PopPK-Based Dosing Optimization for Triazoconazole

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1 Introduction

Brontogen fibropathy (BF) is an inherited disorder that leads to changes in lung tissue and airflow over time. Patients with BF develop infection from *Spirgilus viridicaulis*, a fungal species that grows in warm and humid regions. This fungus can be treated using the antimycotic drug triazoconazole. This drug is administered to children with BF for off-label use, as it is originally indicated for patients with bronchiectasis.

2 Objectives

The purpose of the simulation was to evaluate whether the administered dose of 150 mg once a day evoked sufficient exposure with area under the curve from time zero to 24 hours ($AUC_{0\text{-}24}$) of 28 mg · h/L for children with BF. The goal was also to suggest an optimal dosing regimen based on the simulation results.

3 Methods

A study of 48 pediatric patients was simulated over 100 replicates, resulting in a total of 4800 simulated patients. The simulation was performed using `mrgsolve` package in `R`. A dosing event was created for the administered regimen of **150 mg q24h**, which was used to simulate the individual predicted plasma concentration-time profile (IPRED) and the cumulative area under the curve (cAUC). $AUC_{0\text{-}24}$ was calculated using the **continuous AUC integration** method of adding cAUC from 0 to 24 hours. Five empirical dosing regimens were simulated in the same manner as the administered regimen, these were as follows: **150 mg q8h, 150 mg q12h, 240 mg q24h, 300 mg q24h and 340 mg q24h**. Higher doses were selected based on the assumption of dose proportionality [1]. The probability of target attainment (PTA, %) was calculated for all regimens, with the target $AUC_{0\text{-}24}$ set at **28 mg · h/L**. The target PTA was set at 95% [2]. The next page shows the simulation model script.

4 Simulation Code

The model used for the simulation is shown in the script below. It is a one-compartment model with oral absorption and linear elimination. The pharmacokinetic parameters absorption rate constant (`ka`), clearance (`CL`) and volume of distribution (`V`) are correlated with the body weight (`BW`) using power function.

```
$PARAM
TVCL   = 7.95,  // L/h
TVV    = 190,   // L
TVka   = 0.17,  // 1/h

$CMT DEPOT CENT cAUC // 1-compartmental model with absorption

$INPUT BW = 38 // kg, covariate which has effect on PK parameters

$MAIN
double BWEffCL = 0.75    ; // BW effect on CL
double BWEffV  = 1       ; // BW effect on V
double BWEffka = -(0.25) ; // BW effect on ka

double CL  = TVCL * pow((BW/70),BWEffCL) * exp(ETA(1)) ;
double V   = TVV  * pow((BW/70),BWEffV)                ;
double ka  = TVka * pow((BW/70),BWEffka)               ;

double k10 = CL/V ;

$OMEGA 0.1415863641 // CV_CL = 39%

$SIGMA
0.0974896213 // EPS(1)
0.0324       // EPS(2)

$ODE
dxdt_DEPOT   = -(ka) * DEPOT                ;
dxdt_CENT    =  (ka) * DEPOT  - (k10) * CENT ;
dxdt_cAUC    =                  CENT/V       ;

$TABLE
double IPRED  = CENT/V                      ;
double DV     = IPRED * (1+EPS(1)) + EPS(2)  ;
double BWsim  = BW                          ;

$CAPTURE IPRED DV
```

5 Results

The table below (Table 1) demonstrates the tested dosing regimens for a pediatric patient with median body weight of **38 kg**, along with their summary statistics for $AUC_{0\text{-}24}$. The probability of target attainment (PTA, %) has also been included in the table, with a target $AUC_{0\text{-}24}$ of **28 mg · h/L**. The dosing regimen of interest (150 mg q24h, corresponding to **3.95 mg/kg q24h**) elicits an $AUC_{0\text{-}24}$ of 17.6138 mg · h/L, which corresponds to a PTA of zero percent. Only regimen **9.50 mg/kg q24h** has a PTA of at least 95%.

Table 1: AUC (0–24 h, in mg · h/L) Summary by Regimen for Median BW of 38 kg.

Regimen	Median	Mean	SD	PTA (%)
3.95 mg/kg q12h	26.2739	26.0425	3.3592	30.4167
3.95 mg/kg q24h	17.6138	17.4282	2.6493	0.0000
3.95 mg/kg q8h	34.7943	34.4913	4.0777	93.3542
6.32 mg/kg q24h	28.0988	27.7908	4.1770	50.8333
8.00 mg/kg q24h	35.7749	35.4176	5.3428	91.0417
9.50 mg/kg q24h	42.2843	41.9010	6.3366	97.7292

Given that the body weight in this study was added as a covariate for PK parameters (see previous page), it was important to assess the dosing regimen across studied body weight range. Table 2 shows summary statistics of $AUC_{0\text{-}24h}$ of dosing regimen **9.50 mg/kg q24h** for the minimum, median and maximum body weight.

Table 2: AUC (0–24 h, in mg · h/L) Summary by BW for 9.50 mg/kg q24h.

Body Weight (kg)	Dose (mg)	Median	Mean	SD	PTA (%)
24 (min)	228.0	41.4092	40.9909	6.7824	96.4583
38 (median)	361.0	42.2843	41.9010	6.3366	97.7292
75 (max)	712.5	43.5812	43.1496	5.5848	99.2917

Below is Figure 1 that shows the IPRED plotted against time for regimen of 9.50 mg/kg for minimum, median and maximum body weight.

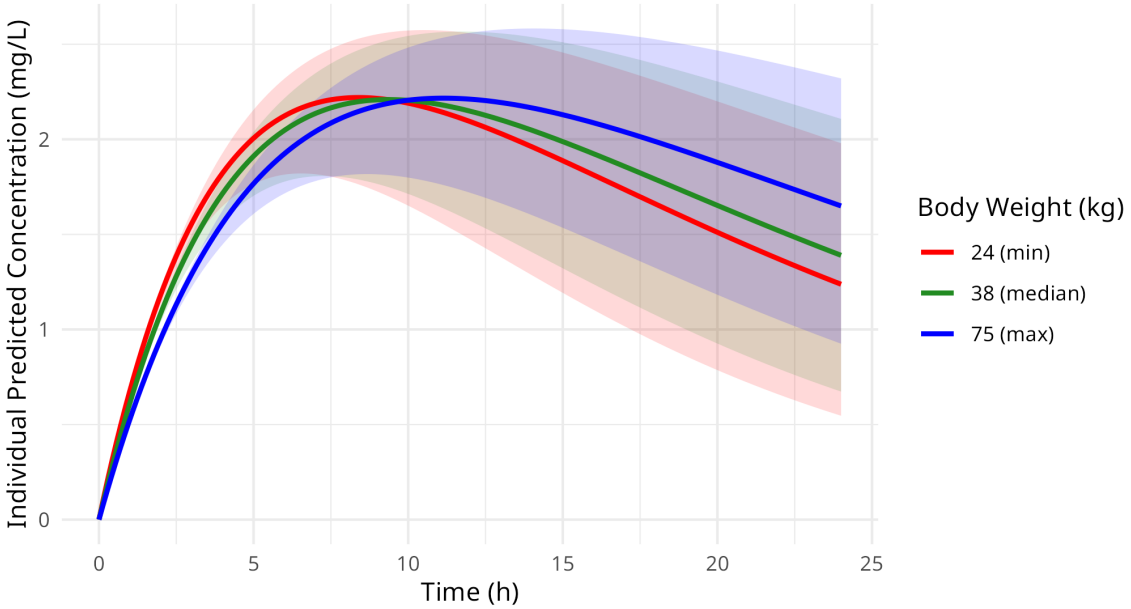

Figure 1: Comparison of concentration-time profiles for tested dosing regimens, using the median (line), 5th and 95th percentile (shaded ribbon) of IPRED

6 Discussion

In this study, a model was used for the simulation of regimens for dose optimizations of triazoconazole in children with Brontogen fibropathy (BF). As seen in Table 1, the PTA was zero percent for dosing regimen of **150 mg q24h**. This means that none of the virtual patients evoked sufficient exposure. Increasing the dose led to an increase in exposure, while the same effect was achieved from reducing the inter-dose interval. However, administering the dose more frequently might lead to reduced patient compliance. Therefore, regimens **340 mg q24h** was regarded as suitable dosing regimens.

There were limitations in the study: due to limited data on response and toxicity profile, the safety of the dosing regimens of triazoconazole could not be assessed. Furthermore, no exposure-response relationship could be established. Once sufficient response and toxicity data are available, the safety of the proposed dosing regimens will be evaluated, and exposure-response analysis will be carried out.

7 Conclusion

The study suggests that the dosing regimen of **150 mg q24h** proposed by Dr. Tagore, elicits an insufficient exposure. Dosing regimen of **9.50 mg/kg q24h** is proposed and expected to achieve the target exposure and elicit optimal response against *S. viridicaulis* in children with Brontogen fibropathy.

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We would like to express our gratitude to Emmanuel Niyigena and his creative mind for coming up with this research.

References

[1] Why should you evaluate dose proportionality? Certara n.d.

[2] Zheng Q. Systematic evaluation of dose proportionality studies in clinical pharmacokinetics. Current Drug Metabolism 2010;11:526–37. https://doi.org/10.2174/138920010791636185.

Appendix: R Scripts

```
if (!require("pacman")) {install.packages("pacman")
  library(pacman)}

pacman::p_load(mrgsolve, ggplot2, kableExtra, tidyverse, bookdown)
```

```
mod <- mread("project")

set.seed(123)       # reproducibility
N      <- 100L      # number of replicates
N_id   <- 48L       # number of patients per replicate
delta  <- 0.1       # hours (h)
tot_id <- N * N_id
```

```
BWmin = 24    # BW (kg) median and range given in supplementary data
BWmedian = 38
BWmax = 75

dose1 = 150 / BWmedian     # administered dose normalized by body weight
dose2 = dose1 / 17.61 * 28 # dose proportionality, determined for BWmedian

run_regimen <- function(dose, body_weight, interval, addl_dose, label) {
  out <- mrgsim(mod %>% init(cAUC = 0) %>% param(BW = body_weight),
                e      = ev(amt = dose * body_weight, time = 0,
                            ii = interval, addl = addl_dose),
                nid    = tot_id,
                tgrid  = tgrid(start = 0, end = 24, delta = delta),
                output = "df")

  rows24  <- out$time == 24
  auc_vec <- out$cAUC[rows24]

  list(sim = transform(out, regimen = label),
       auc = data.frame(regimen = label, AUC_0_24 = auc_vec))}
```

```
res1 <- run_regimen(dose1, BWmedian, 24, 0, "3.95 mg/kg q24h")
res2 <- run_regimen(dose1, BWmedian, 12, 1, "3.95 mg/kg q12h")
res3 <- run_regimen(dose1, BWmedian,  8, 2, "3.95 mg/kg q8h")
res4 <- run_regimen(dose2, BWmedian, 24, 0, "6.32 mg/kg q24h")
res5 <- run_regimen(8,     BWmedian, 24, 0, "8.00 mg/kg q24h")
res6 <- run_regimen(9.50,  BWmedian, 24, 0, "9.50 mg/kg q24h")
```

```r
auc_all <- bind_rows(res1$auc, res2$auc, res3$auc,
                     res4$auc, res5$auc, res6$auc)
```

```r
##| label: tbl-AUC1
##| tbl-cap: "AUC (0-24 h, in mg·h/L) Summary by Regimen for Median
##            BW of 38 kg."
auc_summary <- auc_all %>%
  group_by(regimen) %>%
  summarize(median_AUC_0_24 = median(AUC_0_24),
            mean_AUC_0_24   = mean(AUC_0_24),
            sd_AUC_0_24     = sd(AUC_0_24),
            PTA             = mean(AUC_0_24 >= 28) * 100,
            .groups = "drop")

auc_summary %>%
  kable(format   = "latex", # PDF/LaTeX output
        booktabs = TRUE,    # nicer horizontal rules
        digits   = 4,       # numeric rounding
        col.names = c("Regimen", "Median", "Mean", "SD", "PTA (%)"),
        align    = c("l", "r", "r", "r", "r"),
        longtable = TRUE)
```

```r
##| label: tbl-AUC2
##| tbl-cap: "AUC (0-24 h, in mg·h/L) Summary by BW for 9.50 mg/kg q24h."
res6 <- res6 %>% map(~ .x %>%
  mutate(regimen = recode(regimen, "9.50 mg/kg q24h" = "38 (median)")))

res7 <- run_regimen(9.50, BWmin, 24, 0, "24 (min)")
res8 <- run_regimen(9.50, BWmax, 24, 0, "75 (max)")

sim_BW <- bind_rows(res6$sim, res7$sim, res8$sim)
auc_BW <- bind_rows(res6$auc, res7$auc, res8$auc)

auc_BW <- auc_BW %>%
  mutate(dose_BW = case_when(regimen == "38 (median)" ~ 38,
                             regimen == "24 (min)" ~ 24,
                             regimen == "75 (max)" ~ 75))

auc_BW$dose_BW = auc_BW$dose_BW * 9.50
```

```r
auc_summary <- auc_BW %>%
  group_by(regimen) %>%
  summarize(actual_dose = unique(dose_BW),
            median_AUC_0_24 = median(AUC_0_24),
            mean_AUC_0_24   = mean(AUC_0_24),
            sd_AUC_0_24     = sd(AUC_0_24),
            PTA             = mean(AUC_0_24 >= 28) * 100,
            .groups = "drop")

auc_summary %>%
  kable(format   = "latex", booktabs = TRUE, digits   = 4,
        col.names = c("Body Weight (kg)", "Dose (mg)", "Median",
                      "Mean", "SD", "PTA (%)"),
        align    = c("l", "r", "r", "r", "r", "r"),
        longtable = TRUE)
```

```r
ipred_summary <- sim_BW %>%
  group_by(regimen, time) %>%
  summarize(IPRED_median = median(IPRED),
            IPRED_lo     = quantile(IPRED, 0.05),
            IPRED_hi     = quantile(IPRED, 0.95),
            .groups = "drop")
```

```r
ggplot(ipred_summary, aes(x = time, color = regimen)) +
  geom_ribbon(aes(ymin = IPRED_lo, ymax = IPRED_hi, fill = regimen),
              alpha = 0.15, color = NA)+
  geom_line(aes(y = IPRED_median), linewidth = 1) +
  scale_color_manual(values = c("red", "forestgreen", "blue")) +
  scale_fill_manual(values =  c("red", "forestgreen", "blue")) +
  guides(fill="none") +
  labs(x = "Time (h)",
       y = "Individual Predicted Concentration (mg/L)",
       color = "Body Weight (kg)") +
  theme_minimal()

ggsave("C_p_plots_regimens.png", width = 6.8, height = 3.7,
       dpi = 300, units = "in")
```