Evaluation of theophylline therapeutic drug monitoring service

Vrednotenje procesa terapevtskega spremljanja serumskih koncentracij teofilina

Neža Rugelj,[1] Katja Čvan Trobec,[2] Mitja Pišlar,[1] Pika Meško Brguljan,[2] Mitja Košnik,[2] Aleš Mrhar[1]

[1] *Faculty of Pharmacy, University of Ljubljana, Slovenia*

[2] *University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia*

Korespondenca/ Correspondence:
Aleš Mrhar, PharmD, PhD, e: ales.mrhar@ffa.uni-lj.si

Ključne besede:
farmakokinetika teofilina; ozko terapevtsko območje; meritve serumskih koncentracij; individualiziran režim odmerjanja

Key words:
theophylline pharmacokinetics; narrow therapeutic range; serum level measurements; individualized dosage schedule

Citirajte kot/Cite as:
Zdrav Vestn 2015; 84: 191–202

Prispelo: 27. apr. 2014,
Sprejeto: 5. okt. 2014

Izvleček

Izhodišča: Pri teofilinu je zaradi ozkega terapevtskega območja in individualne variabilnosti v farmakokinetiki potrebno terapevtsko spremljanje serumskih koncentracij (TDM). V naši raziskavi smo ovrednotili proces TDM v slovenskem kliničnem okolju, kjer se izmerjenih serumskih koncentracij teofilina farmakokinetično običajno ne vrednoti.

Metode: V retrospektivni raziskavi smo ovrednotili 127 naključno izbranih meritev serumske koncentracije teofilina, ki so bile izvedene leta 2010 v slovenskem terciarnem kliničnem okolju. Iz podatkovnih zbirk bolnikov smo pridobili njihove demografske podatke, informacije o odmerjanju teofilina in podatke o odvzemu krvnih vzorcev. Pri procesu TDM smo vrednotili ustreznost odločitve za TDM, časovno pravilnost odvzema vzorca za merjenje serumskih koncentracije ter pravilnost ukrepanja zdravnikov po prejemu rezultata o serumski koncentraciji teofilina. Na podlagi zbranih podatkov smo razvili populacijski farmakokinetični model ter z njegovo pomočjo ponovno ovrednotili ukrepanje zdravnikov glede prilagajanja odmerkov teofilina po meritvi njegove serumske koncentracije.

Rezultati: Izmed 127 meritev serumske koncentracije teofilina je bil razlog za meritev upravičen v 107 primerih (84,3 %). Skoraj polovica meritev (44,9 %) je bila izvedena pred vzpostavitvijo stacionarnega stanja teofilina. 65 % izmerjenih koncentracij je bilo subterapevtskih, povprečna izmerjena koncentracija (53.1 µmol/L) pa je bila pod terapevtskim območjem. Kljub subterapevtskim koncentracijam se odmerki teofilina v večini primerov niso povečali. S pomočjo farmakokinetičnega modela smo izračunali povprečni optimalni dnevni odmerek teofilina, ki je bil značilno večji od povprečnega dejanskega dnevnega odmerka (876 mg vs. 572 mg, $p < 0.001$).

Zaključki: Raziskava je pokazala, da bi bilo v klinični praksi potrebno izboljšati storitev TDM teofilina in vanjo vključiti farmakokinetično interpretacijo izmerjenih serumskih koncentracij.

Abstract

Background: Therapeutic monitoring of theophylline serum levels is required due to its narrow therapeutic range and marked interindividual pharmacokinetic variability. We evaluated therapeutic drug monitoring service for theophylline in Slovenian clinical setting, which currently includes no pharmacokinetic evaluation of measured theophylline serum concentrations.

Methods: We retrospectively evaluated 127 randomly selected theophylline serum level determinations performed in 2010 in a tertiary clinical setting in Slovenia. Demographic data, information on theophylline dosing and blood sampling were collected from patients' data files. Authors evaluated the appropriateness of the following procedures: indications for theophylline serum concentration measurement, timing of blood sampling and dosage adjustments made after theophylline levels had been reported. On the basis of collected data, a population pharmacokinetic model for theophylline was built and further used for the evaluation of dosage adjustments.

Results: Out of 127 cases, 107 (84.3 %) had clinically justified indication for theophylline serum level measurement. Near half of the measurements (44.9 %) were performed before the steady state of theophylline concentrations was established. 65 % of measured concentrations were subtherapeutic and the average measured concentration was below the therapeutic range (53.1 µmol/L). Despite subtherapeutic concentrations, the dose of theophylline was generally not increased. Pharmacokinetic model enabled the calculation of average optimal daily dose which

was significantly higher than the average actual daily dose used (876 mg vs. 572 mg, $p < 0.001$).

Conclusions: Theophylline TDM service should be optimized and pharmacokinetic interpretation of theophylline serum levels should be integrated into clinical practice.

Introduction

Therapeutic drug monitoring (TDM) is defined as clinical laboratory measurement of drug concentration that will directly influence drug prescribing procedures when accompanied with appropriate medical interpretation.[1] It plays a major role in minimizing adverse drug reactions and enhancing optimal therapeutic response.[2] While proper interpretation of measured concentrations provides valuable information, inappropriate use of TDM leads to unnecessary costs for healthcare system, can be misleading and even dangerous for the patient. To avoid misinterpretation of measured drug concentrations, use of pharmacokinetic (PK) models, supported by computer simulation, has been integrated into clinical practice.[3,4] This enables the estimation of individual PK parameters and determination of safe and effective dosing regimens.

Only a minority of drugs fulfilling certain criteria are suitable candidates for TDM.[5,6] Theophylline has a narrow therapeutic range, marked pharmacokinetic variability, poor correlation between doses and serum concentrations and close relationship between serum levels and clinical effect. Consequently, TDM is an important and useful tool in optimizing and individualizing theophylline pharmacotherapy.[7,8]

Poor correlation between doses and serum concentrations is mainly caused by the variation in the rate of theophylline metabolism which could be affected by concomitant disease, altered physiology, pharmacokinetic interactions with other drugs, smoking status, age and diet. Serum theophylline concentrations are increased in heart failure, hepatic cirrhosis, acute hepatitis and febrile infections, and decreased in cystic fibrosis, hyperthyroidism and by chronic smoking.[9,10] Drugs that increase the serum theophylline concentrations by inhibition of liver enzymes CYP 450 are cimetidine, ciprofloxacin, enoxacin, erythromycin, fluvoxamine, propranolol, thiabendazole, ticlopidine and verapamil.[11-19] Drugs that decrease the serum theophylline concentrations by induction of liver enzymes CYP 450 are phenytoin, phenobarbital, carbamazepine, rifampicin and ritonavir.[20-28]

Theophylline is a methylxanthine derivative with spasmolytic and anti-inflammatory effects. It has been replaced by inhaled beta-2-adrenergic receptor agonists and anticholinergics in the treatment of chronic obstructive pulmonary disease (COPD), since it is less effective and less well tolerated than inhaled long-acting bronchodilators. However, it has a modest bronchodilator effect and symptomatic benefit compared with placebo in stable COPD and is therefore still used as an alternative choice in all stages of COPD, especially in elderly patients who have difficulty with inhalers.[7,29]

According to the literature data,[7,30] therapeutic range for theophylline has been set to 55–110 μmol/L (which equals 10–20 mg/L). However, some anti-inflammatory effects were shown to be exerted even at lower theophylline concentrations[31-33] and some adverse effects of theophylline occur already below the upper limit of the interval.[34] This has to be considered when interpreting theophylline levels in clinical practice.

Aim of the study

Several studies have evaluated the appropriateness of TDM for various drugs.[35-40] The aim of our study was to assess appropriateness of theophylline TDM service in our tertiary clinic as acknowledged in the article of Gross et al.[6] For this purpose, a pharmacokinetic model for theophylline based on measured theophylline concentrations was developed and further used for the evalua-

tion of theophylline dose adjustments made by clinicians.

Methods

Data collection

This retrospective study was conducted at the University Clinic of Respiratory and Allergic Diseases Golnik in Slovenia. We selected all determinations of theophylline serum levels performed in the year 2010, which had been measured by kinetic interaction of microparticles in a solution (KIMS) on Cobas 501 system (Roche Diagnostics) using an original application.[30] Single measurements were grouped if they were performed during the same hospitalization. From this initial pool of data we randomly selected 100 hospitalizations using an on-line program "Research Randomizer".[41] Hospitalizations that were shorter than 24 hours were excluded because we could not obtain enough data about theophylline dosage schedule to evaluate theophylline TDM service. The following information was retrieved from patients' data files: demographic data (gender, age, weight and height), smoking status, concomitant diseases and conditions that could influence theophylline pharmacokinetics, concomitant drugs potentially interacting with theophylline, theophylline dosage schedule, date and time of blood sampling and measured serum theophylline concentrations.

Population pharmacokinetic analysis

For population pharmacokinetic (PPK) analysis, only those cases for which theophylline dosing schedule was available for at least two days before theophylline serum level determination were included. A PPK model of theophylline was established with nonlinear mixed effect modeling approach, using program NONMEM®.[42] A one-compartment model with first-order absorption and elimination was assumed as the base model. Absorption rate constant (k_a) and lag time (t_{lag}) were previously determined by analyzing average values of serum theophylline concentrations obtained in the bioequivalence study for Teotard® prolonged-release capsules.[43] The values of k_a and t_{lag} were fixed at 0.102 h^{-1} and 1.54 h, respectively. Consequently, the base model was estimating parameters such as absorption fraction (F), clearance (Cl), and volume of distribution (V_D). Inter-individual variability of the parameters was included as log-normal model. In order to explain parameters inter-individual variability the stepwise covariate model building was used.[44] The following covariates were evaluated: weight, height, age, gender, smoking status, heart failure, pneumonia, COPD, concomitant drugs potentially interacting with theophylline, body mass index (BMI), body surface area (BSA) and lean body weight (LBW). LBW was calculated using the method of James (Equations 1 and 2)[45,46] and BSA was calculated using the Mosteller formula (Equation 3).[47] The final model was built using an automated covariate model building method where only covariates that are statistically significant according to inclusion and exclusion criteria are incorporated into the model.[44] Inclusion of a covariate was considered statistically significant if the objection function value decreased by 3.84 units ($p < 0.05$). Subsequently, each included covariate was retested with statistically significant level of $p < 0.01$.

$$LBW\ (men) = 1.10 * W - 128 * \frac{W^2}{(100 * H)^2}$$

Equation 1

$$LBW\ (women) = 1.07 * W - 148 * \frac{W^2}{(100 * H)^2}$$

Equation 2

$$BSA = \sqrt{\frac{W * H * 100}{3600}}$$

Equation 3

LBW–lean body weight (kg)
W –body weight (kg)
H –height (m)
BSA –body surface area (m^2)

Evaluation of TDM service

The appropriateness of theophylline TDM service was evaluated with regard to

the following aspects: indication for theophylline level monitoring, time of blood sampling in relation to theophylline administration and appropriateness of theophylline dosage adjustments made after the laboratory report was available. We defined indications for theophylline level monitoring, which were considered clinically justified (Table 4). Indications that could not be classified into any of the categories mentioned were considered inadequate. Time of blood sampling was considered appropriate if it was done after steady state had been attained (defined as 2 days, which is approximately 5 half-lives after theophylline initiation or dose change).[48] Dose adjustments made after the laboratory results had been reported, were evaluated with PK model. Therapeutic range for theophylline was specified between 55 and 110 µmol/L.

The evaluation of theophylline dosing

Dose adjustments, made after the theophylline serum level was reported, were considered appropriate if the dose was elevated in cases of subtherapeutic concentrations, reduced in cases of toxic concentrations and remained unchanged in cases of therapeutic concentrations. Dose adjustments were also evaluated with the use of developed PPK model. We compared the actual daily doses that patients were given within 24 hours after the blood sampling with optimal daily doses that were calculated using Equation 4 and 5.

$$D(optimal) = \frac{83\ \mu\frac{\mathbf{mol}}{\mathbf{L}} * D\left(actual_{before}\right)}{Css\ \left(actual_{before}\right)}$$

Equation 4

$$D(optimal\ daily\ dose) = D\ (optimal) * 2$$

Equation 5

D (optimal) – optimal dose for a patient
D (optimal daily dose) – optimal daily dose for a patient
D (actual_before) – the last theophylline dose before the blood sampling
Css (actual_before) – actual average theophylline serum concentration in the last 12 hours before the blood sampling

Concentration of 83 µmol/L was assumed as optimal average theophylline serum concentration because it represented the arithmetic mean of theophylline therapeutic range (55 to 110 µmol/L). The actual average theophylline concentration at steady-state was calculated using PPK model in NONMEM based on the estimated AUC in the last 12 hours before blood sampling. After the calculation of optimal daily doses (Equations 4 and 5), the doses were rounded to the nearest value that could be achieved by a combination of 200 mg and 350 mg capsules, which are currently available on the Slovenian market. Comparison between actual and optimal daily doses was made by paired sample t-test, which was performed using SPSS version 16.0 (SPSS Inc., Chichago, IL). A p-value of less than 0.05 was con-

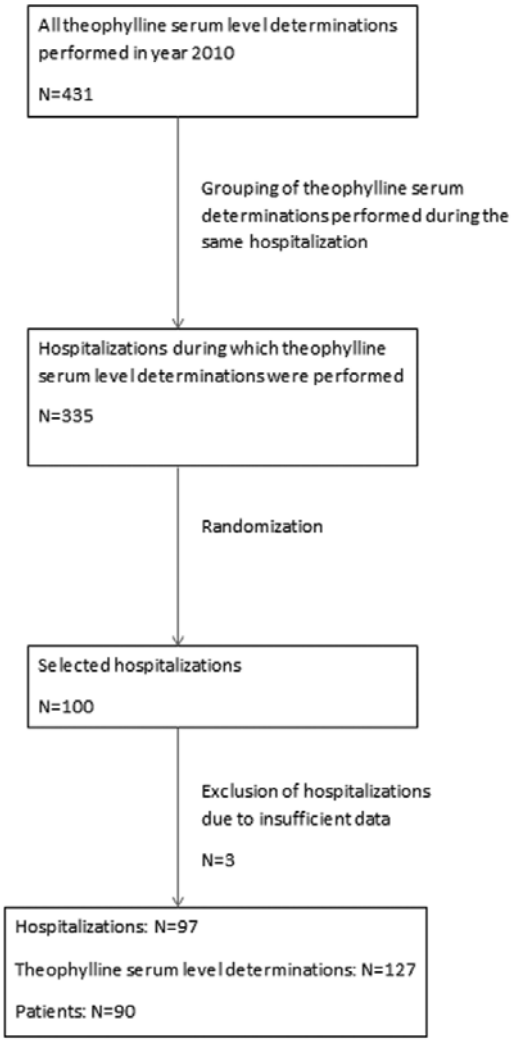

Figure 1: Selection of theophylline serum level determinations for analysis

sidered statistically significant for all statistical analyses.

Evaluation with PPK model requires data on the theophylline dosing regimen before and after each blood sampling, so only measurements with sufficient data were included. Moreover, Equation 4 is based on the assumption that blood was sampled in steady state and we therefore excluded all measurements that were not performed in steady state condition.

The evaluation of time within the therapeutic range

We simulated two different theophylline serum profiles within 72 hours after blood sampling. One profile was based on the actual dosing of theophylline and the other on the optimal dosing (as described in the previous section). The percentage of time when theophylline concentration was within the therapeutic range was estimated for both profiles and compared with paired sample t-test.

Table 1: Patients' characteristics (N = 90)

		SD	N
Male: N (%)	55 (61 %)		90
Age in years: average (range)	72 (55–88)		90
Body size descriptor			
Body weight (kg)	76.7	19.8	81
Height (cm)	164.3	9.1	84
BMI (kg/m^2)	28.3	6.9	79
BSA (m^2)	1.9	0.3	79
LBW (kg)	52.4	10.1	79
Diagnosis (% of patients)			
COPD	67.7 %		
Chronic heart failure	43.3 %		
Pneumonia	26.8 %		
Hypothyroidism	6.7 %		
Liver disease	2.2 %		
Smoking status (% of patients)			
Current smokers	6.7 %		
Former smokers	60.0 %		
Non-smokers	30.0 %		
No data available	3.3 %		
Concomitant therapy (% of patients)			
Drugs potentially ↑ rate of theophylline metabolism [1]	2.4 %		
Drugs potentially ↓ rate of theophylline metabolism [2]	32.3 %		

SD–standard deviation, BMI – body mass index, BSA – body surface area, LBW – lean body weight, COPD – chronic obstructive pulmonary disease
[1] *carbamazepine, rifampicin*
[2] *ciprofloxacin, amlodipine, verapamil, nifedipine, isoniazid, haloperidol, sertraline, bicalutamide, propafenone*

Table 2: Characteristics of theophylline serum level measurements (N = 127)

		SD
Average measured theophylline serum level (µmol/L)	53.1	29.5
Average dose (mg)	572	148
Theophylline serum level (N, %)		
Subtherapeutic concentration	83 (65 %)	
Therapeutic concentration	39 (31 %)	
Toxic concentration	5 (4 %)	
Route of administration (N, %)		
Oral	83 (65 %)	
Intravenous	12 (9 %)	
Oral + intravenous	13 (10 %)	
Via percutaneous endoscopic gastronomy tube	1 (< 1 %)	
No data available	18 (14 %)	

SD–standard deviation

Results

Data collection

Out of 431 theophylline serum level determinations made in year 2010, 127 were selected for further analysis. The flow chart of selection process is shown in Figure 1.

Patients were mostly male, at an average age of 72 years. 68 % of included patients had COPD and the majority of patients were former smokers (Table 1). Chronic heart failure was common comorbidity in our population (more than 40 % of patients). Complete demographic information was not available for every patient, but the scarcity of data was present in less than 15 % of cases.

The average measured theophylline concentration was 53.1 (standard deviation 29.5) µmol/L, which is below the defined therapeutic range (Table 2). Indeed, 65 % of measured concentrations were subtherapeutic.

Population PK analysis

Eighty theophylline determinations in 53 patients were included in the development of population pharmacokinetic model. Out of all covariates tested, LBW and presence of COPD statistically influenced theophylline clearance in the final PPK model (covariate model is described in Equation 6). They reduced the interindividual variability (IIV) of Cl and V_D, from 39 % to 31 % and from 71 % to 56 %, respectively. COPD was modeled as dichotomous variable (1 – no diagnosis of COPD, 0 – diagnosis of COPD). Both LBW and COPD increased the clearance of theophylline. No covariate was found to be a significant predictor of volume of distribution.

The goodness-of-fit-plots for the final PPK model are presented in Figure 2. Generally, there was good agreement between the observed and population model-predicted concentrations, as well as between the observed and individual model-predicted concentrations. By the ranges of scattered dots and the trends of regression lines it can be seen that the inclusion of covariates si-

$$Cl = TVCl \cdot (1 + k_1 \cdot (LBW - 53.36\ kg)) \cdot k_2^{COPD}$$

Equation 6

Cl – clearance, TVCl – typical value of clearance (clearance for a typical patient with LBW 53.36 kg and COPD diagnosis, LBW – lean body weight, COPD – chronic obstructive pulmonary disease, k_1 – covariate constant for LBW, k_2 – covariate constant for COPD)

Table 3: Estimated pharmacokinetic parameters

Parameter	Estimated value	IIV(%)
TVCl (L/h)	1.66	31
V_D (L)	16.8	56
K_e (h^{-1})	0.0988	
$t_{1/2}$ (h)	7.0	
F (%)	68.6	
k_1 (kg^{-1})	0.0187	
k_2 (-)	0.628	
Residual variability		
Wa (µg/mL)	1.48	
Wp (%)	0.183	

IIV – interindividual variability, TVCL – typical value of clearance, V_d – distribution volume, F – extent of absorption, Wa – additive residual variability, Wp – proportional residual variability, CV – coefficient of variation

gnificantly improves the accuracy of model prediction.

Evaluation of TDM service

Out of 127 theophylline serum levels measured, 107 cases (84.3 %) were assessed as having an appropriate indication, while 20 (15.7 %) had no appropriate indication (Table 4). In 70 out of 127 (55.1 %) cases, measurement of theophylline levels was performed after steady state concentration was achieved, while 57 (44.9 %) measurements were done before steady state conditions.

The evaluation of theophylline dosing

Actions undertaken by the corresponding physician, after he received the laboratory report on the measured theophylline concentration, were evaluated in 120 out of 127 theophylline measurements. One patient died soon after theophylline level measurement, and for 6 patients there were not

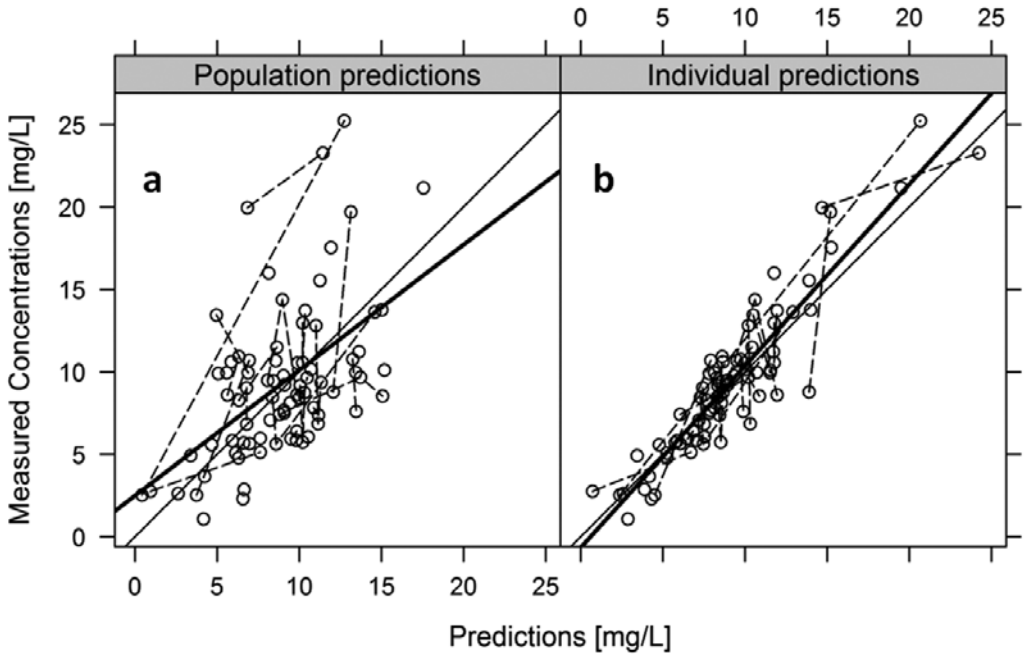

Figure 2: The goodness of fit plots for the final PPK model: *a) Scatter plot of population model-predicted concentrations without included covariates versus observed concentrations. b) Scatter plot of individual model-predicted concentrations with included covariates versus observed concentrations. Concentrations from the same patient are bound together with dashed line, identity (x = y) is shown by a full line and linear regression line is represented by a bold full line.*

Table 4: Indications for measurement of theophylline concentration

	Frequency, N (%)
Appropriate indication	
Initiation or restart of theophylline therapy	18 (14.2)
Change of theophylline dosage regimen[1]	25 (19.7)
Initiation or discontinuation of a drug that interacts with theophylline levels	6 (4.7)
Admission to hospital[2]	39 (30.7)
First theophylline level determination during hospitalization	19 (15.0)
Inappropriate indication	20 (15.7)

[1] *except after stopping theophylline*
[2] *before receiving the first dose of theophylline in the hospital*

sufficient data about theophylline dosage regimen after its measurement. The actions were considered appropriate only in 38 (31.7 %) out of 120 actions (Table 5). Most common inappropriate action was no dose adjustment in patients with subtherapeutic theophylline concentrations (49 % of cases).

Since the evaluation with PK model requires more data on the theophylline dosing regimen before and after each blood sampling, we were only able to implement this method in 41 level determinations that were performed in steady state and provided sufficient data on dosing regimen. Actual daily dose was significantly lower than calculated optimal daily dose (572 mg vs. 876 mg, $p < 0.001$) (Table 6).

The evaluation of time within the therapeutic range

The optimal dosing regimen, provided with the use of PPK model, would enable the patients to remain within the therapeutic range for a significantly longer period of time. The percentage of time theophylline concentration remains within the therapeutic range 72 hours after measurement would increase from 36.6 % to 92.6 % if optimal dosing were used ($p < 0.001$) (Table 6).

Discussion

In this study, the current status of theophylline TDM service in our tertiary clinic was reviewed. The service was most often applied in elderly population of former smokers with COPD, which is the target population for theophylline use. The indications for theophylline measurement were found appropriate in a majority of cases, although our assessment was done retrospectively. However, we did not examine the underuse of theophylline TDM, which could in some cases be helpful in speeding up optimal dosing.

When evaluating the time of sampling, we found that near half of the cases measured theophylline concentration before the steady state was achieved. The interpretation of such results without PPK model can be misleading and potentially dange-

Table 5: Physician's action after receiving the laboratory report of theophylline concentration (N = 120)

	Dose increase	No dose adjustment	Dose decrease or theophylline discontinuation
Subtherapeutic concentration	**13***	59	8
Therapeutic concentration	4	**21**	11
Toxic concentration	0	0	**4**

**Bolded numbers represent the actions that are considered appropriate.*

Table 6: Average optimal and actual theophylline doses and percentage of time theophylline concentration was within the therapeutic range (N = 41)

	Optimal	Actual	Difference	p-value
Theophylline dose in mg (SD)	876 (207)	572 (148)	304 (168)	< 0.001
% of time within the therapeutic range (SD)	92.6 (5.5)	36.6 (44.2)	56.0 (41.0)	< 0.001

SD–standard deviation

rous. Moreover, in 68 % of cases, physician did not make the correct theophylline dose adjustment, which poses a question of the reasonability of theophylline measurement. Most outstanding is probably the fact that out of 80 patients whose serum theophylline levels were subtherapeutic, only 13 were switched to increased doses. On the other hand, all 4 patients with toxic theophylline levels were immediately switched to lower doses or were discontinued. It has to be stressed, however, that because of the retrospective study design we were not able to consider all the factors that contributed to physicians' decisions about dose adjustments.

In the final PPK model, the observed clearance and distribution volumes were lower than literature data, although the comparison among different studies is hindered by heterogeneous study populations.[49-52] However, the calculated half-life (7 hours) is comparable to the findings of the previous studies (6.7 h,[53] 7.1 h[54] and 9.2 h[48]). From all measured and calculated covariates, only LBW and COPD were identified as significant covariates influencing theophylline clearance. According to our pharmacokinetic model, theophylline clearance increases with the increase in LBW and is higher in patients with COPD. The impact of COPD in our model is not in line with our expectations and could be due to the fact that we run a small study population and that non-appropriate coding of COPD diagnosis could be present. In the study of Tanigawara et al., they found theophylline clearance to be increased in smokers (+ 12 %), decreased in elderly patients (> 65 years) (- 13 %), and reduced in the presence of COPD (- 35 %).[49] In our model, the effect of age on theophylline pharmacokinetics was not observed since our population included only elderly patients at an age from 55 to 88 years.

The comparison of actual daily doses with calculated optimal daily doses using final PPK model revealed that the patients should receive on average 300 mg higher daily doses. The recommended daily dose of Teotard® is between 400 and 700 mg. Our patients received on average 572 mg daily, which is in line with the recommendation, but the calculated average optimal daily dose was much higher (876 mg). Clearly, patients do not reach the desired therapeutic concentrations with the recommended daily doses. The same was observed in study of McKay et al., where 1200 mg daily dose was needed in order to achieve a mean concentration of 18 mg/L in COPD patients.[55] Malabsorption of theophylline could be the cause since our population consisted of elderly COPD patients. Indeed, the absorption fraction we estimated with final PPK model was only 70 % while in the Summary of Product Characteristics for Teotard® the complete absorption is stated. However, in some studies absorption fractions for theophylline in healthy volunteers were comparable to our results and thus argue the proposed mechanism.[56,57]

In 65 % of the values measured, theophylline concentration was below therapeutic range and in a majority of these cases the physicians did not increase the dose of theophylline. Since the final PPK model suggested much higher doses, exceeding the general recommendations, it is understandable why the physicians decided not to increase the dose. Since it has recently been suggested that anti-inflammatory actions of theophylline are exerted at concentrations lower than 55 µmol/L, this could also affect the clinical decision.[31,32] Regarding this, it would probably seem reasonable to

evaluate the theophylline dosing with respect to the wider therapeutic range (28 µmol/L–110 µmol/L). In this case, the therapeutic window is so wide that the majority of our patients are expected to be within the therapeutic range even without any dose adjustments. This would put the usefulness of theophylline monitoring under question and may lead to justification of monitoring only in cases where theophylline toxicity is suspected.

We have also shown that the percentage of time when theophylline concentration lies within therapeutic range can be significantly increased from 36.6 % to 92.6 % by using PPK model for dose optimization. With the use of PPK model in TDM process, dosage regimen could be individualized in order to reach desired serum concentrations and eventually improving the efficacy and reducing the toxicity of theophylline. Moreover, the use of PPK models has the additional advantage of utilization and interpretation of measurements done at inappropriate sampling times.

Conclusion

Our study identified the need for theophylline TDM optimization in our clinical setting. Theophylline level measurements are sometimes requested without an appropriate indication, almost half of blood samplings are done at incorrect time points and most of the results are left without appropriate dose adjustment, especially in patients with theophylline concentrations below the therapeutic range. With the use of PPK model, we were able to predict optimal individual doses and to significantly increase the time when theophylline concentration was within the therapeutic range. In order to improve the safety and efficacy of theophylline treatment and to reduce unnecessary costs caused by inappropriate sampling times and lack of appropriate dose adjustments, higher involvement of clinical laboratory professionals and clinical pharmacists in TDM service is warranted. Moreover, the interpretation of laboratory results with PPK model would furthermore improve the accuracy of theophylline dosing.

References

1. Touw D, Neef C, Thomson A, Vinks A. Cost-effectiveness of therapeutic drug monitoring: a systematic review. Ther Drug Monit 2005; (27): 10–7.
2. Jaquenoud Sirot E, van der Velden J, Rentsch K, Eap C, Bauman P. Therapeutic drug monitoring and pharmacogenetic test as tool in pharmcovigilance. Drug Saf 2006; 29(9): 735–68.
3. Jellife R. Some comments and suggestions concerning population pharmacokinetic modeling, especially of digoxin, and its relation to clinical therapy. Ther Drug Monit 2012; 34(4): 368–77.
4. El Deskoy E, Meinshausen J, Buhl K, Engel G, Harings-Kaim A, Drewelow B, et al. Generation of pharmacokinetic data during routine therapeutic drug monitoring: Bayesian approach vs. pharmacokinetic studies. Ther Drug Monit 1993; 15(4): 281–8.
5. Kang J, Lee M. Overview of therapeutic drug monitoring. Korean J Intern Med 2009; 24(1): 1–10.
6. Gross A. Best practice in therapeutic drug monitoring. Br J Clin Pharmacol 2001; 52: 5–10.
7. Halloworth M, Watson I. Therapeutic drug monitoring and laboratory medicine; 2008.
8. Touv D, Neef C, Thomson A, Vinks A. Cost-effectiveness of therapeutic drug monitoring: an update. Ther Drug Monit 2005; 27(1): 10–7.
9. Antoniou T, Gomes T, Mamdani MM, Juurlink DN. Ciprofloxacin-induced theophylline toxicity: a population-based study. Eur J Clin Pharmacol 2011; 67: 521–6.
10. Kroon LA. Drug interactions with smoking. Am J Health Syst Pharm 2007; 64(18): 1917–21.
11. Powell JR, Vozeh S, Hopewell P, Costello J, Sheiner LB, Riegelman S. Theophylline disposition in acutely ill hospitalized patients. The effect of smoking, heart failure, severe airway obstruction, and pneumonia. Am Rev Respir Dis 1978; 118(2): 229–38.
12. Rieder MJ, Spino M. The theophylline-erythromycin interaction. J Asthma 1988; 25(4): 195–204.
13. Van den Brekel AM, Harrington L. Toxic effects of theophylline caused by fluvoxamine. CMAJ 1994; 151(9): 1289–90.
14. Sperber AD. Toxic interaction between fluvoxamine and sustained release theophylline in an 11-year-old boy. Drug Saf 1991; 6(6): 460–2.
15. Miners JO, Wing LM, Lillywhite KJ, Robson RA. Selectivity and dose-dependency of the inhibitory effect of propranolol on theophylline metabolism in man. Br J Clin Pharmacol 1985; 20(3): 219–23.
16. Schneider D, Gannon R, Sweeney K, Shore E. Theophylline and antiparasitic drug interactions. A case report and study of the influence of thiabendazole and mebendazole on theophylline pharmacokinetics in adults. Chest 1990; 97(1): 84–7.
17. Colli A, Buccino G, Cocciolo M, Parravicini R, Elli GM, Scaltrini G. Ticlopidine-theophylline interaction. Clin Pharmacol Ther 1987; (200): 358–62.

18. Stringer KA, Mallet J, Clarke M, Lindenfeld JA. The effect of three different oral doses of verapamil on the disposition of theophylline. Eur J Clin Pharmacol 1992, 43(1): 35–8.
19. Nielsen-Kudsk JE, Buhl JS, Johannessen AC. Verapamil-induced inhibition of theophylline elimination in healthy humans. J Pharmacol Toxicol 1990; 66(2): 101–3.
20. Adebayo GI. Interaction between phenytoin and theophylline in healthy volunteers. Clin Exp Pharmacol Physiol 1988; 15(11): 883–7.
21. Sklar SJ, Wagner JC. Enhanced theophylline clearance secondary to phenytoin therapy. Drug Intell Clin Pharm 1985; 19(1): 34–6.
22. Miller M, Cosgriff J, Kwong T, Morken DA. Influence of phenytoin on theophylline clearance. Clin Pharmacol Ther 1984; 35(5): 666–9.
23. Saccar CL, Danish M, Ragni MC, Rocci ML, Greene J, Yaffe SJ, Mansmann HC. The effect of phenobarbital on theophylline disposition in children with astma. J Allergy Clin Immunol 1985; 75(6): 716–9.
24. Landay RA, Gonzalez MA, Taylor JC. Effect of phenobarbital on theophylline disposition. J Allergy Clin Immunol 1978; 62(1): 27–9.
25. Rosenberry KR, Defusco CJ, Mansmann HC, McGeady SJ. Reduced theophylline half-life induced by carbamazepine therapy. J Pediatr 1983, 102(3): 472–4.
26. Boyce EG, Dukes GE, Rollins DE, Sudds TW. The effect of rifampin on theophyllinekinetics. J Clin Pharmacol 1986; 26(8): 696–9.
27. Gillum JG, Sesler JM, Bruzzese VL, Israel DS, Polk RE. Induction of theophylline clearance by rifampin and rifabutin in healthy male volunteers. Antimicrob Agents Chemother 1996; 40(8): 1866–9.
28. Straughn AB, Henderson RP, Lieberman PL, Self TH. Effect of rifampin on theophylline disposition. Ther Drug Monit 1984; 6(2): 153–6.
29. Global initiative for chronic obstructive pulmonary disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. December 2011. Dosegljivo 1.12.2012 s spletne strani: www.goldcopd.com
30. Method Sheet Theo 2, Roche Diagnostics.
31. Cosio B, Iglesias A, Rios A, Noguera A, Sala E, Ho K, et al. Low-dose theophylline enhances the anti--inflammatory effects of steroids during exacerbations of COPD. Thorax 2009; 64(5): 424–9.
32. Ford P, Durham A, Russel R, Gordon F, Adcock I, Barnes P. Treatment effects of low-dose theophylline combined with an inhaled corticosteroid in COPD. Chest 2010; 137(6): 1338–44.
33. Culpitt S, de Matos C, Russel R, Donnelly L, Rogers D, Barnes P. Effects of theophylline on induced sputum inflammatory indices and neutrophil chemotaxis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002; 165: 1371–6.
34. Johnston I. Difficult drugs to use, few clinical indications. Br Med J. 1990; 300.
35. Affolter N, Krähenbühl S, Schlienger R. Appropriateness of serum level determinations of antiepileptic drugs. Swiss Med Wkly 2003; 133: 591–7.
36. Mordasini M, Krähenbühl S, Schlienger R. Appropriatness of digoxin level monitoring. Swiss Med Wkly 2002; 132: 506–12.
37. Ratanajamit C, Soorpan S, Doang-ngern T, Waenwaisart W, Suwanchavalit L, Suwansiri S, et al. Appropriateness of therapeutic drug monitoring for lithium. J Med Assoc Thai 2006; 89(11): 1954–60.
38. Sharma S, Joshi S, Mukherji S, Bala K, Tripathi C. Therapeutic drug monitoring: appropriateness and clinical utility in neuropsychiatry practice. Am J Ther 2009; 16(1): 11–6.
39. Irshaid Y, Hamdi A, Al Homrany M. Evaluation of therapeutic drug monitoring of antiepileptic drugs. Int J Clin Pharmacol Ther 2003; 41(3): 126–31.
40. Babaei A, Eslamai M. Evaluation of therapeutic drug level monitoring of phenobarbital, phenytoin and carbamazepine in Iranian epileptic patients. Int J Clin Pharmacol Ther 2007; 45(2): 121–5.
41. Urbaniak G, Plous S. Research Randomizer (version 3.0), Computer software. 2011. Dosegljivo 23.3.2012 s spletne strani: www.randomizer.org
42. Beal S, Sheiner LB, Boechmann A, Bauer RJ. NONMEM User's Guides. Icon Development Solutions. Ellicott City, MD; 2011.
43. Mušič E, Paulin A, Šuškovič S. Clinical study of Theotard capsules. 1986.
44. Jonsson E, Karlsson M. Automated covariate model building with NONMEM. Pharm Res 1998; 15: 1463–8.
45. Hallynck T, Soep H, Thomis JA, Boelaert J, Daneels R, Dettli L. Should clearance be normalised to body surface or to lean body mass? Clin Pharmacol 1981; 11: 523–6.
46. James W. Research on obesity. London; 1976.
47. Mosteller R. Simplified calculation of body surface area. N Engl J Med 1987; 317(17): 1098.
48. Trepanier E, Nafziger A, Amsden G. Effect of terbinafine on theophylline pharmacokinetics in healthy volunteers. Antimicrob Agents Chemother 1998; 42(3): 695–7.
49. Tanigawara Y, Komada F, Shimizu T, Iwakawa S, Iwai T, Maekawa H, et al. Population pharmacokinetics of theophylline. III. Premarketing study for a once-daily administered preparation. Biol Pharm Bull 1995; 18(11): 1590–8.
50. Yano I, Tanigawara Y, Yasuhara M, Okumura K, Kawakatsu K, Hori R. Population pharmacokinetics of theophylline. II: Intravenous infusion to patients with stable chronic airway obstruction. Biol Pharm Bull 1993; 16(5): 501–5.
51. Antal E, Kramer P, Merick S, Chapron D, Lawson I. Theophylline pharmacokinetics in advanced age. Br J Clin Pharmacol 1981; 12(5): 637–45.
52. Steinijans V, Eicke R, Ahrens J. Pharmacokinetics of theophylline in patients following short-term intravenous infusion. Eur J Clin Pharmacol 1982; 22(5): 417–22.
53. Qiu F, Wang G, Zhao Y, Sun H, Mao G, Sun J. Effect of danshen extract on pharmacokinetics of theophylline in healthy volunteers. Br J Clin Pharmacol 2008; 65(2): 270–4.
54. Kinzig-Schippers M, Fuhr U, Cesana M, Müller C, Staib A, Rietbrock S, et al. Absence of effect of rufloxacin on theophylline pharacokinetics in steady state. Antimicrob Agents Chemother 1998; 42(9): 2359–64.
55. McKay S, Howie C, Thomson A, Whiting B, Addis G. Value of theophylline treatment in patients

handicapped by chronic obstructive pulmonary disease. Thorax 1993; 48: 227–32.
56. Milavetz G, Vaughan L, Weinberger M, Harris J, Mullenix T. Relationship between rate and extent of absorption of oral theophylline from Uniphyl brand of slow-release theophylline and resulting serum concentrations during multiple dosing. J Allergy Clin Immunol 1987; 80(5): 723–9.
57. Lagas M, Jonkman J. Influence of food on the rate and extent of absorption of theophylline after single dose oral administration of a controlled release tablet. Int J Clin Pharmacol Ther Toxicol 1985; 23(8): 424–6.