PopPK-Based Dosing Optimization for Triazoconazole

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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.

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 Brontogen fibropathy. The goal was also to suggest an optimal dosing regimen based on the simulation results.

Methods

A study of 33 adolescent patients was simulated over 100 replicates, resulting in a total of 3300 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 330 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 90% [2]. The next page shows the simulation model script.

Simulation Code

```
$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)              ;
// power function for scaling

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)     ; // populatiion prediction PRED
double BWsim  = BW                              ;

$CAPTURE
IPRED DV
```

Results

The table below (Table 1) demonstrates the tested dosing regimens, along with their summary statistics for $AUC_{0\text{-}24}$, as well as the probability of target attainment (PTA, %). The target $AUC_{0\text{-}24}$ was **28 mg · h/L**. The dosing regimen of interest (**150 mg q24h**) elicits an $AUC_{0\text{-}24}$ of 17.5586 mg · h/L, which corresponds to a PTA of zero percent. Regimens **150 mg q12h and 240 mg q24h** have a PTA below 90%, whereas regimens **150 mg q8h, 300 mg q24h and 330 mg q24h** have a PTA of at least 90%.

Table 1: AUC (0–24 h, in mg · h/L) Summary by Regimen

Regimen	Median	Mean	SD	PTA (%)
150 mg q12h	26.3050	26.0180	3.3547	29.7576
150 mg q24h	17.5586	17.4161	2.6269	0.0000
150 mg q8h	34.7381	34.3727	4.1833	92.3333
240 mg q24h	28.0554	27.7690	4.2458	50.9091
300 mg q24h	35.1274	34.8211	5.2272	90.0909
330 mg q24h	38.8471	38.3121	5.9088	94.8182

Below is Figure 1 that shows the IPRED plotted against time for all tested regimens.

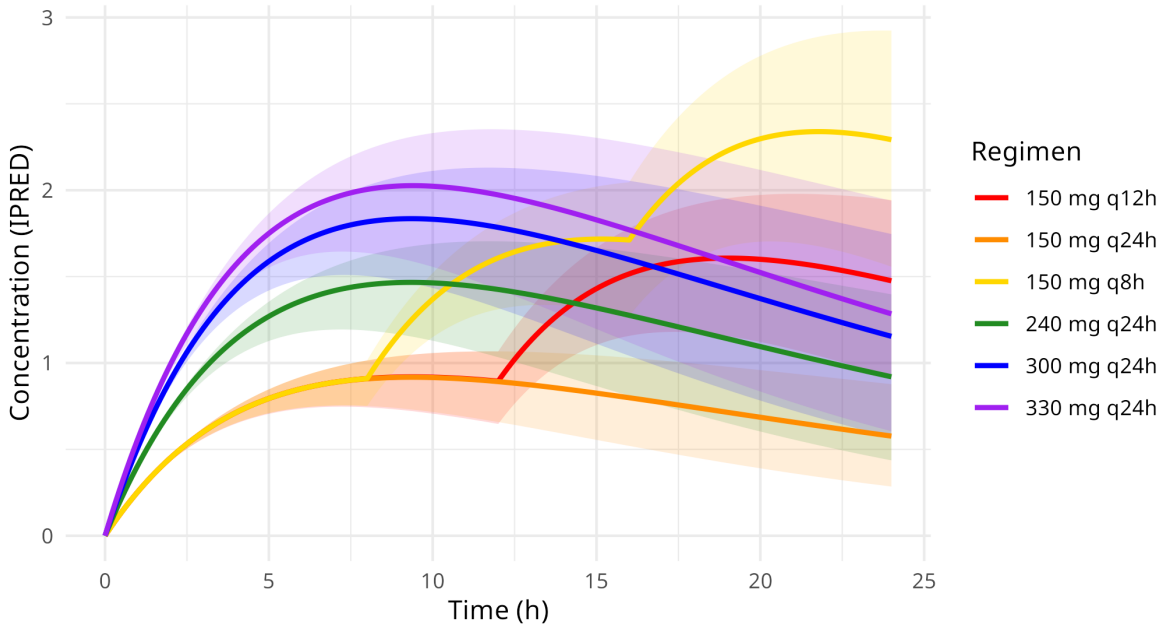

Figure 1: Comparison of concentration-time profiles for tested dosing regimens, using the median (line), 5th and 95th percentile (shaded ribbon) of IPRED

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 **300 or 330 mg q24h** were 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.

Conclusion

The study suggests that the dosing regimen of **150 mg q24h** proposed by Dr. Tagore, elicits an insufficient exposure. Dosing regimens of **300 and 330 mg q24h** are proposed and expected to achieve the target exposure and elicit optimal response against *S. viridicaulis* in children with Brontogen fibropathy.

Acknowledgement

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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

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

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

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

set.seed(123)      # reproducibility
N      <- 100L     # number of replicates
N_id   <- 33L      # number of patients per replicate
delta  <- 0.1      # hours (h)
tot_id <- N * N_id
```

```r
ev1 <- ev(amt = 150, time = 0)
ev2 <- ev(amt = 150, time = 0, ii = 12, addl = 1)
ev3 <- ev(amt = 150, time = 0, ii = 8,  addl = 2)
ev4 <- ev(amt = 240, time = 0)
ev5 <- ev(amt = 300, time = 0)
ev6 <- ev(amt = 330, time = 0)

# Force a grid that includes 24 exactly
tg <- tgrid(start = 0, end = 24, delta = delta)

run_regimen <- function(ev_obj, label) {
  out <- mrgsim(mod %>% init(cAUC = 0),
                e      = ev_obj,
                nid    = tot_id,
                tgrid  = tg,
                output = "df")

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

  stopifnot(length(auc_vec) == tot_id) # Robustness check: one AUC per ID!

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

```r
res_24_150 <- run_regimen(ev1, "150 mg q24h")
res_12_150 <- run_regimen(ev2, "150 mg q12h")
res_08_150 <- run_regimen(ev3, "150 mg q8h")
res_24_240 <- run_regimen(ev4, "240 mg q24h")
res_24_300 <- run_regimen(ev5, "300 mg q24h")
res_24_330 <- run_regimen(ev6, "330 mg q24h")

sim_all <- bind_rows(res_24_150$sim, res_12_150$sim, res_08_150$sim,
                     res_24_240$sim, res_24_300$sim, res_24_330$sim)
auc_all <- bind_rows(res_24_150$auc, res_12_150$auc, res_08_150$auc,
                     res_24_240$auc, res_24_300$auc, res_24_330$auc)
```

```r
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   = 2,       # numeric rounding
    caption  = "AUC (0-24 h) Summary by Regimen",
    col.names = c("Regimen", "Median", "Mean", "SD", "PTA (%)"),
    align    = c("l", "r", "r", "r", "r"),
    longtable = TRUE
  )
```

```r
ipred_summary<- sim_all %>%
  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", "darkorange", "gold",
                                "forestgreen", "blue", "purple")) +
  scale_fill_manual(values =  c("red", "darkorange", "gold",
                                "forestgreen", "blue", "purple")) +
  guides(fill="none") +
  labs(x = "Time (h)",
    y = "Concentration (IPRED)",
    color = "Regimen") +
  theme_minimal()

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