32.5) days, 146 plasma samples were collected. A one-compartment model described the data best, with an estimated clearance of 0.0147 L/hour for a typical infant of 0.87 kg with a serum creatinine concentration of 60 μmol/L and volume of distribution of 0.844 L. Clearance was found to increase with 16% per 100 g increase in actual body weight, and to decrease with 12% per 10 μmol/L increase in creatinine concentration once PNA was above 1 week. Dose adjustments based on serum creatinine and daily dosing are required for therapeutic target attainment.

Conclusion In preterm neonates, fluconazole clearance is best predicted by actual body weight and serum creatinine concentration. Therefore, fluconazole dosing should not only be based on body weight but also on serum creatinine concentration to achieve optimal exposure in all infants.

Ethics statement The Erasmus MC ethics review board approved the protocol of the DINO Study (MEC-2014-067) and the Radboud UMC ethics review board waived the need for informed consent for cohort 2 (CMO-2021-8302). Written informed consent from parents/legal guardians was obtained prior to study initiation.

INTRODUCTION

Fluconazole is an important antifungal in the prevention and treatment of invasive Candida infections, affecting 4%–8% of infants with a birth weight below 1000 g.

What is already known on this topic?

- Invasive candidiasis in preterm infants requires immediate and effective treatment.
- Fluconazole is the drug of choice for invasive candidiasis due to its efficacy and high tolerability.
- Fluconazole is administered off-label in preterm infants.

What this study adds?

- Fluconazole clearance significantly increases with actual body weight in preterm infants.
- Beside body weight and serum creatinine concentrations were found to predict fluconazole clearance.
- A serum creatinine-based and weight-based dose adjustment is developed to achieve appropriate exposure in all preterm infants.

With C. albicans still being a common pathogen for invasive candidiasis, treatment aims to obtain a target exposure to fluconazole. The pharmacodynamic index for fluconazole is defined as the area under the plasma concentration-time curve per 24-hour period (AUC24h) over minimally inhibitory concentration (MIC) ratio to be above 100. The clinical breakpoint for in vitro susceptibility of C. albicans treated with fluconazole is 2 mg/L. This would translate the need for obtaining a minimal target AUC24h of 200 mg×hour/L for a systemic infection in a worst-case scenario. In the case of Candida meningitis, the target AUC24h is increased to 400 mg×hour/L to account for reduced tissue penetration into the cerebrospinal fluid.

Currently, there is no licensed dosing regimen for treatment of invasive candidiasis with fluconazole in preterm neonates. For term neonates with invasive candidiasis, a maintenance dose of 6–12 mg/kg is recommended every 72 hours for neonates with a postnatal age (PNA) 0–14 days, every 48 hours for neonates with a PNA 14–28 days and daily for infants with a PNA above 28 days. To ensure a minimal AUC24h of 400 on day 1, a loading dose of 25 mg/kg was suggested by Piper et al. Recently, Leroux et al proposed a daily dose adjusted to gestational age (GA), based on a study with 18 neonates. More studies on fluconazole pharmacokinetic (PK)
in preterm infants are lacking and therefore the regimen designed for term neonates is frequently applied to preterm infants. It is, however, not known whether preterm infants receive optimal exposure to fluconazole when treated as term infants.

In the current study, a population PK model was developed to evaluate which patient characteristics are predictive of the PK of fluconazole in preterm infants. This model was then used to evaluate currently used dosing strategies and develop a therapeutic dosing regimen for preterm infants. Fluconazole doses were selected aiming for a target AUC_{24h} of 400 mg×hour/L based on a suspected worst-case scenario of *Candida* meningitis and aiming for a target AUC_{24h} of 200 mg×hour/L based on a systemic invasive candidiasis with a maximum MIC of 2 mg/L.

**METHODS**

**Patients and samples**
Data from two cohorts were combined. Patients in cohort 1 were included in the DINO Study (Drug dosage Improvement in Neonates, NCT02421068) between 2014 and 2017, which was designed to evaluate the PK and pharmacodynamics of frequently used off-label drugs in preterm neonates based on opportunistic sampling. Infants with a GA below 32 weeks and an indication for one of the nine study drugs were included and treated according to standard of care. Prophylactic fluconazole therapy consisted of 3 mg/kg two times per week, and therapeutic doses were 6–12 mg/kg with a loading dose of 12 or 25 mg/kg. Blood samples of 0.2 mL were collected in EDTA tubes and withdrawn from an indwelling arterial catheter or with routinely scheduled samples for clinical purposes.

Cohort 2 consisted of patients submitted to the neonatal intensive care unit of the Radboud Medical Centre Nijmegen or University Medical Centre Groningen who required treatment with fluconazole. Patients received 6–12 mg/kg once daily or every 2 days. Plasma samples were collected opportunistically or for therapeutic drug monitoring (local target trough concentration 10–50 mg/L).

**Bioanalytical analysis**
Fluconazole plasma concentrations from both cohorts were measured in the same laboratory using a validated assay using liquid chromatography coupled with tandem mass spectrometry (validated range 0.0302–30.21 mg/L, coefficient of variation intra-assay: 2.8%, interassay: 1.5%).

**Population PK model**
The population PK model was developed in NONMEM V.7.3 (ICON Development Solutions, Ellicott City, Maryland, USA) supported by Perl-speaks-NONMEM V.4.7.0. Model development was based on comparison of the objective function value (OFV) for nested models, along with numerical and graphical model performance, that is, relative SE of <50% (OFV) for nested models, along with numerical and graphical model performance, that is, relative SE of <50% (OFV) for nested models. Model performance, that is, relative SE of <50% (OFV) for nested models, along with numerical and graphical model performance, that is, relative SE of <50% (OFV) for nested models.

**Evaluations of the current and proposed dosing regimens**
Using the final model, exposure to fluconazole was evaluated for typical preterm infants with a GA of 25.5 weeks whose treatment was initiated at a PNA of 3, 10 or 17 days. Median birth weight and actual body weight were extracted from https://www.growthcalculator.org/ based on a male infant, and S_cr was set at 60 µmol/L once PNA was above 1 week. For the evaluation of the term neonate dosing regimen as advised by the Dutch Paediatric Formulary for term neonates and the label, treatment was initiated with a loading dose of 25 mg/kg, followed by 12 mg/kg every 72 hours when PNA was below 15 days, 15 mg/kg every 48 hours for PNA 15–28 days and 12 mg/kg daily when PNA was above 28 days. Loading and maintenance doses were optimised to achieve 100% target attainment in all patients across the S_cr and actual body weight range (30, 50, 80 or 100 µmol/L and 700–1500 g with 100 g increments, respectively). Target attainment after the loading dose was defined as a minimal AUC_{24h} of 400 mg×hour/L on day 1 of treatment based on the worst-case scenario of the infant suffering from *Candida* meningitis. Target attainment of the maintenance dose was defined for two scenarios: the first assumes that the infant does have confirmed *Candida* meningitis or is awaiting lab results for this diagnosis and requires a minimal AUC_{24h} of 400 mg×hour/L. The second scenario assumes that a lower exposure suffices because of a negative lumbar puncture and an MIC <2 µg/mL, requiring a minimal AUC_{24h} of 200 mg×hour/L. To evaluate the exposure to fluconazole following the optimised dosing regimen, S_cr was set at either 30, 50, 80 or 100 µmol/L. The 1000 simulations were run for each preterm infant of which the median concentrations were extracted and individual AUC_{24h} was calculated.

The exposure to fluconazole following prophylactic treatment of 3 and 6 mg/kg two times per week, initiated at the first day of life, for infants with a GA of 24, 25.5 and 27 weeks, was simulated over 30 days. S_cr was set at 60 µmol/L once PNA was above 1 week and 1000 simulations were run for each preterm infant. Due to the lack of a PK target, dose optimisation was not performed for prophylactic treatment.

**RESULTS**

**Population**
Data from a total of 41 infants were available, 28 in cohort 1 and 13 in cohort 2, and included 146 plasma samples. Median GA was 25.3 (range 24.0–35.1) weeks, and median birth weight was 0.76 (range 0.49–2.00) kg. Population characteristics are presented in table 1.

**Population PK model**
Data were best described by a one-compartment model with a proportional error. Actual body weight was found to be most predictive of clearance (CL) with a linear relationship (p<0.001...
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Table 1  Patient characteristics (median (range)) and dosing information of the two study cohorts, and the total study population

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 2</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of neonates</td>
<td>24</td>
<td>13</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>10/14</td>
<td>7/6</td>
<td>18/23</td>
<td>18/23</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>25.0 (24.0–27.1)</td>
<td>25.0 (24.3–26.4)</td>
<td>26.1 (24.6–35.1)</td>
<td>25.3 (24.0–35.1)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>0.73 (0.49–0.99)</td>
<td>0.76 (0.54–0.95)</td>
<td>0.94 (0.64–2.00)</td>
<td>0.76 (0.49–2.00)</td>
</tr>
<tr>
<td>Small for gestational age (n (%))</td>
<td>3 (13)</td>
<td>1 (25)</td>
<td>1 (8)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Current weight during treatment (kg)*</td>
<td>0.82 (0.50–1.58)</td>
<td>0.90 (0.66–1.35)</td>
<td>1.00 (0.70–2.20)</td>
<td>0.87 (0.50–2.20)</td>
</tr>
<tr>
<td>Postnatal age at treatment initiation (days)</td>
<td>0.9 (0.2–16.0)</td>
<td>21.2 (3.9–32.5)</td>
<td>10.0 (3.0–18.0)</td>
<td>1.4 (0.2–32.5)</td>
</tr>
<tr>
<td>Postmenstrual age during treatment (weeks)*</td>
<td>27.4 (24.1–28.4)</td>
<td>28.2 (25.7–31.3)</td>
<td>28.4 (26.0–38.9)</td>
<td>26.7 (24.1–38.9)</td>
</tr>
<tr>
<td>Number of patients with at least one available plasma creatinine observation (%)</td>
<td>23 (96)</td>
<td>3 (75)</td>
<td>0 (0)</td>
<td>26 (63)</td>
</tr>
<tr>
<td>Serum creatinine concentration during treatment (µmol/L)*</td>
<td>61 (22–127)</td>
<td>58 (32–63)</td>
<td>Unknown</td>
<td>60 (22–127)</td>
</tr>
<tr>
<td>Urine output during treatment (mL/hour/kg)*</td>
<td>4.1 (2.8–4.8)</td>
<td>7.3 (7.3–7.3)</td>
<td>Unknown</td>
<td>4.2 (2.8–7.3)</td>
</tr>
<tr>
<td>Co-administration of ibuprofen (number of neonates (%))</td>
<td>19 (79)</td>
<td>4 (100)</td>
<td>Unknown</td>
<td>23 (56)</td>
</tr>
<tr>
<td>Time after last ibuprofen dose at fluconazole plasma sample time (hours)</td>
<td>126 (13–1140)</td>
<td>173 (1–815)</td>
<td>Unknown</td>
<td>130 (1–1140)</td>
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<tr>
<td>Co-administration of antibiotics (number of neonates (%))</td>
<td>21 (75)</td>
<td>0 (0)</td>
<td>Unknown</td>
<td>21 (51)</td>
</tr>
<tr>
<td>Time after last antibiotics dose at fluconazole plasma sample time (hours)</td>
<td>41 (1–409)</td>
<td>–</td>
<td>Unknown</td>
<td>41 (1–409)</td>
</tr>
<tr>
<td>Number of plasma samples per neonate (n (range))</td>
<td>6 (1–13)</td>
<td>5 (2–7)</td>
<td>1 (1–2)</td>
<td>5 (1–13)</td>
</tr>
<tr>
<td>Duration of fluconazole treatment (days)</td>
<td>22 (6–67)</td>
<td>8 (2–19)</td>
<td>5 (2–18)</td>
<td>12 (2–67)</td>
</tr>
<tr>
<td>Loading dose (mg/kg) (number of patients)</td>
<td>– (0)</td>
<td>18.2 (11.1–27.0)</td>
<td>18.2 (11.1–27.0)</td>
<td>18.2 (11.1–27.0)</td>
</tr>
<tr>
<td>Maintenance dose (mg/kg)</td>
<td>2.9 (1.9–5.8)</td>
<td>10.1 (2.5–12.6)</td>
<td>11.1 (5.4–15.1)</td>
<td>3.01 (1.9–15.1)</td>
</tr>
<tr>
<td>Time of fluconazole plasma sample after last dose (hours)</td>
<td>29.2 (0.6–270)</td>
<td>23.8 (23.0–24.0)</td>
<td>23.8 (0–270)</td>
<td>23.8 (0–270)</td>
</tr>
<tr>
<td>Fluconazole plasma concentration (mg/L)</td>
<td>2.61 (0.04–13.6)</td>
<td>22.00 (4.38–29.60)</td>
<td>16.05 (10.90–26.00)</td>
<td>3.09 (0.04–29.60)</td>
</tr>
</tbody>
</table>

*Of time-varying characteristics (current weight, postnatal age during treatment, postmenstrual age, plasma creatinine concentrations and urine output), the median of the individual medians is given.

Figure 1  Clearance of fluconazole versus current body weight with colour intensity increasing with serum creatinine concentrations. Dots represent the individual post hoc clearance values and the solid lines represent the estimated relationship between clearance and actual body weight for an infant with a serum creatinine concentration of either 30, 60 or 100 µmol/L. Dashed lines represent expected clearance values for combinations of current weight and serum creatinine concentration not present in the current study population. This is an original figure with permission to reuse.

Simulations to evaluate term infant dosing in preterm infants

Figure 2 shows the concentration time plots and exposure to fluconazole in a preterm neonate with median GA of 25.5 weeks and median Scr of 60 µmol/L receiving the licensed dose for a term neonate, that is, 12 mg/kg every 72 hours when PNA is below 15 days, 12 mg/kg every 48 hours for PNA 15–28 days and 12 mg/kg daily when PNA is above 28 days, with a loading dose of 25 mg/kg as recommended by Piper et al.2 Despite varying

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(−65 points in OFV)), explaining 21% of the IIV in CL. Second, CL was found to decrease with increasing Scr observed from a PNA of 8 days or higher (p<0.001 (−23 points in OFV)), explaining 7.3% of IIV on CL. The relationship between CL and actual body weight and Scr is visualised in figure 1. Actual body weight was also found to predict volume of distribution (Vd) with a linear relationship (p<0.001 (−17 points in OFV)). Addition of this relationship decreased IIV on Vd from 37% to 9% after which IV on Vd could be removed from the model. The increase in CL and Vd with actual body weight could be described with one parameter, which was not different to estimating two separate parameters (p>0.05 (+0.3 points in OFV)). Individual CL and V are estimated by equations 1 and 2, respectively, where CLind is the individual predicted CL, Weight ind is the actual body weight, Scr,ind is the most recent measured Scr and Vind is the individual predicted V. Parameter estimates of the final model and the respective bootstrap estimates are presented in online supplemental table 1. The GOF plots of the final model (online supplemental figure 1) and results of the NPDE analysis (online supplemental figure 2) show that the model describes the data well across different body weights and Scr.

CLind (L/H) = 0.0147L/H* (1 + 1056(Weightind) – 0.87kg)*
(1 – 0.0118(Scre ind – 60µmol/L))

Vind (L) = 0.844 L*(1 + 1.56(Weightind – 0.87 kg))
(2)

Figure 2 shows the concentration time plots and exposure to fluconazole in a preterm neonate with median GA of 25.5 weeks and median Scr of 60 µmol/L receiving the licensed dose for a term neonate, that is, 12 mg/kg every 72 hours when PNA is below 15 days, 12 mg/kg every 48 hours for PNA 15–28 days and 12 mg/kg daily when PNA is above 28 days, with a loading dose of 25 mg/kg as recommended by Piper et al.2 Despite varying

Drug therapy

Figure 1

Serum creatinine concentration (µmol/L)

Individual clearance (L/H)

Current weight (kg)


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Drug therapy exposure, an AUC24h of 400 mg×hour/L is achieved on the first day of treatment in all infants due to the loading dose of 25 mg/kg that is administered independent of PNA. The figure also shows that the PNA-dependent dosing intervals (ie, 72 hours for PNA 0–14 days, 48 hours for PNA 14–28 days) lead to varying exposure on different PNAs at treatment initiation, and to different AUCs per 24 hours in one patient. In addition to that, in the majority of patients, the target AUC24h of 400 mg/L was assumed to remain constant throughout the treatment period. (A) Median fluconazole concentration of 1000 simulations versus time since first dose, and (B) AUC24h of 1000 simulations. The horizontal line in (B) represents a target AUC24h of 400 mg×hour/L as target for suspected Candida meningitis. This is an original figure with permission to reuse.

Optimisation of the dosing regimen
Figure 3 shows the exposure to fluconazole for a model-based PNA and SCr-based dosing regimen, which is presented in figure 4, based on online supplemental figure 5. This dosing regimen aims to achieve a target AUC24h of 400 mg×hour/L immediately after the loading dose and throughout the following treatment period for a worst-case scenario of suspected Candida meningitis. The figure shows that the target of 400 mg×hour/L is achieved immediately after the loading dose. This minimum AUC is maintained using the newly proposed daily maintenance doses in a child born at 25.5 weeks (median of the population, figure 3), 24 or 28 weeks (on online supplemental figure 6). As presented in figure 4, during the first week of life, a loading dose of 25 mg/kg and a daily maintenance dose of 12 mg/kg are advised for all infants, independent of SCr. If treatment is initiated above 1 week of age, an increased loading dose of 30 mg/kg is suggested for infants with an SCr below 70 µmol/L (figure 4, left panel). Above 1 week of PNA, the maintenance dose should be adjusted to SScr as follows: 9 mg/kg if SScr is above 100 µmol/L, 12 mg/kg is SScr is between 70 and 99 µmol/L, 15 mg/kg if SScr is between 40 and 69 µmol/L, and 18 mg/kg if SScr is below 40 µmol/L (figure 4, middle panel). Once a clean lumbar puncture confirms the absence of Candida meningitis and the determined MIC suggests that a lower target AUC24h of 200 mg×hour/L is sufficient, all maintenance doses can be reduced by 50% (figure 4, right panel).

DISCUSSION
In this study, we successfully characterised the PK of fluconazole in a large cohort of preterm infants who received multiple and varying doses. Using the developed model and in absence of a dosing regimen for preterm infants in the label, we evaluated the
performance of the recommended current dosing regimen for term infants, and adapted this to a suggested optimised dosing regimen for treatment of preterm infants.

Renal function was found to be an important predictor of fluconazole CL in addition to bodyweight after the first week of life. Recently, in adults, a dose adaptation based on renal function was suggested.\(^{10}\) Whereas for adults, renal function is usually represented by glomerular filtration rate, the best marker for renal function in preterm infants remains a topic of debate.

In our study, we used absolute $S_{cr}$ observations\(^{9,11-14}\) with 63% of the infants having one or more $S_{cr}$ observations. As during the first week of life, $S_{cr}$ might reflect maternal creatine, only $S_{cr}$ observations taken on or after PNA day 8 were included in the analysis. Using this approach, the effect of $S_{cr}$ on CL was highly significant with CL increasing by 12% when $S_{cr}$ decreases from 60 to 50 $\mu$mol/L. Estimated model parameters and covariate relationships are well in line with previously published fluconazole PK reports.\(^{5,9,13,14}\) Momper et al also identified $S_{cr}$ as predictor

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**Figure 3** Concentration-time profiles (upper panel) and corresponding area under the curve per 24 hours (AUC\(_{24h}\)) of fluconazole when the loading and maintenance doses are adjusted to postnatal age (PNA) and serum creatinine concentration as proposed in figure 4, when aiming for a target AUC\(_{24h}\) of 400 $\text{mg} \times \text{hour/L}$. (A) The median concentration-time profile of 1000 simulations and (B) the corresponding AUC\(_{24h}\). Results are shown for a typical individual with a gestational age of 25.5 weeks and median birth weight and growth, and treatment was initiated at day 3 (left panel), 10 (middle panel) or 17 (right panel). Serum creatinine concentration was set at either 30, 50, 80 or 100 $\mu$mol/L and was assumed to remain constant during the treatment period. This is an original figure with permission to reuse.

**Figure 4** Proposed model-based dose adaptation based on postnatal age and serum creatinine concentrations. Left: proposed loading dose aiming for a target area under the curve per 24 hours (AUC\(_{24h}\)) of 400 $\text{mg} \times \text{hour/L}$ for worst-case scenario of suspected Candida meningitis or an unknown minimally inhibitory concentration (MIC). Middle panel: proposed maintenance dose when aiming for a target AUC\(_{24h}\) of 400 $\text{mg} \times \text{hour/L}$. Right panel: proposed maintenance dose when aiming for a target AUC\(_{24h}\) of 200 $\text{mg} \times \text{hour/L}$ that can be used for pathogens with an MIC <2 mg/L. This is an original figure with permission to reuse.
of CLₚ, although with a non-linear relationship where the largest effect of Sₚ was predicted for the lowest Sₚ observations, and the decrease in CL plateaus at high Sₚ observations. It is likely that this plateau was identified due to a wider range in Sₚ in their study (8.8–318 µmol/L vs 22–127 µmol/L in the current population). Recently, van Donge et al developed a population model for Sₚ to get a better understanding of (gestational) age-dependent Sₚ reference values. Upon further expanding of this method, such models could be of great value in future investigations of Sₚ-based renal function as covariate in preterm infants. Ibuprofen was found as predictor of CL of other renally cleared drugs but was not more predictive than Sₚ in our study, probably because the effects of ibuprofen are incorporated in the observed Sₚ.

In this study, we optimised the therapeutic dosing regimen for a clinical scenario where the infant is suspected to have invasive candidiasis or Candida meningitis and requires effective treatment immediately, without time to await microbiological blood culture results. Therefore, treatment is designed to achieve optimal exposure for the worst-case scenario, that is, Candida meningitis caused by a pathogen with an MIC of 2 mg/L but with confirmed susceptibility, corresponding to a target AUC₂₄h of 400 mg×hour/L. We propose a loading dose and daily maintenance dose to maintain optimal exposure, which was also the conclusion of Leroux et al. The Infectious Diseases Society of America already recommends 12 mg/kg daily for neonatal candidiasis but without a loading dose, while our and previous results strongly advise on a loading dose. We propose to adjust both the loading and maintenance dose to Sₚ, while Leroux et al found GA as best predictor for fluconazole CL and therefore adjust the maintenance dose to GA. In the present study, GA was not found as predictor of CL, but might be represented in Sₚ, since renal function is expected to increase with GA. According to our model, infants with good renal function (Sₚ <70 µmol/L) require a loading dose of 30 mg/kg to reach an AUC₂₄h of 400 mg×hour/L on day 1 of treatment if treatment is initiated above 1 week of PNA. This increased loading dose has not been previously studied in preterm infants, but might be comparable with the loading dose of 25 mg/kg with which no safety concerns were found. Leroux et al increased the maintenance dose to 20 mg/kg for infants with a GA ≥32 weeks, which did not result in any fluconazole-associated safety concerns. These results suggest that no safety concerns are to be expected for the Sₚ-based dosing administered daily (figure 4) that we propose in our study, which has a maximum of 18 mg/kg, but safety should be monitored with, for example, liver function tests when applying the suggested dosing strategy. Most studies, including Leroux et al, aim for a target AUC₂₄h of 400 mg×hour/L usually based on an MIC of 4 or even 8 mg/L. The variety in reported MICs and target MIC:AUC₂₄h indicate that consensus is lacking, and that the future might lie in more individualised therapy using biomarkers. While fluconazole is usually well tolerated, unnecessary overexposure is considered unwanted. Therefore, we advise to decrease the maintenance dose once the need for a lower target AUC₂₄h is confirmed by the lab results, for example, as a result of a clean lumbar puncture or an MIC <2 mg/L, and to seek alternative treatment if the MIC is determined to be >2 mg/L (figure 4, right panel). Because no Sₚ observations were available from infants weighing more than 1.5 kg, the developed dosing regimen is applicable for preterm infants with a maximum actual body weight of 1.5 kg.

The recommendation for prophylactic fluconazole treatment is dependent on the rate of invasive candidiasis of a medical centre, since beneficial effects are observed in centres with a high rate of infections while for centres with low numbers of invasive candidiasis, the number needed to treat is very high. A meta-analysis of placebo-controlled studies reported a reduction in invasive fungal infection upon prophylaxis with fluconazole, but did not identify a dose effect. While large variation in exposure to fluconazole is expected upon different dosing strategies and patient characteristics (online supplemental figure 6), it is complicated to determine which strategy is best for all preterm infants. In conclusion, because fluconazole CL is well predicted by actual body weight and Sₚ in preterm infants with a PNA above 1 week, both loading and maintenance doses should be adjusted to Sₚ once PNA is above 1 week to achieve adequate exposure.

REFERENCES

1 Arendrup MC, Friberg N, Mares M, et al. How to interpret MICs of antifungal compounds according to the revised clinical breakpoints V. 10.0 European Committee on antimicrobial susceptibility testing (EUCAST). Clin Microbiol Infect 2020;26:1464–72.
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Supplementary

**Supplementary Table 1 Parameter estimates of the final model and the corresponding bootstrap estimates.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final parameter estimate (RSE %)</th>
<th>Bootstrap estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural model parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( CL_{ind} = CL_{pop} \times (1+\theta_{\text{Weight}} \times (\text{Weight}<em>{ind} - \text{Weight}</em>{med})) \times (1+\theta_{\text{Creatinine}} \times (\text{Creatinine}<em>{ind} - \text{Creatinine}</em>{med})) )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( CL_{pop} ) (L/h)</td>
<td>0.0147 (4%)</td>
<td>0.0154 (0.0143 – 0.0168)</td>
</tr>
<tr>
<td>( \theta_{\text{Weight}} )</td>
<td>1.56 (16%)</td>
<td>1.56 (1.07 – 1.98)</td>
</tr>
<tr>
<td>( \theta_{\text{Creatinine}} )</td>
<td>-0.0118 (19%)</td>
<td>-0.0069 (-0.0109 - -0.0028)</td>
</tr>
<tr>
<td><strong>Variable model parameters [shrinkage]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( V_{ind} = V_{pop} \times (1+\theta_{\text{Weight}} \times (\text{Weight}<em>{ind} - \text{Weight}</em>{med})) )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( V_{pop} ) (L)</td>
<td>0.844 (6%)</td>
<td>0.837 (0.749 – 0.933)</td>
</tr>
<tr>
<td><strong>IIV on CL (%)</strong></td>
<td>16.6 (19%) [26%]</td>
<td>16.8 (9.7 – 23.1)</td>
</tr>
<tr>
<td><strong>Proportional residual error (%)</strong></td>
<td>25 (15%)</td>
<td>25 (0.17 – 0.31)</td>
</tr>
</tbody>
</table>

RSE: relative standard error, CI: confidence interval, \( CL_{ind} \): individual predicted clearance, \( CL_{pop} \): population mean value of clearance for a neonate with a median weight of 0.87 kg and a median serum creatinine concentration of 60 µmol/L, \( \theta_{\text{Weight}} \): slope parameter for clearance and volume of distribution with weight, \( \text{Weight}_{ind} \): observed actual bodyweight in kg, \( \text{Weight}_{med} \): median actual bodyweight of the population (0.87 kg), \( \theta_{\text{Creatinine}} \): slope parameter for clearance with serum creatinine concentration, \( \text{Creatinine}_{ind} \): observed serum creatinine concentration in µmol/L, \( \text{Creatinine}_{med} \): median serum creatinine concentration (60 µmol/L), \( V_{ind} \): individual predicted volume of distribution, \( V_{pop} \): population mean value of volume of distribution for a neonate with a weight of 0.87 kg, IIV: inter-individual variability.
**Supplementary Figure 1** Goodness-of-fit of the final model. CWRES: conditional weighted residuals. The colour of the dots represents the serum creatinine observations (A-D) or actual bodyweight (E-H).

**Supplementary Figure 2** Normalized prediction distribution error (NPDE) analysis of the final model. Top left: quantile-quantile plots, top right NPDE quantiles with a normal distribution overlay, bottom left: NPDE versus time after dose (TAD) in hours, bottom right, NPDE versus predicted concentrations of fluconazole (DV). Global adjusted p-value: $9.6 \times 10^{-7} (p<0.001)$. 

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Supplementary Figure 3 Exposure to fluconazole in a typical infant (gestational age 25.5 weeks, S\textsubscript{cr} either 30, 60 or 100 µmol/L) when the dosing interval of the maintenance dose is adjusted to postnatal age as currently advised by the label\textsuperscript{1} and Dutch Paediatric Formulary\textsuperscript{9}, i.e. every 72 h if postnatal age is below 14 days, every 48 h if postnatal age is 14-28 days and daily if postnatal age is above 28 days. Treatment was initiated at a postnatal age of 3, 10 or 17 days, presented in the left, middle and right panels, respectively, and consisted of a loading dose of 25 mg/kg and a maintenance dose of 12 mg/kg. The typical infant has a gestational age of 25.5 weeks and is expected to follow median growth for a male, resulting in current weights of 738, 771 and 856 g at postnatal ages 3, 10 and 17 days, respectively. Serum creatinine concentrations were assumed to remain constant throughout the treatment period. Figure 2.A: Median fluconazole concentration of 1000 simulations versus time since first dose, and Figure 2.B: area under the curve per 24 h (AUC\textsubscript{24h}) versus time since first dose of all serum creatinine concentrations combined (1000 simulations per S\textsubscript{cr}). The horizontal line in Figure 2.B represents a target AUC\textsubscript{24h} of 400 mg*h/L for suspected Candida meningitis.
Supplementary Figure 4 Exposure to prophylactic fluconazole treatment as currently advised by the Dutch Paediatric Formulary (A. & B.), and as suggested by Momper et al. (C. & D.). The Dutch Paediatric Formulary recommends 3 mg/kg twice weekly, and Momper et al. recommend 6 mg/kg twice weekly, aiming for a trough concentration of 2 mg/L (dashed line in A. & C.). A. and C. represent the median concentration of 1000 simulations, and B. and D. represent the corresponding area under the curve per 24h of all serum creatinine concentrations combined (each 1000 times simulated).
Supplementary Figure 5 Probability of target attainment of examined loading- and maintenance doses across the weight range and for infants with a serum creatinine concentration of either 30, 50, 80 or 100 µmol/L. A.: Target attainment on the first day of treatment aiming for an AUC\(_{24h}\) of 400 mg*h/L, upon a loading dose of either 20, 25 or 30 mg/kg. B.: Target attainment on the seventh day of treatment aiming for an AUC\(_{24h}\) of 400 mg*h/L, upon a loading dose of 25 mg/kg and a maintenance dose of either 9, 12, 15 or 18 mg/kg. C.: Target attainment on the seventh day of treatment aiming for an AUC\(_{24h}\) of 200 mg*h/L, upon a loading dose of 25 mg/kg and a maintenance dose of either 4.5, 6, 7.5 or 9 mg/kg. Each combination of current weight and S\(_{cr}\) was simulated 1000 times and the lines represent the percentage of each combination achieving the target AUC\(_{24h}\). Current weight and S\(_{cr}\) were assumed to remain constant during the treatment period.
Supplementary Figure 6 Performance of the developed model-based dosing regimen as depicted in Figure 4 in typical infants with a gestational age of 24 (A. and B.) or 28 (C. and D.) weeks. The concentration-time profiles (A. and C.) and corresponding area under the curve per 24 h (AUC_{24}, B. and D.) are presented for infants with a S_{cr} of 30, 50, 80 or 100 µmol/L, each simulated 1000 times. Treatment was initiated at a postnatal age of 3 (left panel), 10 (middle panel) or 17 (right panel) days. Median birth weight and growth for the corresponding gestational ages were assumed.