Can clinically useful POPULATION PK MODELS FOR CARBAMAZEPINE IN PEDRIATIC EPILEPSY PATIENTS be developed based on routine therapeutic drug monitoring (TDM) data?

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INTRODUCTION

Carbamazepine (CBZ) is an effective anticonvulsive drug for partial and generalized seizures in both adults and children (1). CBZ has a narrow margin between the minimal effective concentration in most patients, and the concentration causing toxicity. This makes it important to find the right dosage regimen for each patient.

Clinical software has been developed to interpret laboratory results based on a pharmacokinetic (PK) model. These programs permit the use of therapeutic drug monitoring (TDM) data for the calculation of individual PK parameters and dosing regimens by Bayesian adaptive control strategies. For most routinely monitored drugs only sparse TDM data are available. A prerequisite for a good structural PK model is informative data. This analysis explores the utility of sparse carbamazepine TDM data (1 sample/patient) for the development of clinically useful pediatric population PK models.

CBZ pharmacokinetics is well described by a one compartment model with first order elimination. The problem with using a sparse dataset with this model, is the lack of information about elimination rate. This results in a high correlation between volume of distribution (V_d) and the elimination rate constant (k_{el}), so that clearance ($CL = k_{el} * V_d$) can not be estimated independently from V_d.

MATERIALS AND METHODS

Patient and TDM data were identified from our neurology outpatient clinic database. 556 entries with one or more serum concentration measurements were found. Each entry contained information on patient demographics, date of birth, gender, ethnicity, drug used and concomitant medication, dosing regimen, time and amount of last dose and a laboratory result from a plasma sample collected at a stated time. AXSYM Immunoassay (Abbott Laboratories) was used to analyze the samples as part of routine monitoring of the patients. The assay error pattern was calculated as SD = 0.0073 + 0.037x 0.002x^2. Exclusion criteria were: combination therapy with other anticonvulsants, concomitant medication known to interact with CBZ, CBZ therapy of shorter duration than one month, suspected non-compliance and missing or conflicting information in the database *vs.* medical chart. Data were analyzed with an iterative 2-stage Bayesian (IT2B) and nonparametric adaptive grid algorithm (NPAG)*. A model with zero order input was chosen to mimic the release of drug from the sustained release formulations used (Fig. 1). Duration of input were set equal to the individual dosing intervals. The apparent bioavailability (F) was fixed to 1.00. Boundaries for the initial parameter estimates were based on parameter values found in the literature (2). A model with low correlation between the estimated parameters was sought. The models were compared by log likelihood, ME (mean error) as a measure of bias and RMSE (root mean squared error) as a measure of precision.

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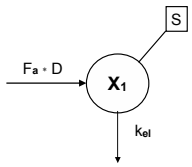

D: Dose = Zero order input rate * τ

S: Sample = X_1 / V_d

$V_d = V_I + V_{s1} * BW$

$k_{el} = k_I - k_{s1} * age$

Fig. 1
The final model used for the population. Rate into the central compartment (1) is equal to the bioavailable dose $F_a * D$ per dose interval τ. S is the concentration in the central compartment. The concentration is equal to mass in central compartment X_1 per volume of distribution V_d. F_a is the bioavailable fraction of the dose. k_{el} is the elimination rate constant , k_{s1} is given in $h^{-1} * yr^{-1}$, $k_I = 0.173\ h^{-1}$. V_d is the apparent volume of distribution (L), $V_I = 11.5$ L, V_{s1} is given in L/kg. BW = body weight.

RESULTS

57 carbamazepine monotherapy patient data sets (36 male, 21 female) were identified from the database and used in the analysis. Demographic data are shown in Table 1. Preliminary models estimating CL or k_{el} gave good prediction, but had high correlations between CL and V_d or between k_{el} and V_d. To address this problem, different covariate models were tested. The final model is described in Figure 1. The elimination rate constant (k_{el}) and apparent volume of distribution per kilo body weight (V_d/kg) were chosen as the estimated parameters. Age was set as a negative covariate for K_{el}. The k_{el} intercept was set to 0.173 h^{-1} (giving a minimum elimination half life, $t_{1/2}$ = 2 h) and the V_d intercept was set to 11.5 L to mimic the smallest patient. The results from the final model are shown in Tables 2a-b. The individual Bayesian posterior values (based on individual parameter estimates) gave better predictions than prior values (based on population mean estimates). The final model had good prediction (R^2 = 0.98) with little bias (ME = -0.107) and good precision (RMSE = 0.343).

Table 1 **Demographic data**

	Mean	± SD	Median	Range
Age at draw	9.1	± 4.4 years	9	2 - 21
Weight	40.2	± 21. 6 kg	37.3	11.5 - 93.3
Height	135	± 25 cm	137.6	86.4 -177
Daily dose (DD)	552	± 271 mg	600	180 -1400
DD/kg	14.7	± 4.7 mg/kg	14.7	6.4 - 32.1
Doses pr day	2.22	± 0.42	2	2 - 3
Time between dose and draw	9h 32min	± 4h 29min	10h 25min	2h 15min -18h 45min
Formulation:				
Syrup	8 patients			
Immediate release tablets (incl. chewable tablets)	11 patients			
Sustained release tablets or capsules*	38 patients			

*Tegretol CR or Carbatrol

Table 2a **Correlation between predicted versus observed concentrations**

	Individual predicted concentrations						
	Prior (based on population mean estimates)			Posterior (based on individual parameter estimates)			
	R^2	ME	RMSE	R^2	ME	RMSE	Object function
IT2B	0.2718	-0.03263	3.0237	0.9525	-0.08738	0.5092	-192.12
NPAG	0.2679	-0.2780	3.1395	0.9798	-0.1073	0.3430	-113.38

Table 2b **Parameter estimates**

	Ks ($h^{-1}*yr^{-1}$)		Vs (L/kg)		Kel (h^{-1})		t ½ (h)	
	IT2B	NPAG	IT2B	NPAG	IT2B	NPAG	IT2B	NPAG
Mean	0.0030	0.00479	0.3426	0.4783	0.1472	0.1367	4.7791	5.9154
Median	0.0029	0.00263	0.3075	0.2380	0.1478	0.1479	4.6901	4.6856
SD	0.0025	0.00597	0.2973	0.5179	0.0772	0.0378	0.6176	3.3569

	Vd/F (L)		Vd/F*kg (L/kg)		CL/kg*F (L/h/kg)		CL/F (L/h)	
	IT2B	NPAG	IT2B	NPAG	IT2B	NPAG	IT2B	NPAG
Mean	25.4350	31.5846	0.7260	0.8616	0.1090	0.1088	3.7463	3.7580
Median	21.7502	21.4646	0.6467	0.7263	0.0959	0.0904	3.0095	3.1041
SD	12.1247	24.7972	0.3534	0.5430	0.0576	0.0654	1.9286	2.0566

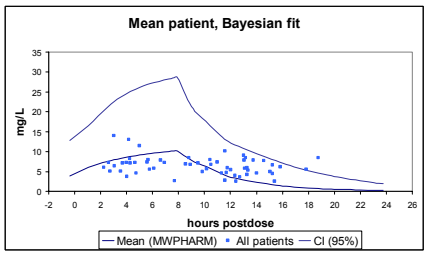

Fig. 2
The observed data correspond well with the mean patient predicted plasma concentration versus time curve (MWPHARM*). The individual concentration for the 57 patients vs. time after draw lie within the 95 % confidence interval except for two patients.

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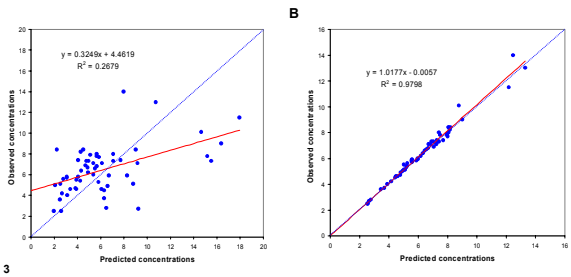

Fig. 3
NPAG plot of predicted *vs.* observed carbamazepine concentrations based on A) population means (prior fit) and on B) individually fitted dose intervals (posterior fit). The regression for the posterior fit is almost superimposing the line of identity.

DISCUSSION AND CONCLUSIONS

Little information has been obtained on carbamazepine absorption characteristic in children during steady-state monotherapy. Unfortunately, TDM data are mostly trough data that do not give any information on absorption. In our dataset we had one sample per patient, obtained over a 2 to 19 h post dose period. By linking the two estimated parameters k_{el} and V with relevant covariates, it was possible to minimize correlation between the parameters. Due to the sparse sampling, it was necessary to use strict boundaries for the estimated parameters to achieve physiological relevant results. The data did provide some useful information on carbamazepine elimination and volume of distribution in our pediatric population. To describe bioavailability and the absorption of carbamazepine, and to be able to develop a full PPK model, more intense sampling will be necessary.

There is little information on absorption and bioavailability of the frequently used sustained release preparations. A few studies investigating relative bioavailability compared to syrup formulations suggest reduced bioavailability of the sustained release formulations (3,4). The use of these formulations reduces fluctuations in plasma concentrations during a typical dosing interval. This will be of clinical benefit, but for a drug with slow elimination as CBZ, prolonged absorption will result in even less information about elimination rate in a sparse data set like the one used in this study. The 57 patients in the study population were retrospectively collected from a large clinical database. Errors and missing values were found in many of the excluded patient files in the database. Correct collecting of data is crucial especially when the data are going to be used to develop population PK (PPK) models.

With a change in sampling strategies in epilepsy clinics more informative data can be obtained for PPK modelling. Subsequently, once a good PPK model has been developed, sparse sampling could be implemented with PPK model-based interpretation as part of routine monitoring (5).

Conclusion:

Routinely collected TDM data can be used for PPK modelling of carbamazepine in children with epilepsy. However, it will be necessary to combine such data with additional rich data. This will allow for the development of more informative and clinically useful PPK models that can then be used as part of Bayesian dose individualization strategies.

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