



Quantitative assessment of drug response in male patients with severe Nocturia receiving a combined medication of solifenacin and tamsulosin

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Background

Nocturia, defined currently by the ICS as the complaint that an individual has to wake at night one or more times to void, is a common disorder affecting both elderly (over 70 years) men and elderly women. It is known that increased urination frequency, 24-hr urine volume and nocturnal urine volume are the major symptoms of nocturia, and some researchers have reported that a combined medication of alpha 1 blocker and anticholinergic drug provides a better therapy for nocturia patients with benign prostatic hyperplasia than traditional mono-therapies. However, so far there has been no method that is able to quantitatively evaluate the drug effect on the improvement of symptoms. A nonlinear mixed effects model, by quantitatively describing the time course of drug response and incorporating random individual differences, can become a solution for this problem and help understand the characteristics of the change in drug effect or disease status over time.

Method

1. Data

To quantitatively assess the improvement of combined medication of alpha 1 blocker and anticholinergic drug for male patients with severe nocturia, we selected male patients with more than 3 times of nocturia a day who was treated with tamsulosin (harnal^R) as an a1 blocker and solifenacin (vesicare^R) q.d. as an anticholinergic drug with the same dose amount q.d. Data were collected for three periods, before the medication, 3 months and 6 months after starting the medication. Obtained data were not from the clinical trial but from the real patients treated in outpatient clinics, which were collected using frequency volume chart (FVC) from the Department of Urology of Chung-Ang university Hospital, collaborated with the department of Urology of Severance Hospital Seoul, Korea.

2. Time varying urination frequency with count model.

To estimate the frequency of urination, a count model with Poisson distribution was used where the urination was considered as an event and the lambda(λ) was described as an expected mean urination frequency in a certain time interval [5]. Modelling was performed using NONMEM 7.2.

* Placebo (before treatment) model

$$f_p(\text{time}) = TVBase * e^{\eta} * (1 + Circ(\text{time}))$$

$$\lambda = f_p(\text{time}) * f_d(\text{time})$$

λ = Lambda in poisson distribution

$f_p(\text{time})$ = Time course function of before medication

Base = baseline Lambda

$f_d(\text{time})$ = Time course function for inhibitory drug effect

e^{η} = Interindividual random effect (proportional error model)

* Multiple dose drug effect model (Inhibitory)

$$f_d(\text{time}) = 1 - AA * (TMP1 - TMP2)$$

k_{10} = Theta(1) : Hypothetical elimination rate constant (1/time)

K_{01} = $k_{10} + \text{Theta}(2)$: Hypothetical absorption rate constant (1/time)

AA = Theta(3) : Maximum inhibitory effect

T (tau) = 24 (hr) : dosing interval

$TMP1 = \exp(-k_{10} * \text{time}) / (1 - \exp(-k_{10} * T))$

$TMP2 = \exp(-K_{01} * \text{time}) / (1 - \exp(-K_{01} * T))$

* Cumulative drug effect model

$$f_{dp}(\text{TIMEDP}) = 1 - BB * (1 - \exp(-K_{dp} * \text{TIMEDP}))$$

concept of "drug progression (K_{dp})" was applied by assuming the exponential decrease of baseline lambda over the treatment time (day) up to BB.

BB = Theta(4) : the maximum decrease expected

K_{dp} = Theta(5) : rate constant (1/day) accounting for the exponential decrease

TIMEDP : Time of day passed (Period 2= 30, Period 3= 90)

* Overall concept of Lambda (λ)

$$\text{Lambda } (\lambda) = \underbrace{f_p(\text{time})}_{\text{placebo model}} * \underbrace{f_d(\text{time})}_{\text{drug model}} * \underbrace{f_{dp}(\text{timedp})}_{\text{drug model}} * \exp(\eta)$$

Conclusions

The present results showed that the developed model described the data adequately and provided the useful information that can be used for predicting the time course of treatment effect. It is hoped that the model developed can be used to assess the improvement of symptom of voiding at night and frequent urination systemically. However, this is the preliminary result and further analyses will be needed including covariates analysis that can characterize individual differences in drug effect across patients, so that the model can be used to provide tailored information for each individual patient. Since not only urination frequency but also 24-hr urine volume and nocturnal urine volume are among the three major symptoms of nocturia, further analyses including 24-hr urine volume and nocturnal urine volume should be conducted in the future. If an appropriate model incorporating all three symptom indices were built, it would become a more accurate and useful tool offering a reliable basis for clinicians to make a better decision and set an optimized treatment plan for clinical outcome and ultimately better quality of life for patients.

Objectives

With urination frequency data observed from dysuria patients, this study was intended to develop a quantitative method that can provide a time course of predicted drug response for the period not only after a short-term treatment but also after a long-term treatment. In particular, it aimed at estimating the rate of drug effect reaching the maximum drug effect, and up to how much the symptom can be reduced at the maximum effect, in an effort to provide the supportive information in designing an optimal treatment plan.

Results

Table 1. Estimated parameters of Placebo (before medication) model

$$Circ(t) = (amp1 * \cos(2\pi(t - acr1) / 24)) + (amp2 * \cos(2\pi(t - acr2) / 8))$$

$$f_p(t) = Base * (1 + Circ(\text{time}))$$

OFV : 522.364		
Parameters	Estimated Values	RSE(%)
Base (lambda)	1.02	6.38
amp1	0.123	38.05
acr1	12	8.33
amp2	0.207	17.54
acr2	5.37	5.29
OMEGA (proportional error model)	6.89E-13	23.08

Table 2. Estimated parameters of Drug (after medication) model

OFV : 1482.495		
Parameters	Estimated Values	RSE(%)
Base (lambda)	FIXED	FIXED
amp1		
acr1		
amp2		
acr2		
k10 (1/time)	0.000155	49.226
K01 - k10(1/time)	0.000436	37.385
AA	0.000189	29.418
BB	0.229	7.5546
KDP (1/day)	0.0319	30.063
OMEGA (Inter-individual random effect : η)	0.0395	34.937

Figure 1. Loess curve of observed urination frequency in 2-hr interval (span:0.2, df=2, gaussian)

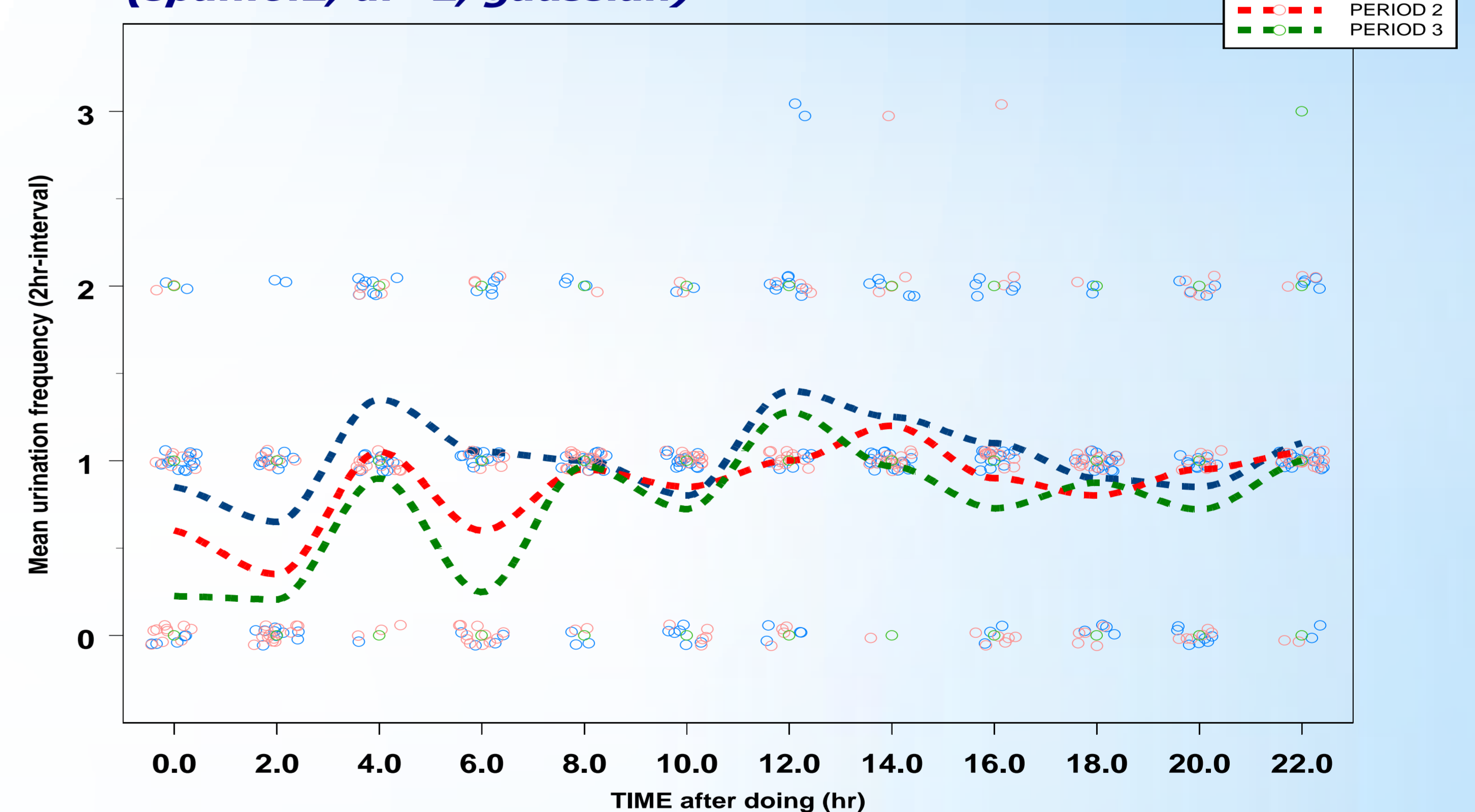


Figure 2. Goodness of fit of Lambda vs. Mean Urination frequency of each period.

