

PopPK-Based Dosing Optimization for Triazoloconazole

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The characteristic theme of the works of Stone is the bridge between culture and society. ...

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 triazocconazole. 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 is to find an optimal exposure-response relationship for children with Brontogen fibropathy.

Packages

The script below shows the packages which were loaded during the report generation. The packages used in this report were:

- `mrgsolve`: For performing simulations using models based on ordinary differential equations (ODEs);
- `ggplot2`: For creating graphics using data frames;
- `tidyverse`: For data formatting;
- `patchwork`: For combining several elements, such as plots, into one element.

```
if (!require("pacman")) {  
  install.packages("pacman")  
  library(pacman)}  
  
pacman::p_load(mrgsolve,  
                ggplot2,  
                tidyverse,  
                patchwork)
```

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

```

set.seed(123)      # reproducibility

N      <- 1000L    # number of replicates
N_id   <- 33L      # number of patients per replicate
delta  <- 0.1      # hours (h)
tot_id <- N * N_id

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_200 <- run_regimen(ev4, "200 mg q24h")
res_24_240 <- run_regimen(ev5, "240 mg q24h")
res_24_300 <- run_regimen(ev6, "300 mg q24h")

sim_all <- bind_rows(res_24_150$sim, res_12_150$sim, res_08_150$sim,
                      res_24_200$sim, res_24_240$sim, res_24_300$sim)
auc_all <- bind_rows(res_24_150$auc, res_12_150$auc, res_08_150$auc,
                      res_24_200$auc, res_24_240$auc, res_24_300$auc)

```

```

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),
            .groups = "drop")

print(auc_summary)

```

```

# A tibble: 6 x 4
  regimen      median_AUC_0_24  mean_AUC_0_24  sd_AUC_0_24
  <chr>           <dbl>          <dbl>          <dbl>
1 150 mg q12h       26.3          26.0          3.33
2 150 mg q24h        17.7          17.5          2.64
3 150 mg q8h         34.8          34.4          4.15
4 200 mg q24h        23.5          23.3          3.51
5 240 mg q24h        28.2          27.9          4.20
6 300 mg q24h        35.2          34.9          5.27

```

```

ipred_summary<- sim_all %>%
  group_by(regimen, time) %>%
  summarize(IPRED_median = median(IPRED),

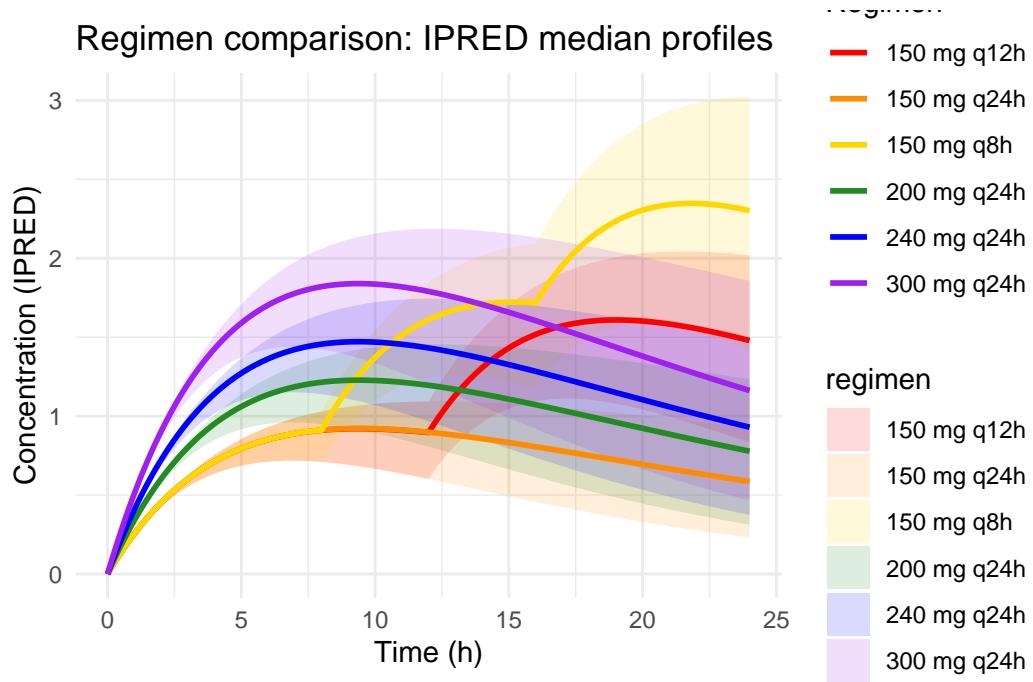
```

```

IPRED_lo      = quantile(IPRED, 0.025),
IPRED_hi     = quantile(IPRED, 0.975),
.groups = "drop")

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")) +
  labs(
    title = "Regimen comparison: IPRED median profiles",
    x = "Time (h)",
    y = "Concentration (IPRED)",
    color = "Regimen") +
  theme_minimal()

```



Results and Discussion

Conclusion