

# **PopPK-Based Dosing Optimization for Triazoconazole**

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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 *Spirigilus 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 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 DEPTO 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),

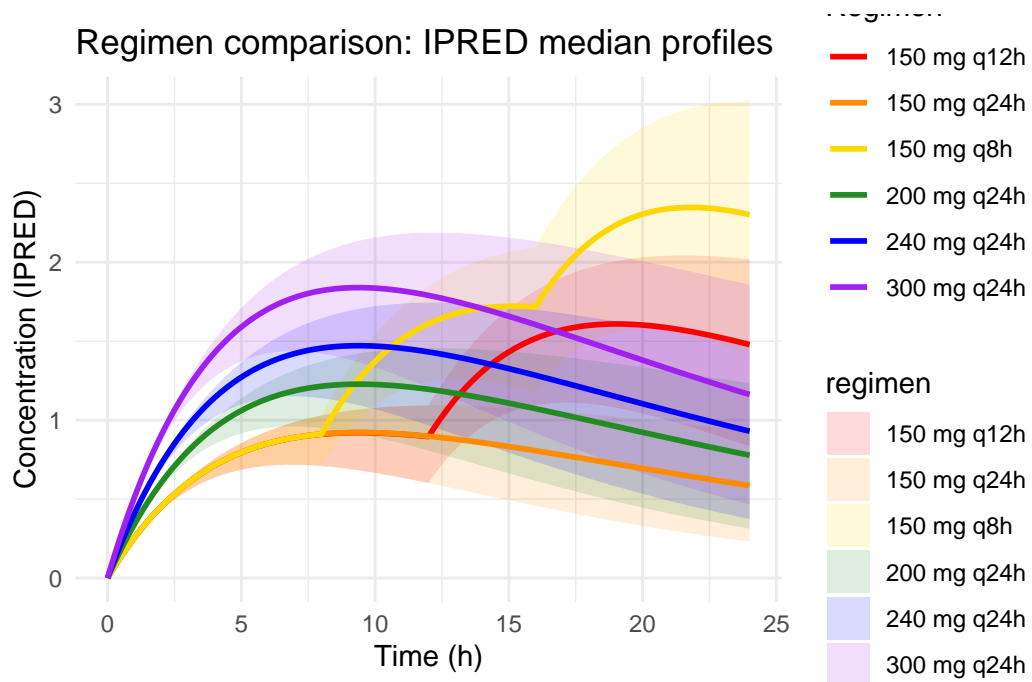
```

```

    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