**Covariate Searching Hands-on  
: A Population Pharmacokinetic Analysis of Fluconazole to Predict Therapeutic Outcome in Burn Patients with Candida Infection *Antimicrob Agents Chemother* 2013;57(2):1006-11**

**Introduction**

|  |
| --- |
| **Subjects**  60 major burn patients with burn injury ranging from 11% to 95% of total body surface area  **Fluconazole administration and blood sampling**  Patients were intravenously infused with 100 to 400 mg of fluconazole for 10 to 40 min every 24 h for the treatment of suspected (47 cases) or confirmed (13 cases) fungal infection. They had received 5 to 17 days (mean 6.5 days) of fluconazole treatment prior to the PK sampling. Eight venous blood samples were obtained via central venous catheter at 0 (just before dosing), 3, 5, 9, 24, 27, 48, and 51 h after the initiation of infusion. Fluconazole dosing was maintained every 24 h regardless of sampling.  **Dataset**  The data set consisted of a total of 409 fluconazole concentration observations from 60 subjects. Demographic and clinical variables such as age, sex (ISM, 0 for female, 1 for male), weight (WT), sepsis condition (SEPS), edema status (EDEM), APACHE II score (AP), creatinine CL calculated by the Cockcroft-Gault equation (CLCR), application of continuous renal replacement therapy (CRRT), total body surface areas burned (TBSA), and time after burn injury (DAI) were included as potential covariates. Because the post-burn hypermetabolic response is maximized between day 7 and day 17 after injury (it decreases thereafter) and varies by subjects, we considered TBI to be a potential covariate explaining the physiological difference. DAI was included as a categorical variable (1 for patients whose time from burn injury was within 30 days and 0 for others), and the cutoff point was determined by consideration of the time course of physiological change. |

**Step 1. Covariate evaluation and screening**

1. **Check the distribution of variables which may be included as potential covariates (potential covariates). Which of those have appropriate distributional characteristics?**
2. **Check the co-linearity between potential covariates. Which of those have correlation to each other?**
3. **Check the co-linearity between parameters.**

* **Add ETAs to the patab**
* **Change run number to 101**

**Which parameters are correlated? Explain the relationship between parameters and ETAs.**

1. **Perform visual covariate screening using Parameter vs Covariate plots.**

* **Only check the ETA vs Covariate plots**

**Which variables have correlative tendency to which parameter?**

1. **Perform numerical covariate screening using GAM.**

**Which variables produce significant AIC decrease for ETA1?**

**Which variables produce significant AIC decrease for ETA2?**

1. **Suggest your covariate modeling strategy.**

**Step 2. Considerations for the obvious covariate**

1. **Include CRRT as the covariate for CL.**

* **Use IF statement in the control file.**
* **Change the run number to 110**
* **Allocated appropriate number to each THETA**
* **Do not estimate BSV for CRRT=1 group**
* **Only include ETA for CL of CRRT=0 group and V in the patab**
* **Remove CRRT from catab**
* **Compare the result to that of PK100**

**7-1. Suggest alternative way to separate CRRT groups**

1. **Allow BSV estimation for CRRT=1 group.**

* **Change the run number to 111**
* **What happens?**

1. **Now, repeat the procedure 4~6**

**Step 3. Covariate modeling**

**Remove parameters having no potential covatriate in the screening step from patab**

**Remove variables not selected in the screening step from cotab or catab**

1. **Include BW as the covariate for V.**

* **Compare 3 structures**

**V = BW \* THETA(3); adjust initial estimate for THETA(3); run number = 121**

**V = BW/(mean BW) \* THETA(3); run number = 122**

**V = BW/(mean BW) \* THETA(3) + THETA(4); run number = 123**

**Is BW meaningful covariate? Why?**

**Which structure is the best?**

1. **Any other covariate for V? How can you find that?**

* **Use the best model obtained so far**
* **Check whether the relationship between ETA~covariate disappeared for included parameter-covariate structure in the model**
* **Repeat the procedure 4~6 & 10   
  (when using linear model, always check for the significance of intercept)**

1. **Perform backward elimination for full V covariate model.**
2. **Proceed to covariate modeling for CL**