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Predictions of Carbamazepine Concentrations Using a Bayesian Program (PKS System, Abbott): A Retrospective Evaluation in an Outpatient Population

J. M. GAULIER*†, R. BOULIEU*†, C. FISCHER‡ AND F. MAUGUIERE‡

*Laboratoire de Pharmacie Clinique, Université Claude Bernard Lyon 1, Institut des Sciences Pharmaceutiques et Biologiques, Lyon; †Service Pharmaceutique, Hôpital Neuro-Cardiologique, Lyon; and ‡Laboratoire d'Electroencéphalographie, Hôpital Neuro-Cardiologique, Lyon, France

Abstract

This work evaluates the performance of a Bayesian program (PKS System, Abbott) for predicting carbamazepine concentrations in an outpatient population. The retrospective study involved 20 epileptic patients (12 adults and 8 children) receiving carbamazepine monotherapy orally. The program was used to predict measured serum levels after feedback of 0, 1 or 2 steady-state concentrations.

A significant negative prediction bias was observed when no feedback concentration was used for estimation. However, the prediction bias (mean prediction error; m.e.) decreased as soon as one feedback concentration was used for estimation. Precision (mean absolute prediction error; m.a.e.) was significantly improved with one feedback concentration and was even better with two concentrations. Likewise, r.m.s.e. (root mean squared error; composite of bias and precision) regularly decreased when the number of feedback concentrations used was increased. Eleven percent of the estimates were unacceptable clinically (prediction error > 2 mg L^{-1}) when 1 feedback concentration was used; less than 3% were unacceptable when two concentrations were used.

Thus the performance of the Bayesian dosing program is acceptable when two feedback concentrations are known, and seems able to help the clinician adjust carbamazepine dosage in an outpatient population.

Carbamazepine is an anticonvulsant drug widely used for the prophylaxis of generalized tonic-clonic and partial seizures. However, dosage adjustment is difficult in clinical practice because of enzymatic induction and inter- and intra-individual pharmacokinetic variability. Furthermore, the problem of compliance represents a major drawback in an outpatient population. In this situation the Bayesian method (Mallet & Trouvin 1990; Thomson & Whiting 1992) can significantly help the clinician's judgement. Bayesian techniques (Garcia et al 1988; Botha et al 1990; Bouvet et al 1992; Ertas et al 1994; El Battah et al 1995) have previously been used for adjustment of carbamazepine dosage but few studies (Ertas et al 1994) have been performed on outpatients.

Thus, we have evaluated the performance of a Bayesian pharmacokinetic dosing program (PKS System) in an outpatient population, considering the predictive performance and the potential practical benefits for clinicians.

Materials and Methods

Patients

The study involved 20 outpatients (12 adults and 8 children (age > 16 years)) attending consultations at a neurological hospital. We did not exclude paediatric patients because many authors (Bertilsson 1978; Morselli & Bossi 1982; Bertilsson & Thomson 1986) consider that the pharmacokinetic parameters of carbamazepine are similar for adults and children, and because no effect of age on carbamazepine concentration or dosage prediction performances has been observed.

To avoid bias arising from non-compliance in this retrospective study, three prerequisites were defined before the subjects were included: positive clinician judgement on a patient's compliance, stable carbamazepine serum levels (less than 20% of variation in concentration) at a constant daily dose and increase in carbamazepine serum levels when doses were increased.

Each patient received oral carbamazepine (tegretol) monotherapy. The dose ranged from 100 to 1000 mg day^{-1}. None had renal or hepatic disease. The therapeutic histories and the individual serum creatinine values required for the estimations were carefully collected according to the fundaments of the Bayesian approach. So, we have collected three to five steady-state carbamazepine serum concentrations for each patient with at least two previous measurable concentrations. These data provided a total of 74 concentrations. The principal characteristics of the patient population studied are summarized in Table 1.

Table 1. Principal characteristics of the population.

Number of patients	20 (12 males, 8 females)
Age (years)	24 ± 15*
Weight (kg)	57 ± 17*
Height (cm)	162 ± 18*
Number of observations used for prediction	74
Dose (mg day^{-1})	535 ± 213*
Serum concn (mg L^{-1})	6·8 ± 1·9*

*Mean ± s.d.

Correspondence: R. Boulieu, Université Claude Bernard Lyon 1, Laboratoire de Pharmacie Clinique, ISPB-Faculté de Pharmacie, 8 Avenue Rockefeller, 693 73 Lyon Cedex 08, France.

Drug assay

Carbamazepine serum concentrations were determined by fluorescence-polarization immunoassay (TDx system, Abbott Laboratories). This assay had a coefficient of variation below 10% with a sensitivity of 1 mg L^{-1}. These two values were implemented in the program. Indeed, the following function included in the program was used in the estimation process to calculate the standard deviation (σ_i) of the concentration:

$$\sigma_i(\text{mg L}^{-1}) = C \times CV_{assay} + S_{assay} \quad (1)$$

where C is the concentration (mg L^{-1}) and CV_{assay} and S_{assay} were, respectively, the coefficient of variation (0·1) and the sensitivity (1 mg L^{-1}) of the assay.

Method of prediction

The predictions were performed using a Bayesian regression analysis program (PKS System, Abbott) on a 486 Cyrix DX4/100CPU computer.

This program is able to fit serum level data (steady-state or non-steady-state concentrations) by non-linear least-squares regression analysis. A patient's pharmacokinetic parameters were estimated and an individual therapeutic schedule was then drawn up and proposed to the clinician.

No database concerning the pharmacokinetic parameters of carbamazepine was available in the program package. Three pharmacokinetic parameters are required to compute carbamazepine concentration predictions: volume of distribution (V), clearance (CL) and absorption constant (k_a). Data on V and k_a are scarce in the literature (Morselli & Bossi 1982; Bouvet et al 1992), so the values of the population pharmacokinetic parameters used are those of Bouvet et al (1992) and Morselli & Bossi (1982) according to the important inter-individual variability usually reported (Table 2).

In this work the Bayesian option of the PKS program was used to predict serum level of carbamazepine from one (estimation set 1CSS, n = 74), or two (estimation set 2CSS, n = 74) steady-state concentrations previously measured. Moreover, the 74 available steady-state concentrations were predicted without feedback using the initial parameters option of the program (estimation set 0CSS).

Statistical analysis

The estimated concentrations of carbamazepine were compared with the true serum concentration measured using the determination of prediction error (Pe), predicted concentration minus true concentration.

Predictive performances of the program were evaluated for each set of estimates by measurement of the prediction bias (mean prediction error: m.e.), the precision (mean absolute prediction error: m.a.e.) and a composite of bias and precision (root mean squared error: r.m.s.e.), calculated as follows (Sheiner & Beal 1981):

$$\text{m.e.} = (1/n)\sum_{i=n}^{n}(\text{Pe}) \quad (2)$$

$$\text{m.a.e.} = (1/n)\sum_{i=n}^{n}[\text{Pe}] \quad (3)$$

$$\text{r.m.s.e} = \sqrt{\{(1/n)\sum_{i=n}^{n}(\text{Pe})^2} \quad (4)$$

where n is the number of predictions.

The relative performance was evaluated by comparing confidence intervals. The significance probability level chosen was $P < 0{\cdot}05$. In addition, analysis of variance was performed on the prediction error obtained for each set (P: 0·05).

To assess the practical clinical performance of the program, we systematically pointed out the percentage of prediction errors higher than 2 mg L^{-1} which represented the proportion of rejected estimates (Garcia et al 1988). The observed prediction errors were classified in three groups: errors higher than 2 mg L^{-1} (unacceptable errors), errors between 1 and 2 mg L^{-1} (acceptable errors) and errors below 1 mg L^{-1} (low errors).

Results

Table 3 lists the predictive performance of the three estimation sets. There was significant negative bias when no feedback concentration was used to fit the predictions (m.e. −1·77 mg L^{-1} in set 0CSS). Values of m.e. decreased significantly as soon as one previous serum level datum was used to fit the

Table 2. Population pharmacokinetic parameters used for prediction of carbamazepine dose.

Parameter	Mean value	Coefficient of variation	Source
Volume of distribution (L kg^{-1})	1·15	40	Bouvet et al 1992
Clearance (L kg^{-1} h^{-1})	0·0805	69	Morselli & Bossi 1982
Absorption constant (h^{-1})	0·69	29	Bouvet et al 1992

Table 3. Predictive performance of the three sets of estimates.*

	Mean prediction error (95% confidence interval) (mg L^{-1})	Mean absolute prediction error (95% confidence interval) (mg L^{-1})	Root mean squared error (95% confidence interval) (mg L^{-1})
No feedback concentration	− 1·77 (− 2·10; 1·44)	1·97 (1·71; 2·24)	1·45 (0·90; 1·85)
One feedback concentration	0·08 (− 0·19; 0·35)	0·76 (0·56; 0·97)	1·18 (0·87; 1·42)
Two feedback concentrations	0·24 (0·02; 0·46)	0·66 (0·50; 0·83)	0·95 (0·68; 1·16)

*n = 74.

Table 4. Evolution of prediction errors over the three groups of estimates.

	Percentage of total estimates in the range		
	< 1 mg L^{-1}	1–2 mg L^{-1}	> 2 mg L^{-1}
No feedback concentration	30	55	45
One feedback concentration	71	18	11
Two feedback concentrations	90	7	3

estimates according to the 95% confidence intervals; m.e. remained low in set 2CSS.

The value of m.a.e. was high without feedback concentration. However, precision was significantly improved when one feedback concentration was used.

Likewise, r.m.s.e. decreased regularly from set 0CSS to set 2CSS. This parameter showed a clear, but not significant, improvement of bias and precision when the number of feedback concentrations used was increased. Furthermore, the results obtained by analysis of variance showed that Pe values were significantly different between set 0CSS and set 1CSS (F, 71·5; $P < 0{\cdot}0001$) and not significantly different between set 1CSS and set 2CSS (F, 0·82; P, 0·37).

In addition, no significant difference (Student's t-test) was observed in prediction errors between the two sub-populations: paediatric patients and adult patients. Values of m.e. and m.a.e. were, respectively, 0·26 and 0·82 for paediatric patients and 0·23 and 0·57 for adult patients with one and two feedback concentrations, respectively.

Table 4 shows the evolution of the three degrees of prediction error for the three estimation sets. From a clinical point of view, the percentage of unacceptable errors (> 2 mg L^{-1}) reached 45% of the total number of estimates when no feedback concentration was used for prediction and only 30% of the concentrations were predicted with an error of prediction < 1 mg L^{-1}. The percentage of errors > 2 mg L^{-1} was as high as 11% of the total in set 1CSS and decreased to 3% for set 2CSS.

Discussion

Without any previous individual concentration data, the method tends to under-predict with a serious lack of precision—45% of the estimates were unacceptable clinically. The use of one feedback concentration to fit the estimates significantly increased the precision of the method. However, even if the percentage of unacceptable prediction is reduced, the error remains unacceptable in clinical practice. With an additional feedback concentration, the precision became acceptable and the percentage of unacceptable errors became negligible.

This work shows that Bayesian prediction method could significantly help the clinician to adjust carbamazepine dosage. However, for safe use two feedback concentrations appear necessary. The need for two feedback concentrations to obtain minimum dosing errors is in agreement with the conclusions of previous studies using the Bayesian approach (Garcia et al 1988; Ertas et al 1994).

The predictive performances (m.e., m.a.e. and r.m.s.e.) observed are similar to those obtained in previous studies (Garcia et al 1988; Ertas et al 1994). We did not find any difference between predictive errors for paediatric and adult patients as reported previously (Bertilsson 1978; Morselli & Bossi 1982; Bouvet et al 1992). Further studies in a large paediatric population are required to confirm this preliminary result.

Thus, this study shows the acceptable performance of the Bayesian dosing program which seems to be appropriate for providing significant help to the clinician for carbamazepine monitoring in an outpatient population.

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