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 $\cdot$ 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 plasms 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, 200 mg q24h, 240 mg q24h and 300 mg q24h**. Higher doses were selected based on the assumption of dose proportionality []. 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)    ;
double BWsim  = BW                             ;

$CAPTURE
IPRED DV
```

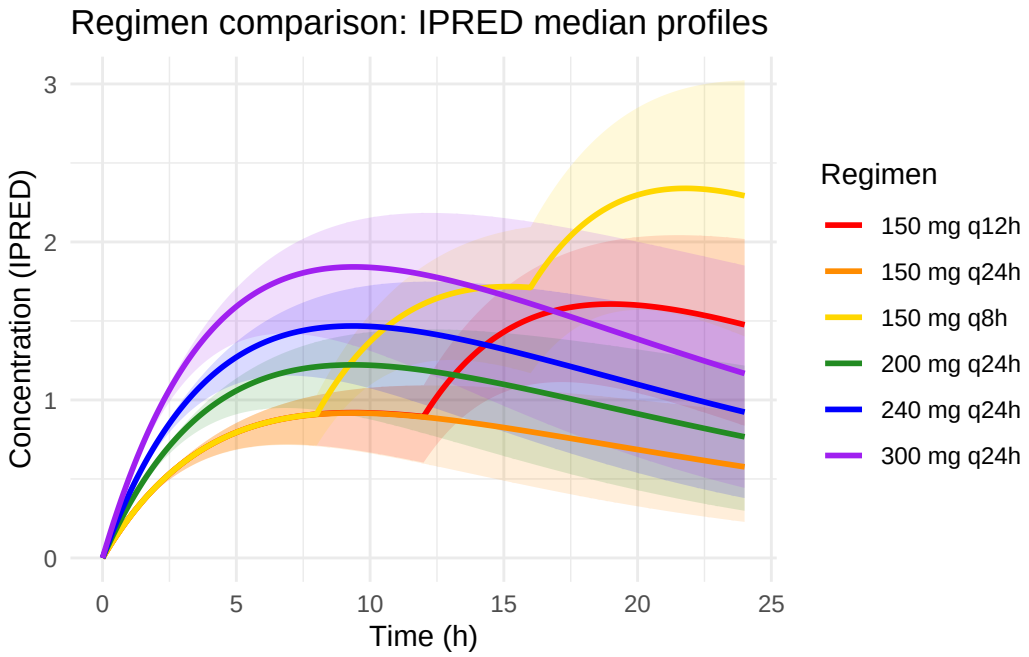
Results

The study suggests that the dosing regimen of **150 mg q24h** elicits an $AUC_{0\text{-}24}$ of 17.69 mg · h/L, which is below the anticipated exposure of 28 mg · h/L. Based on these results, dosing regimens (**150 mg q8h, 240 mg q24h or 300 mg q24h**) are proposed. **Table 1** shows summary statistics of $AUC_{0\text{-}24}$ for the tested dosing regimens below.

Table 1: AUC (0–24 h) Summary by Regimen

Regimen	Median	Mean	SD
150 mg q12h	26.31	26.02	3.35
150 mg q24h	17.56	17.42	2.63
150 mg q8h	34.74	34.37	4.18
200 mg q24h	23.38	23.14	3.54
240 mg q24h	28.10	27.86	4.18
300 mg q24h	35.32	34.83	5.37

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



VPC using xpose4 toolchain (vpc package)

This section produces a Visual Predictive Check (VPC) for **all dosing regimens** using the *xpose4 toolchain* via the `{vpc}` package (which underpins VPCs in xpose). We treat the **first replicate (first `N_id` subjects)** as the observed dataset and overlay it against prediction intervals computed from **all replicates**.

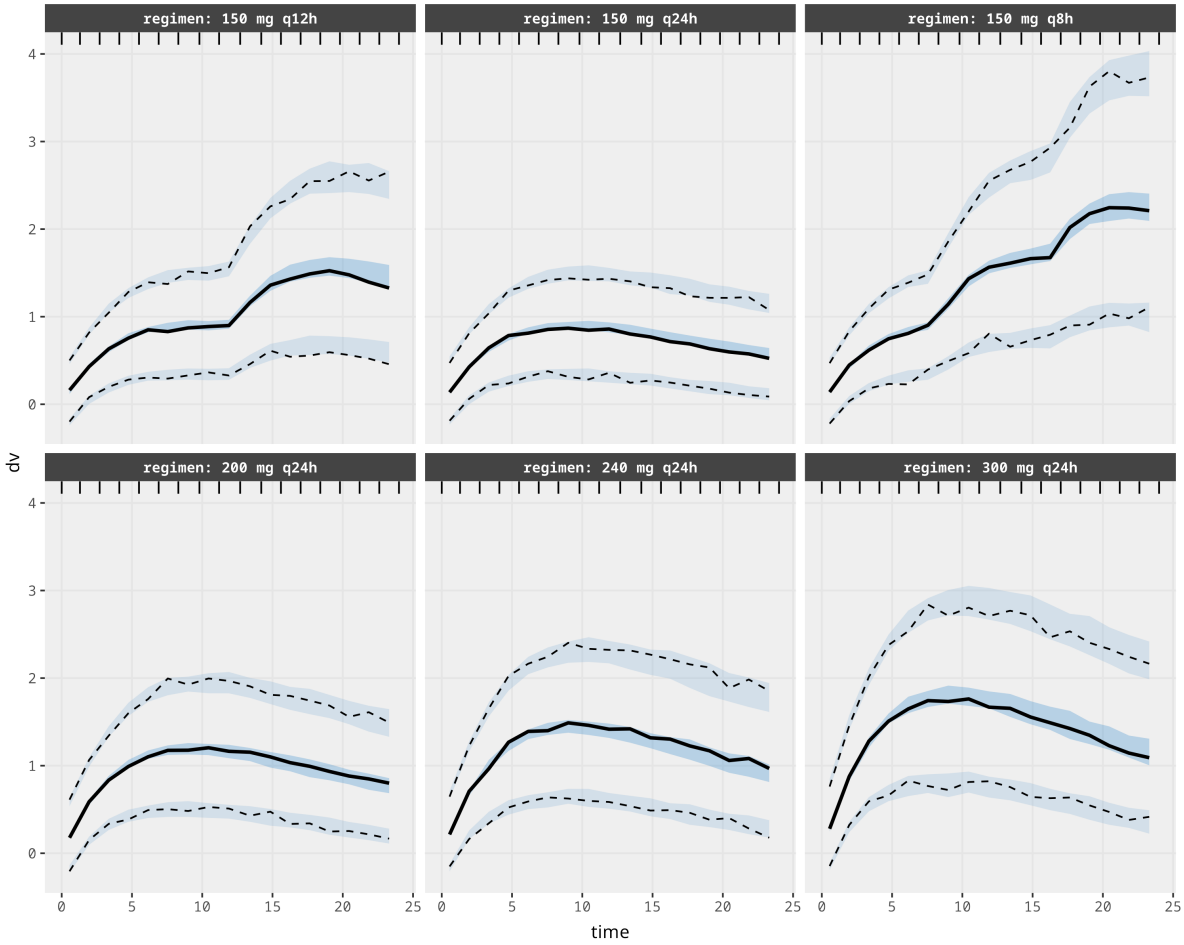


Figure 1: VPC plots by dosing regimen

Conclusion