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A sequential Bayesian algorithm for dose individualisation of carboplatin

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Abstract Carboplatin is associated with significantly less nephrotoxicity and neurotoxicity than is cisplatin. The dose-limiting toxicity of carboplatin is myelotoxicity. A number of dosing methods have been described that allow a value for the area under the concentration-time curve to be targeted on the basis of the patient's renal function. Recently a formalised analysis of the pharmacodynamic response to carboplatin revealed a therapeutic window in which the response rate was maximal and toxicity, tolerable. Optimal therapy would result from targeting this window in the individual patient. The aim of this study was to develop a Bayesian dose-individualisation method for carboplatin. The method involved (1) development of a high-performance liquid chromatography (HPLC) method to measure serum concentrations of carboplatin; (2) a pharmacokinetic study in 12 women receiving carboplatin for ovarian cancer to estimate the population pharmacokinetic values for this group of patients; (3) development of population models to describe the concentration-time course of carboplatin in serum along with associated errors; and (4) development of an algorithm that uses a sequential Bayesian design, which enables estimation of future doses of carboplatin on the basis of feedback from serum concentrations. The results of each of the stages were (1) the coefficient of variation of the assay was 6.3% within day and 8.4% between days ($r^2 = 0.9993$), and the limit of detection was 0.25 mg/l; (2) Patients' ages ranged from 49 to 68 years, their weights varied from 46 to 85 kg, and their glomerular filtration rate ranged from 3.2 to 7.4 l/h. A geometric mean clearance (Cl) of 6.8 L/h and a steady-state volume of distribution (Vss) of 22 l were estimated, which are similar to previously published data; (3) and a two-compartment model best described the data. Two error models were developed, the first describing the error associated with the assay and the second, the error of the two-compartment model, i.e. error due to individual variation in pharmacokinetics and error due to model mis-specification. Finally, (4) the development of a sequential Bayesian dose-individualisation method for carboplatin is described. To our knowledge, this is the first sequential design that has been used for dose individualisation of chemotherapy. The program is specific for carboplatin and operates independently of commercially available Bayesian software. Doses predicted by this program are being tested prospectively against conventional dosing methods.

Key words Bayesian algorithm · Carboplatin · Pharmacokinetics · Markov Chain Monte Carlo technique

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Introduction

Carboplatin [*cis*-diammine(1,1-cyclobutanedicarboxylato)platinum] is a structural analogue of cisplatin. Carboplatin has an antitumor profile similar to that of cisplatin but has a lower incidence of emesis, nephrotoxicity, neurotoxicity and ototoxicity. The dose-limiting toxicity of carboplatin is myelotoxicity, with thrombocytopenia being more marked than leucopenia. Thrombocytopenia generally occurs with doses on the order of 400 mg/m^2, whereas hepatotoxicity, nephrotoxicity and ototoxicity are more commonly associated with doses in excess of 1,000 mg/m^2 [28].

Carboplatin is usually dosed every 4 weeks in the treatment of ovarian cancer, which results effectively in total elimination of the drug between doses.

A dose-response relationship has been suggested for myelotoxicity, and a number of researchers have attempted to quantify the relationship, with varying degrees of success. A dose-response relationship has also been suggested for efficacy in ovarian cancer [24], and failure to achieve an adequate area under the concentration-time curve (AUC) has been associated with failure to cure testicular cancer [15]. A therapeutic window of between 5 and 7 mg ml^{-1} min may exist for the use of carboplatin in the treatment of ovarian cancer. In a retrospective analysis involving 1,028 patients, in which carboplatin was the sole agent, the tumour response was found to be proportional to the AUC of carboplatin, although the relationship was non-linear [16]. The maximal response rate ($\approx 60\%$) reported by Jodrell et al. [16] was achieved with AUCs above 4–5 mg ml^{-1} min. Similarly, the 50% likelihood of grade III thrombocytopenia and neutropenia was also related to AUC values of 8 and 10 mg ml^{-1} min, respectively. Various authors have published guidelines describing the relationship between dose and AUC [5, 6], or dose and clinical response, in terms of thrombocyte nadir [3, 10, 11, 20, 27].

After intravenous administration, the platinum moiety of carboplatin may be isolated within either carboplatin itself, free platinum (diammine platinum II) or bound diammine platinum II (usually bound irreversibly to albumin and erythrocytes). Carboplatin and "free" platinum have very similar distribution and elimination kinetics, with an α-phase half-life ($t_{1/2}$) ranging from 0.5 to 1.5 h and a β-phase $t_{1/2}$ varying from 1.7 to 17 h, depending largely on renal function [28]. Data presented by Mulder et al. [19] and in a review by van der Vijgh [28] showed that the serum concentration-time profiles of free platinum and carboplatin were superimposable for the first 12–24 h. This suggests that free platinum in the serum is almost solely present as carboplatin for the majority of the concentration-time profile. Both are thought to be cleared almost entirely renally, with renal clearance approximating the glomerular filtration rate (GFR) [5, 10, 28]. A linear relationship has been reported between the dose of carboplatin and the AUC for both unchanged carboplatin and "free" platinum [20, 28].

Currently, no method of individualising carboplatin dosage in adults exists that allows incorporation of subsequently acquired data (serum drug concentrations or thrombocyte nadir) from the individual. Recently Peng et al. [21] reported on the use of Bayesian analysis of carboplatin data in children. Their method applies a standard maximum a posteriori estimation (MAP) Bayesian analysis using Adapt II software. Our study addressed the development of a sequential Bayesian dose-individualisation method for carboplatin by estimating population pharmacokinetic parameters, developing models to describe the concentration-time course and associated errors, and establishing equations that allow Bayesian estimation of posterior values of parameters. The algorithm developed does not use commercially available software and can in essence be applied to any drug, although the equations described in this article are specific for carboplatin. Equations are described from which the Bayesian estimates of the posterior distribution of the serum carboplatin concentrations can be calculated in closed form. Unlike the MAP algorithm, the design is sequential since the a priori model for any given patient changes to become more individualised for that patient as new data become available.

Patients and methods

Pharmacokinetic analysis

Patient characteristics

A pharmacokinetics study was performed on 12 patients who met the following eligibility criteria: receipt of carboplatin as a single agent; histologically confirmed ovarian carcinoma; an age of between 18 and 75 years, performance levels ranging between 0 and 2 (ECOG - Zubrod scale), i.e. ambulatory more than 50% of waking hours and capable of self-care; absence of other life-threatening conditions; adequate venous access; and written informed consent.

Pretreatment investigations

Investigations performed prior to the administration of carboplatin included a complete blood count, differential white cell count, full biochemical profile (including serum creatinine), and determination of the GFR using [^{99m}Tc]-diethylene-triaminepentaacetic acid (DTPA). DTPA was given intravenously, and four serial blood samples were taken for calculation of its clearance. The alternative, Cr-EDTA, is not available in our institution. DTPA clearance is described to correlate well with that of Cr-EDTA [12].

Method of drug delivery

Carboplatin was given according to the local hospital protocol. The dose was calculated using the formula of Calvert et al. [5], the aim being to achieve an AUC of 5–7 mg ml^{-1} min. The Calvert formula is given as:

$$\text{Dose (mg)} = \text{AUC desired} \times (\text{GFR} + 25), \quad (1)$$

where *GFR* is the glomerular filtration rate (in milliliters per minute) and 25 represents the non-renal elimination. Calvert et al. estimated the GFR from Cr-EDTA clearance. The dose was infused in 500 ml of 5% dextrose (D5W) over 30 min. The time of administration was standardised at between 11 a.m. and 2 p.m. Routine hydration (500 ml of D5W and 500 ml of 0.9% saline) was given if required over the following 12 h. Anti-emetic therapy was prescribed according to the local hospital guidelines.

Treatment investigations

A cannula was inserted in the arm opposite that into which the carboplatin was infused. Blood samples were drawn immediately

prior to the infusion and at 10 min as well as 1, 3, 6, 12 and 24 h after completion of the infusion. If the patient's GFR was less than 60 ml/min, then an additional blood sample was drawn at 48 h. The exact time of sampling was recorded in each case. The samples were immediately centrifuged at 3,000 rpm for 10 min, and the plasma was frozen at $-80\,^{\circ}C$ until assayed.

Assay

Since the flameless atomic absorption spectrophotometry method for measuring unbound platinum is not available at our institution, a high-performance liquid chromatography (HPLC) method was used to measure carboplatin. The carboplatin sample was thawed and ultrafiltered using Centriflo 25k ultrafilters. The samples were cooled to $10\,^{\circ}C$ in the autosampler. An HPLC assay was set up similarly to that described by De Waal et al. [9]. Three columns were set up in series: C18 100-mm × 4.6-mm Brownlie ODSMP RP18 5μ, C18 150-mm × 4.6-mm ICI ODS2RP18 5μ and C8 250-mm × 4.6-mm Lichrosorb RP8 10μ. An aqueous mobile phase was used, buffered to pH 3 with potassium dihydrogen phosphate (0.1 *M*) and 0.1 *M* phosphoric acid, and 1 m*M* dipotassium ethylene- diaminetetraacetic acid (EDTA) was added as a pairing ion. First, 50% acetonitrile was run for between 8 and 15 min. The mobile phase was run at 1.5 ml/min. The injection volume of ultrafiltrate was 80 μl. The retention time of carboplatin was ≈ 7.5 min and the run time, 30 min. A standard curve was constructed at between 2.5 and 50 mg/l, with $r^2 = 0.9993$. The intra-day and inter-day coefficient of variation of the standard curve was 6.3% and 8.4%, respectively. The limit of detection was 0.25 mg/l.

Development of the models

A priori *model*

The analysis was undertaken using a three-stage process similar to that previously described by Maitre et al. [18]:

1. A one-, two- or three-compartment model was fitted as appropriate to the data by a non-linear weighted least-squares method using TOPFIT. Starting values for the pharmacokinetic parameters were thus estimated. The appropriateness of the fit and model used was determined by the least-squares objective function, the Akaike information criterion (AIC), analysis of the residuals, and assessment of covariance between parameters.
2. A covariate analysis involving simple linear regression was used to assess which, if any, covariate correlated significantly with the value of a parameter. Covariates assessed included height, weight, lean body weight, body surface area, serum creatinine, estimated creatinine clearance using the original method of Cockcroft and Gault [7] and an adjusted method (see Table 1), DTPA clearance, age, and carboplatin course. It was decided to use a cut-off value for serum creatinine in the adjusted method where any value lower than a specified value (in this case 60 μ*M*) was set at that value. This was undertaken since very low values of serum creatinine are not necessarily indicative of very high clearances but are more likely due to reduced production. The cut-off value of 60 μ*M* was chosen as it represents a value at the lower end of the normal range given by Canterbury Health Laboratories (Ltd). This value has been tested prospectively in an analysis of gentamicin pharmacokinetics and has been found to be appropriate in this circumstance (Duffull, unpublished data).
3. The results of the above mentioned analyses provided starting values for NONMEM [1] (using the subroutine ADVAN3, from NONMEM-PREDPP, and subroutine TRANS3). The parameters used to describe the two-compartment model were clearance (Cl), volume of distribution at steady state (Vss), volume of the central compartment (V1), and intercompartmental clearance (Clic). Log-normal variability was assumed in the parameters. The error was described using a model that had both a proportional error and a fixed error component, given by: $Y = F^{*}EXP(ERR(1)) + ERR(2)$, where F, from PREDPP, is the serum concentration; $ERR(1)$ denotes the proportional error term; and $ERR(2)$, the fixed component of the error. When covariates were added to the NONMEM analysis the new model was accepted only in circumstances when the objective function improved by more than 5 units. The objective function and the values of the parameters were thus refined further by the addition of covariates into the model. The best model was selected on the basis of the lowest objective function.

The best model was termed the a priori model (i.e. model based on prior data). The AUC extrapolated to infinity was calculated from:

$$\mathrm{AUC}_{0-\infty} = \frac{\mathrm{Dose}}{\mathrm{Clearance}}\,. \tag{2}$$

The AUC was also calculated using the log-trapezoidal rule such that the accuracy of the model could be assessed. This was accomplished using MK-MODEL.

Error of the a priori *model*

The error associated with the a priori model was estimated using a Markov Chain Monte Carlo (MCMC) technique termed the Metropolis-Hastings (MH) algorithm [26]. The error of the a priori model accounts for both patient variability, i.e. differing relationships between any defined covariate(s) and the value of a parameter, and also model mis-specification, i.e. the data defined by the a priori model may have been described better by three or four compartments, although a lack of serum concentration data may not have allowed this to be formalised.

MH algorithm

For assessment of the error associated with the a priori model a modified version of the MH algorithm was used. This represents the first use of the MH algorithm in generating an error model for pharmacokinetic analyses. The output of this algorithm is a probability density function (pdf) that describes the distribution obtained around a single x, y point derived from any given mathematical function, from which the mean and variance can be calculated. In the case of carboplatin the mathematical function is the multicompartment model that describes the decay of serum carboplatin concentrations over time. The output is a pdf around a predicted carboplatin concentration at a specified time. In brief, the MH algorithm is similar to performance of a simulation where approximately 10,000 estimates for each parameter (Cl, V1, Vss, Clic) are generated from their respective distributions. For each generation a concentration at a specified time can be calculated and either accepted or rejected as part of the posterior distribution. The acceptance/rejection procedure is performed using a likelihood function. From those values of concentration that have been accepted, a frequency histogram is constructed and the mean and standard deviation are calculated. This is performed at half-hourly intervals along the concentration-time curve (see Appendix 1 for details).

Error of the assay model

The error associated with any measured serum carboplatin concentration was calculated as a function of the inter- and intra-day coefficient of variation of the assay at different concentrations. This coefficient of variation was plotted against concentration and

a non-linear curve was fitted to the data. The minimal detectable concentration (the limit of detection) was added to represent assay noise.

Development of a sequential Bayesian design

The above mentioned models describe the mean concentration-time course of carboplatin in any patient from a population similar to that studied. A new method is proposed that incorporates both the a priori model and error models such that the most likely concentration-time curve can be estimated (Bayesian posterior estimate). Serum carboplatin concentrations may be incorporated into the algorithm such that the estimates of the patient's pharmacokinetic values can be adapted to approach their actual values. The adaptation occurs explicitly for this patient's a priori model and does not affect the population a priori model.

Serum carboplatin concentrations are incorporated by calculation of the "posterior mode" concentration. The posterior mode concentration combines the statistical information from both the a priori model and the observed carboplatin concentration. An expected serum concentration will have a pdf within which it is most likely to occur. Similarly, an observed serum concentration will have a pdf within which it is likely to occur. These pdfs can be described from the mean and variance of the respective error models. The junction of these two pdfs represents the most common concentration and is termed the posterior mode concentration. An approximation of the posterior mode concentration can be calculated in closed form rather than estimated via an iterative procedure. These are calculated at each observed concentration-time point. A simple graphic representation is given in Fig. 1. An approximation of the junction of the two pdfs (i.e. the posterior mode concentration) can be calculated as a point that is an equidistant number of respective standard deviations (σ_i) from each mean. This intersection closely estimates the true junction of the two curves if the standard deviations do not differ by more than 1 order of magnitude. This holds true over the measurable range of carboplatin concentrations. The intersection is exactly the junction of the two curves if the standard deviations of observed and expected are equal, i.e.:

$$\text{posterior mode concentration} = -N \times \sigma_{\text{exp}} + \text{Cp}_{\text{exp}} \quad (3.0)$$

$$\text{or} = N \times \sigma_{\text{obs}} + \text{Cp}_{\text{obs}}\,, \quad (3.1)$$

where N is given by:

$$N = \frac{\text{Cp}_{\text{exp}} - \text{Cp}_{\text{obs}}}{\sigma_{\text{exp}} + \sigma_{\text{obs}}}\,.$$

The posterior mode concentrations at all measured time-points represent the most likely time course of carboplatin concentrations in this patient with the current data. An appropriate pharmacokinetic model is fitted to these posterior mode concentration-time points using an extended least-squares approach. New values for the patient's pharmacokinetic parameters are therefore estimated and become the new a priori values for this patient.

The new values for each parameter are expressed in terms of the patient's covariates (e.g. height, weight) using the same structure described in the a priori model (Eqs. 5.1–5.4). The next dose for this patient is then individualised from these new a priori starting values. Subsequent carboplatin concentrations are handled in a similar manner. In this sequential technique the most recent serum carboplatin concentrations are given greater weighting.

Application

A single simulated example is followed through to illustrate the process. A patient with the characteristics 60 years of age, female, weight 70 kg, height 175 cm, and serum creatinine value 0.07 mmol/l was given a dose of 500 mg of carboplatin at 10:00 a.m. over 30 min. Two serum concentrations were drawn, one at 11:00 a.m. and one at 3:00 p.m. If we arbitrarily choose concentrations of 30 and 6 mg/l, which are deliberately different from those that would have been expected on the basis of a priori parameter values, the process can be illustrated. As a result of the differences between predicted and observed concentrations, new estimates of the expected concentrations and values for the pharmacokinetic parameters are derived for this patient. If the same dose is given again and the observed carboplatin concentrations, for the purposes of illustration, are the same (indicating that the observed concentration-time profile is more likely to be true for this patient), the calculated pharmacokinetic values and expected concentrations can be seen to approach the patient's true values.

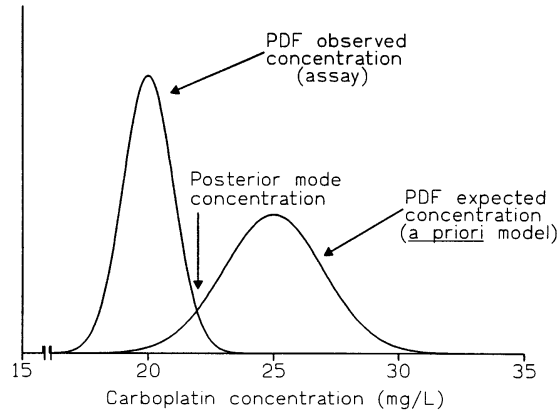

Fig. 1 Diagrammatic representation of the calculation of the Bayesian posterior mode concentration. Two pdfs are shown, one for the expected concentration (as predicted from the a priori model) and one for the observed concentration that accounts for assay variability. The junction of these two pdfs represents the most probable, i.e. posterior mode, concentration

Results

Pharmacokinetic analysis

Patients

A total of 12 patients were studied (Table 1). A standard anti-emetic regimen was given to all patients, consisting of oral ondansetron at 8 mg and dexamethasone at 8 mg/100 ml (normal saline). Seven patients were receiving their first course of carboplatin, two were receiving the second course, one was on the fourth course, and two were on their sixth course (last course).

Pharmacokinetic analysis

A biexponential function provided the best description of the data in all cases using TOPFIT. The values of the parameters were transformed to those appropriate to the subroutine TRANS3, i.e. Cl, Vss, V1, Clic (Appendix 2), and were incorporated into NONMEM as starting values.

Table 1 Patients' characteristics

Characteristic	Mean ± SD (Range)
Age (years)	59.5 ± 6.9 (49–68)
Height (cm)	164 ± 6.8 (152–177)
Weight (kg)	62 ± 10.6 (46–85)
Lean body weight (kg)[a]	56 ± 6 (48–64)
Surface aea (m^2)	1.65 ± 0.16 (1.4–1.9)
GFR (C&G)[b] (ml/min)	74.2 ± 20 (35–98)
GFR (DTPA)[c] (ml/min)	89 ± 19 (54–124)

[a] Lean body weight was calculated as follows: (height[cm] − 150) × 0.9 + 45 kg (+ 5 kg for men) as derived from Pesola et al. [22]
[b] Adjusted Cockcroft and Gault estimation of GFR. The method of Cockcroft and Gault was adjusted as follows: (1) serum creatinine concentrations of $<60\ \mu M$ and were set to be $60\ \mu M$ and (2) the weight used in the equation was the lower of lean body weight and total body weight as per Pesola et al. [22]
[c] DTPA clearance was calculated from standard pharmacokinetic equations on the basis of four blood samples

Table 2 Values recorded population parameters for carboplatin ($n = 12$)

Parameter	Population value		
	Geometric mean	CV%	(range)
Cl (l/h)	6.8	15.1	(3.4–8.8)
Vss (l)	21.6	17.3	(17.6–24)
V1 (l)	14.8	4.1	(11.4–15.6)
Clic (l/h)	4.4	0.4	(3.9–5)
ERR(1) = − 0.003			
ERR(2) = 0.220			

Covariate analysis

The only significant correlates ($P \leq 0.05$) found between a single covariate and any pharmacokinetic parameter using simple linear regression, were those detected between carboplatin clearance and DTPA ($r^2 = 0.32$), age ($r^2 = 0.36$), and adjusted creatinine clearance ($r^2 = 0.65$). The latter correlation is described by the following equation of best fit:

$$\mathrm{Cl_{carboplatin}\ (l/h)} = 1.08 \times \mathrm{ClCr} + 28\,, \qquad (4)$$

where *ClCr* is the creatinine clearance estimated using an adjusted Cockcroft and Gault method [7] (see Table 1). The slope of the line from this equation was not significantly different from 1. Non-renal clearance is given by the constant 28 (95% confidence interal (CI) − 14 to +70), which is not statistically different from that described by Calvert et al. [5].

NONMEM analysis

Incorporation of the output of TOPFIT as starting values for NONMEM and sequential addition of covariates, starting with adjusted creatinine clearance, yielded only two additional covariates that significantly improved the objective function: height and weight. Height was used as an estimate of lean body weight. The geometric means and the percent coefficient of variation (CV%) of the pharmacokinetic parameters Cl, Vss, V1 and Clic were estimated (Table 2). Values of the error model are also shown in Table 2.

The mean AUC calculated using non-compartmental analysis (MK-MODEL) as an external check of the modeling process was 87.8 ± 22 mg l^{-1} h (≈ 5.5 mg ml^{-1} min) as compared with 89.8 ± 21 mg l^{-1} h (≈ 5.6 mg ml^{-1} min) from the compartmental (NONMEM) analysis. These values were not significantly different. The hybrid-rate constants α and β and the proportionality constants A and B were calculated (Appendix 2). The values for $t_{1/2\alpha}$ and $t_{1/2\beta}$ were calculated from the mean of the individual patient's pharmacokinetic parameters, giving 0.85 ± 0.3 and 3.9 ± 1.9 h, respectively.

Development of the models

A priori model

From the output of NONMEM an a priori model (the model that best fitted the data following the addition of covariates) was defined that best describes the concentration-time course of carboplatin for a population of patients who are likely to have characteristics similar to those of the patients studied. The equations that describe the relationship between the patient's covariates and the parameters are:

	CV%	
$\mathrm{Cl\ (l/h)} = 0.15\ x\ \mathrm{LBW}^{0.75} + 0.78\ x\ \mathrm{ClCr}$	15.1%	(5.1)
$\mathrm{Vss\ (l)} = 0.38\ x\ \mathrm{LBW}$	17.3%	(5.2)
$\mathrm{V1\ (l)} = 0.26\ x\ \mathrm{LBW}$	4.1%	(5.3)
$\mathrm{Clic\ (l/h)} = 0.15\ x\ \mathrm{LBW}^{0.75}$	0.4%,	(5.4)

where *LBW* is lean body weight and *ClCr* is the creatinine clearance estimated using the Cockcroft and Gault equation [7], which was modified using LBW instead of total body weight and using a cut-off value for serum creatinine of $60\ \mu M$.

The AUC predicted by this model was compared with that of the Calvert method (originally used to estimate the doses that patients received in this study) in a retrospective manner so as to assess the predictive potential of the a priori model. This was undertaken using the AUC values from the non-compartmental analysis as the standard against which the mean error (ME) and root mean square error (RMSE) [25] of each method was evaluated. Although this is, in effect, a re-analysis of the same data, it is important to ensure that

the a priori model derived from the NONMEM analysis is not seriously flawed. The ME and RMSE of the prediction from the a priori model was − 1.5 (95% CI − 14.8 to + 11.8) and 21.3 (95% CI, 13.0 to 29.6), respectively, and, for the method of Calvert, was − 4.2 (95% CI − 19.8 to + 11.4) and 24.8 (95% CI 14.3 to 35.4), respectively. There was no statistically siginificant difference between the two methods in terms of these errors.

Error of the a priori *model*

The MH algorithm (Appendix 1) was used to estimate the error associated with the a priori model. The output of this algorithm was a pdf around each of a series of mean serum carboplatin concentration-time points predicted using the a priori model.

The standard deviation of the distribution around the expected concentration from the a priori model was then plotted against that concentration and an empirical curve of best fit was modeled to the plot (Fig. 2). From this a standard deviation at any given concentration of carboplatin can be calculated by the following equation:

$$\sigma_{exp}\ (\text{mg/l}) = (3.30 + 5.60\ (1 - e^{(-0.14\,|\,Cp_{exp} - 5.231)}).A).0.5, \quad (6)$$

where σ_{exp} is standard deviation of the expected serum carboplatin concentration, where Cp_{exp} is the expected serum carboplatin concentration calculated from the a priori model, and where A is + 1 if Cp_{exp} is greater than 5.23 and where A is − 1 if Cp_{exp} is less than 5.23. This equation was developed for concentrations in the range of 0.3 to 35 mg/l.

Error of the assay

The error of the assay was estimated by plotting of the coefficient of variation of the assay against concentration (Fig. 3). Empirically a biexponential function was chosen and fitted to this plot, resulting in the following equation:

$$CV_{assay}(\%) = 1.48\ e^{(-2.57.Cp_{obs})} + 0.06\ e^{(-0.013.Cp_{obs})}, \quad (7.0)$$

where CV_{assay} is the coefficient of variation of the assay and Cp_{obs} is the observed serum carboplatin concentration. The error of the observed concentration of carboplatin can therefore be calculated from eq. 7.1 as:

$$\sigma_{obs} = CV_{assay} \times Cp_{obs} + 0.25\ \text{mg/l}, \quad (7.1)$$

where σ_{obs} is the standard deviation of the observed serum carboplatin concentration and 0.25 mg/*l* is the limit of detection of the assay.

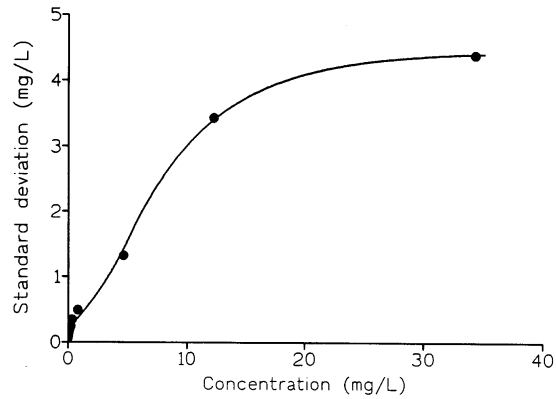

Fig. 2 Error of the a priori model. A graph of standard deviation versus concentration with a curve of best fit

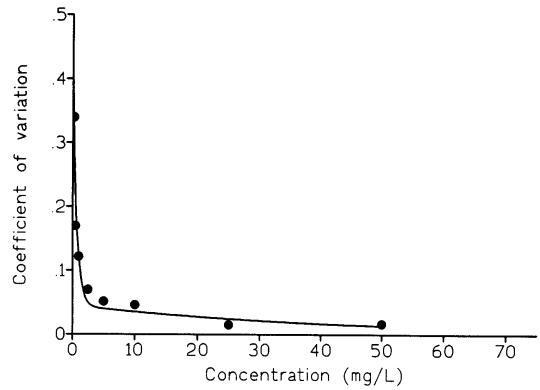

Fig. 3 Error of the assay. A graph of standard deviation versus concentration with a curve of best fit

Development of the sequential Bayesian algorithm

Application

For illustration of the algorithm an example is worked through. This is shown in Table 3. It can be seen that the posterior mode concentrations of carboplatin after the first dose become the new expected concentrations for this patient for the second dose. The values for the pharmacokinetic parameters thereby become a more accurate description of the patient's true values as more doses of carboplatin are given and more serum concentrations are drawn. After analysis of each data set, the covariate model, previously given by equations 5.1–5.4, is modified to become representative of the posterior estimates of the parameters. The value for the Bayesian objective function describes the overall error associated with the use of the a priori model to describe this patient's pharmacokinetics, i.e. the sum of the squares of the relative differences between the expected concentrations and observed concentrations and the expected and observed values for each pharmacokinetic parameter. The value for the Bayesian objective function

Table 3 Example of the adaptive nature of the sequential Bayesian algorithm for carboplatin ($n = 1$)

First dose (500 mg given at 10:00 a.m. over 30 min):

Time	Observed	Concentrations (mg/l, mean ± SD)		
		Posterior mode concentration	Expected	Residual error (percent)[a]
11:00 a.m.	30 ± 1.2	27.7	18.9 ± 4.0	+ 0.5
3.00 p.m.	6 ± 0.3	5.7	4.4 ± 1.4	+ 0.5

Bayesian objective function = 22.3
Cl = 5.2 l/h, Vss = 19.1 l, V1 = 11.4 l, Clic = 2.6 l/h, AUC = 96.6 mg l^{-1} h

Second dose (500mg given at 10:00 a.m. over 30 min):

Time	Observed	Concentrations (mg/l, mean ± SD)		
		Posterior mode concentration	Expected	Residual error (percent)
11:00 a.m.	30 ± 1.2	29.5	27.6 ± 4.3	+ 0.03
3:00 p.m.	6 ± 0.3	5.97	5.7 ± 1.8	+ 0.3

Bayesian objective function = 0.54
Cl = 4.9 l/h, Vss = 17.0 l, V1 = 10.6 l, Clic = 2.4 l/h, AUC = 102.4 mg l^{-1} h

[a] Residual error (percent) is defined in relation to the fit of the biexponential curve to the posterior mode concentrations where extended least squares was used as the minimisation function

decreased from 22.3 for the first dose to 0.54 following the second dose, indicating that the new set of starting values provides a better description of the observed data. It can be seen that the a priori values will approach the patient's true pharmacokinetic values when more carboplatin data become available. This demonstrates the sequential nature of this method of Bayesian analysis.

Discussion

This is the first Bayesian dose-individualisation method for carboplatin in adults. As with other Bayesian methods, serum concentration data can be incorporated such that the model becomes more specific for the patient. After each dose the values for the posterior pharmacokinetic parameters are estimated and future doses, predicted. The advantages of Bayesian analysis as compared with a standard least-squares method include (1) the ability to fit a curve with minimal data points, i.e. information from the a priori model "fills" in the gaps; (2) the model accounts for both expected population effects and observed serum drug concentrations and hence, serum drug concentrations that are outliers are recognised and given less weighting; (3) the ability of the model to adapt to approach the patient's true pharmacokinetic profile; and (4) the ability to weight effectively the most recent serum carboplatin concentrations more than earlier serum concentrations.

Bayesian dose-individualisation methods have been used for a number of drugs, e.g. gentamicin and vancomycin, and have been shown to have greater precision and less bias than other methods [4, 13]. Instead of using these methods for targeting of specific serum drug concentrations as with vancomycin, AUC values are also becoming acceptable targets. In addition to AUC targeting for carboplatin dosing, we have targeted AUC values for once-daily dosing of aminoglycosides [2]. Bayesian adaptive control methods have recently been developed for some chemotherapy agents, including serum concentration monitoring with suramin [17] and targeting of an AUC value for carboplatin in paediatrics [21] and for teniposide [8].

One of the limitations of this study is the small number of patients used to develop the population pharmacokinetics. This results in larger errors associated with the a priori model, which therefore tends to weight towards observed data. It should be noted, however, that unlike other population analyses that rely on sparse data sets, each patient in this study had sufficient data points for calculation of the AUC using non-compartmental analysis. Therefore, fewer patients are required for estimation of the parameters of a two-compartment model.

It was interesting that the adjusted creatinine clearance (using the lower of LBW or total body weight and adjusting serum creatinine values of < 0.06 mmol/l to 0.06 mmol/l) provided a better description of carboplatin clearance than did DTPA clearance, despite the superiority of DTPA clearance as an estimate of GFR. This may result from a poorly understood relationship between the GFR and the total body clearance (Cl_{TB}) of highly renally cleared drugs. We have seen this with aminoglycosides, where Cl_{TB} was predicted better by the creatinine clearance estimated using the formula of Cockcroft and Gault than by the calculated renal clearance of the aminoglycoside [14]. This implies that the

method of approximating creatinine clearance using the method of Cockcroft and Gault incorporates factors other than GFR alone in accounting for some of the clearance of drugs.

There is a need to test the sequential Bayesian algorithm against current standard dosing regimens and other Bayesian methods (e.g. those that use MAP) such that their predictive performance in terms of dosing can be assessed prospectively. This is currently under way. Pharmacokinetic data from the prospective trial will ultimately be incorporated into a new a priori model for the population.

The Bayesian algorithm described herein differs from the MAP algorithm in that it attempts to quantify the error associated with the prediction of a serum drug concentration at any time point. This error is termed the error of the a priori model. Once the error of the a priori model and that of the assay are known, a simple manipulation will yield the posterior estimate of the concentration-time curve in an individual and, hence, a new covariate model can be developed for this patient. In attempts to quantify the error of the a priori model, two assumptions are made: (1) that there will always be a quantifiable error associated with the a priori model and this error can be explained by Eq. 6, and 2 that this error holds true for all similar patients and within the same patient. It should be noted that the MAP algorithm also makes these assumptions about the a priori error. The difference between the methods is that the sequential Bayesian algorithm proposed herein amalgamates the variance of all the parameters into a single error term rather than treating them separately.

The use of a Bayesian dose-individualisation method for carboplatin is expected to be associated with more accurate attainment of the desired AUC than is achieved with the commonly used nomogram-type methods. If, from the work of Jodrell et al. [16], a therapeutic window exists for carboplatin, this technique should reduce the probability of overdosing, resulting in unnecessary treatment delays or toxicity, and the risk of underdosing, leading to potential treatment failures.

This method of Bayesian dose individualisation is different from others described in the literature in that it uses a sequential analysis design. Unlike other Bayesian dose-individualisation programs that use MAP and analyse all data simultaneously, this program alters the a priori values for each patient following each dose for which serum drug concentration data are available. This alleviates the need to fit complex dosing histories simultaneously. Another potential advantage of the sequential Bayesian algorithm over the MAP method lies in the method of estimating parameters. The method of MAP assumes that the values of all parameters remain constant (with respect to some observable covariate) over time, whereas the sequential algorithm does not require this to be true. This may offer an advantage in that as the number of treatment courses increases there are likely to be physiological changes that may result in changes in the values for the parameters without leading to any obvious change in observable covariates (e.g. age, serum creatinine). In patients with ovarian carcinoma these changes may occur as the tumor responds to chemotherapy, resulting in reduced peritoneal tumour mass, a subsequent reduction in ascites and potentially altered pharmacokinetics. In theory, therefore, the sequential nature of the proposed Bayesian method is likely to be useful for patients who are acutely unwell and are receiving either symptomatic or curative treatment, e.g. cancer and antimicrobial chemotherapy. This variability in parameters has been supported by a recent study that showed a significant decline in vanomycin clearance (13%) over 13 days of treatment with no significant change in covariates (e.g. serum creatinine) [23]. These potential differences need to be studied further.

In summary, a sequential Bayesian algorithm has been developed for carboplatin using standard population pharmacokinetic methods. This Bayesian method has potential advantages over currently accepted methods of carboplatin dosing as well as currently accepted methods of Bayesian analysis.

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Appendix 1

From a Bayesian perspective the model and analysis would be described as follows. Let t be any given fixed time and let θ_t denote the true mean serum carboplatin concentration taken over a hypothetical, large group of similar patients. Let x_t denote the sample mean of serum carboplatin concentration at time t of the 12 patients used to develop the a priori model. We assume from past experience that θ_t is a function of four other variables denoted by Cl, Vss, V1 and Clic and that this function is known in the sense that, given any set of values for these parameters, a value for θ_t can be computed. Thus, we can write:

$$\theta_t = g(Cl, Vss, V1, Clic, t), \tag{8}$$

where the expression $g(Cl.. ..t)$ represents a function that describes the relationship between the parameters and the plasma concentration at any given time (in this case a two-compartment intermittent intravenous infusion model). Now we treat the four parameters as unknowns with prior distributions that describe our uncertainty about them. The prior distribution of each parameter is obtained from the output of NONMEM. Since θ_t is an unknown mean concentration, our best description of it, after having observed the 12 patients, is to compute what is termed in the Bayesian model the "posterior" mean and the associated posterior variance, i.e. the error in the estimate. In this case the posterior distribution of θ_t cannot be calculated (i.e. is not available in closed form) due to the complicated relationship of x_t and θ_t to the unknown parameters Cl, Vss, V1 and Clic. However, we can still obtain the mean and variance (and other statistics if required) by using the recently developed methods of MCMC. One of the simplest forms of these MCMC methods is the MH algorithm, which we briefly describe below. (A more complete treatment and other references can be found in Smith and Roberts [26]).

For simplicity, let V denote the vector of the four parameters and let $P(V)$ denote the prior distribution of this vector. The likelihood function of the data x_t denoted by $f(x_t|V)$ is then assumed to be normal with mean θ_t and variance σ_{x_t}. Then, by Bayes' theorem the posterior distribution of V is given by:

$$P(V \mid x_t) = \frac{f(x_t \mid V) \,.\, P(V)}{f(x_t)} \,. \tag{9.0}$$

This can also be written in the form:

$$P(V \mid x_t) = \frac{f(x_t \mid V) \,.\, P(V)}{\int \cdots \int f(x_t \mid V) \,.\, P(V) \delta V} \,, \tag{9.1}$$

where the denominator is the integral of the numerator with respect to V taken over the set of vector values for V. Since the denominator contains no value for the parameters (i.e. does not contain the term V) the theorem can be simplified to:

$$P(V \mid x_t) \propto f(x_t \mid V) .\, P(V) \,, \tag{9.2}$$

i.e. the posterior distribution of V given x_t is proportional to the product of a likelihood function and the prior distribution of V.

The idea of the Markov Chain procedure is to generate sample values of V from $P(V \mid x_t)$. For each V value, θ_t [i.e. from $g(V, t)$] is computed, thus generating a large sample of θ_t from the posterior $P(\theta_t \mid x_t)$. From this simulated sample we can compute the mean and variance, i.e. the posterior mean and the posterior variance, of θ_t, which is our ultimate goal. Since the denominator in Eq. 9.1 is difficult to calculate, a straightforward simulation of values for V is not possible, but the MH algorithm accommodates this. In summary, this procedure basically says:

1. Generate V values from the known prior $P(V)$. Calculate θ_t values from V (using Eq. 8).
2. Use the formula given below for deciding which of these observations of V to accept.
3. The accepted observations of V and, hence, also of θ_t can be treated as observations from the unknown posterior distribution $P(\theta_t \mid x_t)$, and after sufficient iterations the mean and variance of θ_t can be calculated.

Mathematically the MH algorithm proceeds as follows:

1. Start by using the known normal priors of V and generate $V^{(0)}$ and $V^{(1)}$.
2. Calculate the corresponding values of $\theta_t^{(0)}$ and $\theta_t^{(1)}$, respectively, using the relationship between V and θ_t (Eq. 8).
3. The decision either to retain $V^{(1)}$ as a new value for $V^{(0)}$ or to accept it as a term to be incorporated into the posterior pdf of $P(V \mid x_t)$ is made below.
4. Compute the ratio (R) as:

$$R(V^{(0)}, V^{(1)}) = \frac{f(x_t \mid V^{(1)}) \,.\, P(V^{(1)})}{f(x_t \mid V^{(0)}) \,.\, P(V^{(0)})} \,, \tag{10}$$

where:

$$P(V^{(i)}) = P_1(Cl^{(i)}) \,.\, P_2(Vss^{(i)}) \,.\, P_3(V1^{(i)}) \,.\, P_4(Clic^{(i)})$$

$$f(x_t \mid V^{(i)}) = \frac{1}{\sqrt{2\pi\sigma_{x_t}^2}} \,.\, exp^{-0.5}((x_t - g[V^{(i)}, t^{(i)}])/\sigma_{x_t})^2 \,,$$

where by σ_{x_t} denotes the standard deviation of the sample mean concentration.
5. Retain $V^{(1)}$ as the next term in the sequence with probability equal to the calculated ratio (R) above; i.e. draw a uniform random number $u^{(1)}$ and accept $V^{(1)}$ if $R(V^{(0)},V^{(1)}) \geq u^{(1)}$; if the ratio is a value greater than unity, then accept automatically and set $V^{(0)} = V^{(1)}$. Thus, the next term in the generated sequence of Vs is either the new value for $V^{(1)}$ or a repeat of the previous value.
6. Now generate $V^{(2)}$ in a similar fashion to $V^{(1)}$ and set $V^{(1)} = V^{(2)}$.
7. From the accepted values of V, θ_t can be directly calculated (using Eq. 8). These are observations from the posterior distribution given by $P(\theta_t \mid x_t)$.
8. Iterate in this fashion for a large number of generations ($\approx$ 10,000).
9. The cumulative frequency of the accepted values of θ_t provides the pdf of a serum concentration of carboplatin at time t, from which the Bayesian posterior mean and variance can ultimately be calculated.
10. The above listed steps are repeated at intervals along the concentration-time curve such that the error of the a priori model can be estimated at multiple time points.

Appendix 2

The proportionality constants (A, B), micro-rate constants ($k12$, $k21$, kel), and hybrid-rate constants (α, β) are calculated as follows:

$$\mathrm{k12} = \mathrm{Clic/V1}$$
$$\mathrm{k21} = (\mathrm{Clic} \,.\, \mathrm{V1})/(\mathrm{Vss} - \mathrm{V1})^2$$
$$\mathrm{Kel} = \mathrm{Cl/V1}$$

$$\mathrm{A} = \mathrm{Dose} \,.\, (\alpha - \mathrm{k21})/(\mathrm{V1} \,.\, (\alpha - \beta))$$
$$\mathrm{B} = \mathrm{Dose} \,.\, (\mathrm{k21} - \beta)/(\mathrm{V1} \,.\, (\alpha - \beta))$$

$$\alpha = \mathrm{Z} - \beta$$
$$\beta = (-\mathrm{Z} - \sqrt{(\mathrm{Z}^2 - 4 \,.\, \mathrm{Y})})/2 \,,$$

where:

$$\mathrm{Z} = \mathrm{k12} + \mathrm{k21} + \mathrm{kel}$$
$$\mathrm{Y} = \mathrm{k21} \,.\, \mathrm{Kel}.$$

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