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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 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.

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.

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.

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 (AUC_{24h}) 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.[1] This would translate the need for obtaining a minimal target AUC_{24h} of 200 mg×hour/L for a systemic infection in a worst-case scenario. In the case of *Candida* meningitis, the target AUC_{24h} is increased to 400 mg×hour/L to account for reduced tissue penetration into the cerebrospinal fluid.[2]

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.[3] To ensure a minimal AUC_{24h} of 400 on day 1, a loading dose of 25 mg/kg was suggested by Piper *et al*.[4] Recently, Leroux *et al* proposed a daily dose adjusted to gestational age (GA), based on a study with 18 neonates.[5] More studies on fluconazole pharmacokinetic (PK)

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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% and evaluation of goodness-of-fit (GOF) plots that included individual-predicted and population-predicted concentrations versus observed concentrations, conditional weighted residuals versus times after dose and observed concentrations. Actual body weight, GA, PNA, postmenstrual age, gender and being small for GA were evaluated as covariates, and, where applicable and available, serum creatinine concentration (S_{cr}) and co-administration with ibuprofen or antibiotics (tobramycin, gentamycin or vancomycin) within 1 week of a fluconazole dose. Covariates were first selected based on a visual trend with interindividual variability (IIV) where possible, and/or evaluation of GOF plots split for the covariate of interest. Selected covariates were examined in a stepwise manner and added based on significant improvement in OFV ($p<0.01$ and $p<0.001$ for forward inclusion and backward exclusion, respectively), a decrease in IIV and improved (split) GOF. Body weight was interpolated linearly if not measured daily and S_{cr} observations were interpolated in a forward manner. For patients without any S_{cr} observation (n=15), the median of the available serum creatinine (60 µmol/L) was imputed. Only S_{cr} observed from a PNA higher or equal to 8 days as used in the covariate analysis, since during the first week the S_{cr} may also reflect maternal S_{cr}.[6] The final model was evaluated with a bootstrap and a normalised prediction distribution error analysis (NPDE), both based on 1000 simulations.[7]

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[8] and the label,[3] 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, 12 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 mg/L, 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[8 9] 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 ($p<0.001$

Table 1 Patient characteristics (median (range)) and dosing information of the two study cohorts, and the total study population

	Cohort 1		Cohort 2	
Patient characteristics	Prophylactic indication	Therapeutic indication	Therapeutic indication	**Total population**
Number of neonates	24	4	13	41
Gender (male/female)	10/14	1/3	7/6	18/23
Gestational age (weeks)	25.0 (24.0–27.1)	25.0 (24.3–26.4)	26.1 (24.6–35.1)	25.3 (24.0–35.1)
Birth weight (kg)	0.73 (0.49–0.99)	0.76 (0.54–0.95)	0.94 (0.64–2.00)	0.76 (0.49–2.00)
Small for gestational age (n (%))	3 (13)	1 (25)	1 (8)	5 (12)
Current weight during treatment (kg)*	0.82 (0.50–1.58)	0.90 (0.66–1.35)	1.00 (0.70–2.20)	0.87 (0.50–2.20)
Postnatal age at treatment initiation (days)	0.9 (0.2–16.0)	21.2 (3.9–32.5)	10.0 (3.0–18.0)	1.4 (0.2–32.5)
Postmenstrual age during treatment (weeks)*	27.4 (24.1–28.4)	28.2 (25.7–31.3)	28.4 (26.0–38.9)	26.7 (24.1–38.9)
Number of patients with at least one available plasma creatinine observation (%)	23 (96)	3 (75)	0 (0)	26 (63)
Serum creatinine concentration during treatment (µmol/L)*	61 (22–127)	58 (32–63)	Unknown	60 (22–127)
Urine output during treatment (mL/hour/kg)*	4.1 (2.8–4.8)	7.3 (7.3–7.3)	Unknown	4.2 (2.8–7.3)
Co-administration of ibuprofen (number of neonates (%))	19 (79)	4 (100)	Unknown	23 (56)
Time after last ibuprofen dose at fluconazole plasma sample time (hours)	126 (13–1140)	173 (1–815)	Unknown	130 (1–1140)
Co-administration of antibiotics (number of neonates (%))	21 (75)	0 (0)	Unknown	21 (51)
Time after last antibiotics dose at fluconazole plasma sample time (hours)	41 (1–409)	–	Unknown	41 (1–409)
Number of plasma samples per neonate (n (range))	6 (1–13)	5 (2–7)	1 (1–2)	5 (1–13)
Duration of fluconazole treatment (days)	22 (6–67)	8 (2–19)	5 (2–18)	12 (2–67)
Loading dose (mg/kg) (number of patients)	– (0)	18.2 (11.1–27.0) (4)	– (0)	18.2 (11.1–27.0) (4)
Maintenance dose (mg/kg)	2.9 (1.9–5.8)	10.1 (2.5–12.6)	11.1 (5.4–15.1)	3.01 (1.9–15.1)
Time of fluconazole plasma sample after last dose (hours)	29.2 (0.6–270)	7.7 (0–42.7)	23.8 (23.0–24.0)	23.8 (0–270)
Fluconazole plasma concentration (mg/L)	2.61 (0.04–13.6)	22.00 (4.38–29.60)	16.05 (10.90–26.00)	3.09 (0.04–29.60)

*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.

(−65 points in OFV)), explaining 21% of the IIV in CL. Second, CL was found to decrease with increasing S_{cr} 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 S_{cr} is visualised in figure 1. Actual body weight was also found to predict volume of distribution (V_d) with a linear relationship (p<0.001 (−17 points in OFV)). Addition of this relationship decreased IIV on V_d from 37% to 9% after which IIV on V_d could be removed from the model. The increase in CL and V_d with actual body weight could be described with one parameter, which was not significantly 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 CL_{ind} is the individual predicted CL, $Weight_{ind}$ is the actual body weight, $S_{cr,ind}$ is the most recent measured S_{cr} and V_{ind} 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 S_{cr}.

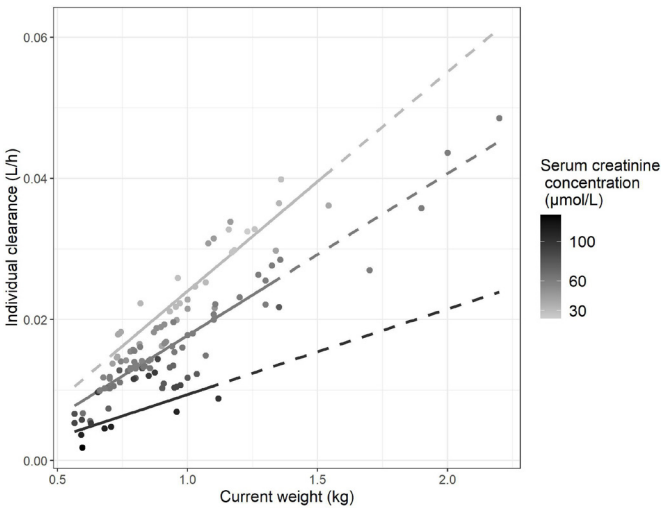

Figure 1 Clearance of fluconazole versus current body weight with colour intensity increasing with serum creatinine concentrations. Dots represent the individual post hoc clearance values and the solid lines represent the estimated relationship between clearance and actual body weight for an infant with 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.

$$CL_{ind}\ (L/H) = 0.0147 L/H^{*}\ (1 + 1056\ (Weight_{ind}) - 0.87 kg))^{*} (1 - 0.0118(S_{cr,ind} - 60 \mu mol/L)) \quad (1)$$

$$V_{ind}\ (L) = 0.844\ L^{*}(1 + 1.56(Weight_{ind} - 0.87\ kg)) \quad (2)$$

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 S_{cr} 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,[3] with a loading dose of 25 mg/kg as recommended by Piper *et al*.[4] Despite varying

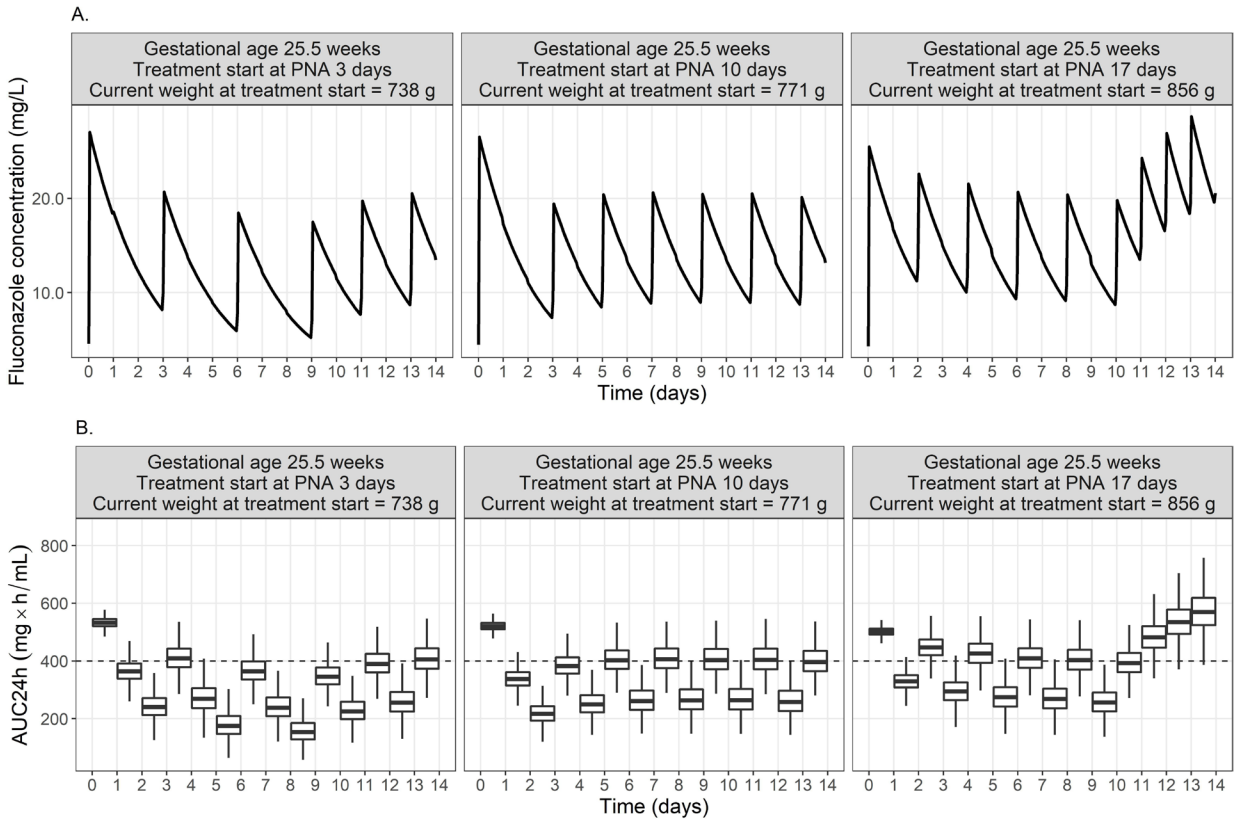

Figure 2 Concentration-time profiles (upper panel) and corresponding area under the curve per 24 hours (AUC_{24h}) of fluconazole in a typical infant (gestational age 25.5 weeks and serum creatinine concentration 60 µmol/L) when the dosing interval of the maintenance dose is adjusted to postnatal age (PNA) as currently advised, that is, every 72 hours if PNA is below 14 days, every 48 hours if PNA is 14–28 days and daily if PNA is above 28 days. Treatment was initiated at a PNA 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 PNAs 3, 10 and 17 days, respectively. A serum creatinine concentration of 60 µmol/L was assumed to remain constant throughout the treatment period. (A) Median fluconazole concentration of 1000 simulations versus time since first dose, and (B) AUC_{24h} of 1000 simulations. The horizontal line in (B) represents a target AUC_{24h} of 400 mg×hour/L as target for suspected *Candida* meningitis. This is an original figure with permission to reuse.

exposure, an AUC_{24h} 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 AUC_{24h} of 400 mg×hour/L is not reached on most of the days (figure 2). Even larger variation in exposure is observed when variation in S_{cr} is taken into account (online supplemental figure 3). Based on these results, a daily maintenance bodyweight-based dose—independent of PNA—seems necessary to reach an effective concentration over time.

The designed model also allowed us to demonstrate the exposure to fluconazole upon prophylactic treatment with 3 or 6 mg/kg two times per week, which is presented in online supplemental figure 4.

Optimisation of the dosing regimen

Figure 3 shows the exposure to fluconazole for a model-based PNA and S_{cr}-based dosing regimen, which is presented in figure 4, based on online supplemental figure 5. This dosing regimen aims to achieve a target AUC_{24h} 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 S_{cr}. If treatment is initiated above 1 week of age, an increased loading dose of 30 mg/kg is suggested for infants with an S_{cr} below 70 µmol/L (figure 4, left panel). Above 1 week of PNA, the maintenance dose should be adjusted to S_{cr} as follows: 9 mg/kg if S_{cr} is above 100 µmol/L, 12 mg/kg is S_{cr} is between 70 and 99 µmol/L, 15 mg/kg if S_{cr} is between 40 and 69 µmol/L and 18 mg/kg if S_{cr} 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 AUC_{24h} 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

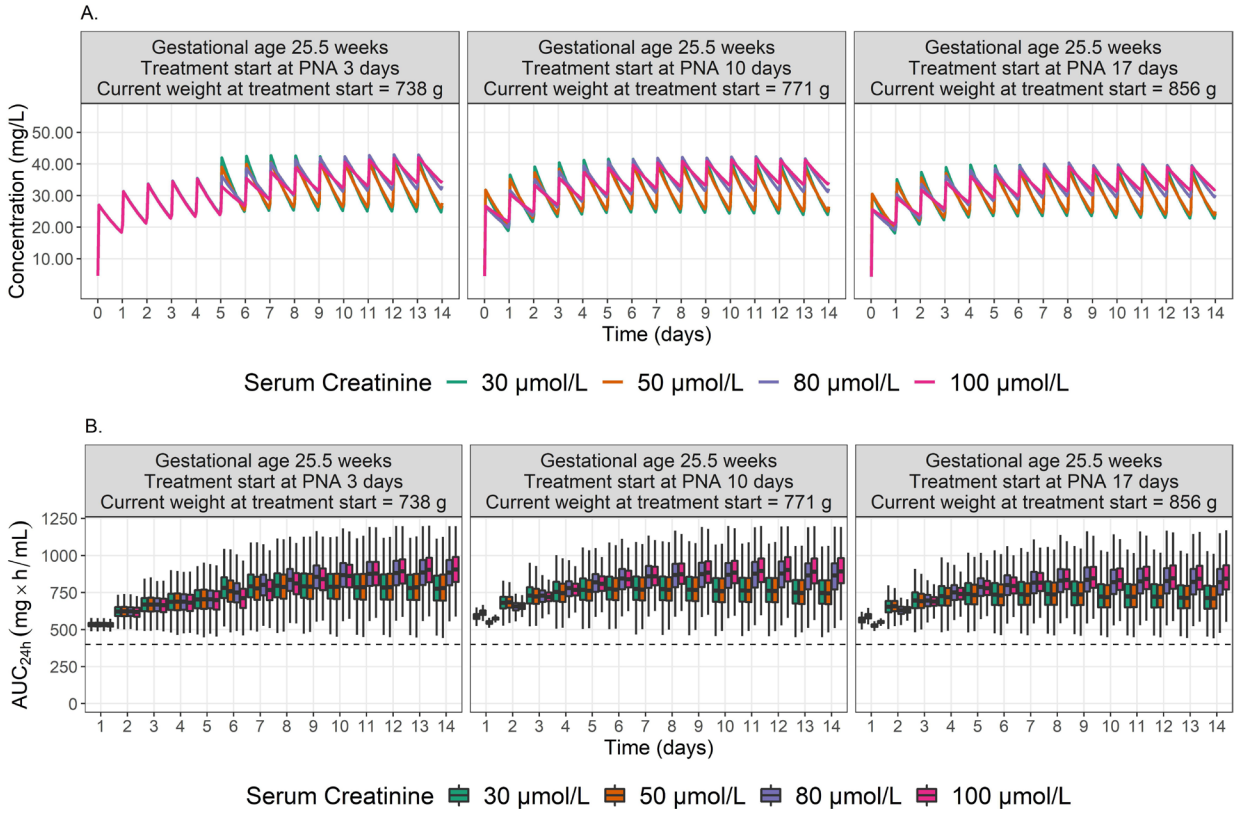

Figure 3 Concentration-time profiles (upper panel) and corresponding area under the curve per 24 hours (AUC_{24h}, lower panel) of fluconazole when the loading and maintenance doses are adjusted to postnatal age (PNA) and serum creatinine concentration as proposed in figure 4, when aiming for a target AUC_{24h} of 400 mg×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 µmol/L and was assumed to remain constant during the treatment period. This is an original figure with permission to reuse.

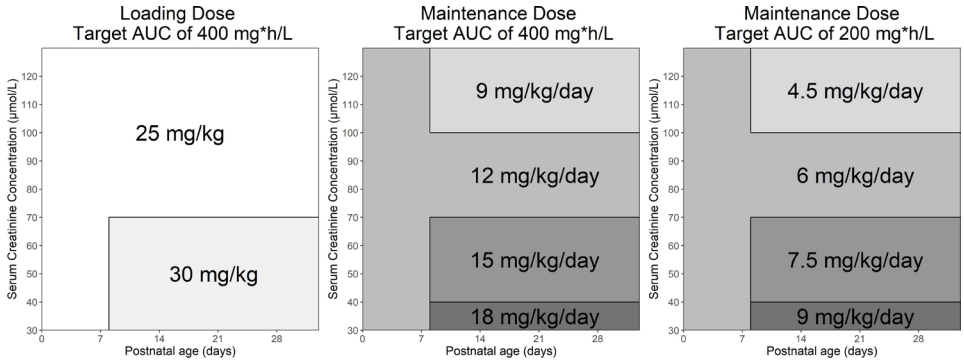

Figure 4 Proposed model-based dose adaptation based on postnatal age and serum creatinine concentrations. Left: proposed loading dose aiming for a target area under the curve per 24 hours (AUC_{24h}) of 400 mg×hour/L for worst-case scenario of suspected *Candida* meningitis or an unknown minimally inhibitory concentration (MIC). Middle panel: proposed maintenance dose when aiming for a target AUC_{24h} of 400 mg×hour/L. Right panel: proposed maintenance dose when aiming for a target AUC_{24h} of 200 mg×hour/L that can be used for pathogens with an MIC <2 mg/L. This is an original figure with permission to reuse.

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 µmol/L. Estimated model parameters and covariate relationships are well in line with previously published fluconazole PK reports.[4 5 9 13 14] Momper *et al* also identified S_{cr} as predictor

of CL, although with a non-linear relationship where the largest effect of S_{cr} was predicted for the lowest S_{cr} observations, and the decrease in CL plateaus at high S_{cr} observations.[9] It is likely that this plateau was identified due to a wider range in S_{cr} 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 S_{cr} to get a better understanding of (gestational) age-dependent S_{cr} reference values.[15] Upon further expanding of this method, such models could be of great value in future investigations of S_{cr}-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 S_{cr} in our study, probably because the effects of ibuprofen are incorporated in the observed S_{cr}.[16 17]

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 AUC_{24h} 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*.[5] 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.[4 5 18] We propose to adjust both the loading and maintenance dose to S_{cr}, while Leroux *et al* found GA as best predictor for fluconazole CL and therefore adjust the maintenance dose to GA.[5] In the present study, GA was not found as predictor of CL, but might be represented in S_{cr} since renal function is expected to increase with GA.[15] According to our model, infants with good renal function (S_{cr} <70 µmol/L) require a loading dose of 30 mg/kg to reach an AUC_{24h} 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.[4 5] 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 S_{cr}-based dose 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 AUC_{24h} of 400 mg×hour/L usually based on an MIC of 4 or even 8 mg/L.[4 5 14 19] The variety in reported MICs and target MIC:AUC_{24h} indicate that consensus is lacking, and that the future might lie in more individualised therapy using biomarkers.[20] 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 AUC_{24h} 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 S_{cr} 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.[21 22] 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.[22] 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 S_{cr} in preterm infants with a PNA above 1 week, both loading and maintenance doses should be adjusted to S_{cr} once PNA is above 1 week to achieve adequate exposure.

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Contributors RJB, RBF and SS conceived the presented idea. IR, KDL, J-WCA, DT and SS collected the data. AGJE, SV, CAJK and RJB analysed the data. AGJE, CAJK and RJB wrote the manuscript with input from all authors. AGJE is the guarantor.

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