PERGAMON

European Journal of Cancer 38 (2002) 52–56

European Journal of Cancer

www.ejconline.com

Impact of the biochemical assay for serum creatinine measurement on the individual carboplatin dosing: a prospective study

F. Léger, S. Séronie-Vivien, J. Makdessi, I. Lochon, J.P. Delord, C. Sarda, P. Canal, E. Chatelut*

Institut Claudius-Regaud, EA3035 and Université Paul-Sabatier, Toulouse, France

Received 24 September 2001; received in revised form 4 October 2001; accepted 5 October 2001

Abstract

We previously developed a formula to estimate the individual carboplatin clearance (CL) based on serum creatinine (Scr) determined by an enzymatic assay using creatinine amidohydrolase. An analytical comparison had shown systematic differences between this method and the commonly used Jaffé method (with Jaffé Scr (in μM) = 1.08 × enzymatic Scr + 1.6, as regression equation). We performed a pharmacokinetic prospective clinical study using the Jaffé assay to evaluate the impact of the method used for Scr measurement on the prediction of the carboplatin CL. In forty patients, carboplatin dosing was performed according to the Chatelut formula where the serum creatinine level was corrected according to the above equation. The population pharmacokinetics of carboplatin were analysed using the NONMEM program to determine the individual carboplatin CL from a limited sampling strategy. Thanks to the correction of the Jaffé Scr, no significant difference was observed between the administered and the optimal dose. In contrast, if no correction of the Scr was done, the patients would have been significantly under-dosed. Moreover, a covariate analysis using NONMEM gave a very consistent result showing that Scr should be decreased by 11.6% when the Jaffé value is used within the Chatelut equation. This study confirmed that differences in the Scr assay has consequences with regard to carboplatin dosing. The correction we propose for Scr obtained by the Jaffé method may help to standardise clinical practice. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Creatinine measurement; Individual dosing; Carboplatin; Population pharmacokinetics

1. Introduction

Individualised carboplatin dosing is now widely performed using several formulae that allow one to predict the carboplatin clearance (CL). The relationships between carboplatin area under the concentration time curve (AUC) and both toxicity and efficacy support this approach [1]. Calvert and colleagues showed that it was possible to predict CL by measuring the glomerular filtration rate (GFR) using the [^{51}Cr]-ethylenediamine tetraacetic acid (EDTA) method according to the equation: CL (ml min^{-1}) = GFR (ml min^{-1}) + 25 [2]. Creatinine clearance (CCr) obtained by the Cockcroft formula [3] is often used as a substitute for GFR in the Calvert formula. However, this substitution led to an underestimation of the GFR and then of carboplatin CL, particularly for patients with good renal functions [4,5]. We have previously developed an equation based on four patient characteristics (i.e. body weight, age, sex and serum creatinine level) to predict carboplatin clearance [6]. Van Warmerdam and colleagues [5] and Donahue and colleagues [7] reported that this equation (known as the Chatelut formula) estimates more accurately the carboplatin CL than the Calvert formula when GFR is substituted by CCr, whatever the mode of determination of CCr.

When the Chatelut formula was designed, the serum creatinine level (Scr), for the 70 patients composing our database, was obtained by an enzymatic assay using creatinine amidohydrolase and a reflectometric detec-

* Corresponding author at present address: 20 rue du Pont-St-Pierre, F-31052 Toulouse, France. Tel.: +33-5-6142-4271; fax: +33-5-6142-4631.

0959-8049/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0959-8049(01)00358-6

tion on Vitros/Ektachem® analyser. Since this enzymatic assay was replaced in our institution's laboratory by a colorimetric kinetic Jaffé assay, we first performed an analytical comparison of the two methods using 244 serum samples [8]. This study revealed a systematic difference between the two methods as the regression equation was: (Jaffé Scr) = 1.08 × (enzymatic Scr) + 1.6, with Scr in μM. The colorimetric Jaffé assay overestimated the serum creatinine level by 13.9% on average. Therefore, we designed a pharmacokinetic prospective clinical study to evaluate the impact of the method used for creatinine measurement on the prediction of the carboplatin CL by the Chatelut formula.

2. Patients and methods

2.1. Patients and treatment schedule

The 40 patients (pts) (from 23 to 83 years old, 20 males and 20 females) who entered this study were receiving carboplatin as part of established protocols in the Institut Claudius-Regaud (Toulouse) in combination with 5-fluorouracil (11 pts), paclitaxel (9 pts), or other drugs. Their mean (range) body weight and serum creatinine were 64 (41–96) kg and 91 (61–172) μM, respectively. A local ethical committee approved the protocol and informed written consent was obtained from each patient. Carboplatin was administered as a 60-minute intravenous (i.v.) infusion at doses ranging from 265 to 1465 mg. For each patient, the target AUC value was chosen with regard to the associated drug and the nature of the pretreatment. The administered dose was calculated by:

$$\text{Dose (mg)} = \text{target AUC} \times \text{CL}$$

with CL estimated *a priori* using the Chatelut formula:

$$\text{CL} = 0.134.\text{weight (kg)} + \frac{218.\text{weight(kg)}.(1 - 0.00457.\text{age(y)}).(1 - 0.314.\text{sex})}{\text{Scr}(\mu\text{M})}$$

where sex = 0 if male, = 1 if female; weight is the body weight or the arithmetic mean between actual and ideal body weight (calculated according the Lorentz equation) for obese patients [9], and Scr is the serum creatinine level.

To calculate the administered dose, we used the Scr determined by colorimetric kinetic Jaffé assay and then corrected according to the equation previously obtained by comparison between the enzymatic and the colorimetric Jaffé methods [8]:

$$\text{Scr} = (\text{Jaffé creatinine} - 1.6)/1.08$$

2.2. Blood sampling and platinum analysis

Two blood samples per patient were collected at time T + 1 and T + 4 h after the end of the 1-h carboplatin infusion. These two samples have been selected according to a limited sampling strategy we previously developed in Ref. [10]. After immediate centrifugation at 4 °C, the plasma was separated and ultrafiltered using the Amicon MPS1 micropartition system with YMT membranes at 4 °C. Plasma ultrafiltrable carboplatin levels were measured by flameless atomic absorption spectrophotometric analysis according to the previously described method in Ref. [11].

2.3. Pharmacokinetic analysis

Plasma ultrafiltrable carboplatin concentrations were analysed according to a population pharmacokinetic method using the NONMEM program [12] (version V, level 1.1, running on Pentium 200 pro) and a two-compartment pharmacokinetic model. A proportional error model was used for residual and inter-patient variabilities. The data of the present study were combined with a database composed of those from 103 patients. Two analyses were performed: (i) The first one was based only on the concentrations versus time data; its objective was to determine the individual carboplatin CL of the 40 patients by Bayesian estimation using POSTHOC option and first-order conditional estimation (FOCE) method on NONMEM. No covariate was taken into account in order to obtain individual carboplatin CL totally independent of these covariates, and particularly of the serum creatinine level. (ii) The objective of the second analysis was to evaluate the impact of serum creatinine measurement method considered as a covariate on the relationship between carboplatin CL and covariates. For this second analysis, all the covariates already known to be significantly correlated with CL, were taken into account according to the Chatelut formula. The covariate MET for serum creatinine measurement method was added. The first-order (FO) method was used for the NONMEM analysis. The value of the objective function represented the statistical criteria for evaluating the goodness of fit corresponding to the model with or without MET.

2.4. Statistical evaluation

For each patient, optimal dose (Dose_{opt}) was obtained by: $\text{Dose}_{\text{opt}} = \text{AUC}_{\text{target}} \times \text{CL}$, where CL is the individual actual carboplatin CL obtained by Bayesian analysis using POSTHOC option method (analysis without patient covariates). Calculated dose ($\text{Dose}_{\text{calc}}$) was obtained by: $\text{Dose}_{\text{calc}} = \text{AUC}_{\text{target}} \times \text{CL}_{\text{pred}}$, where CL_{pred} is the value predicted by the Chatelut formula using the serum creatinine level obtained by Jaffé method either

uncorrected or corrected according to: Scr = (Jaffé Scr − 1.6)/1.08. (The latter calculated dose corresponds to the administered dose.) The relative prediction error, pe_j%, for carboplatin dosing is defined as follows:

$$pe_j(\%)\frac{\text{Dose}_{\text{calc}} - \text{Dose}_{\text{opt}}}{\text{Dose}_{\text{opt}}} \times 100$$

Predictive performance was evaluated by computing the mean relative prediction error ($\text{me}\% = n^{-1}.\sum_{j=1}^{n}(pe_j)$ where n is the number of patients ($n = 40$) as a measure of bias and the root mean squared relative prediction error ($\text{rmse}\% = [n^{-1}.\sum_{j=1}^{n}(pe_j^2)]^{1/2}$) as an assessment of precision.

3. Results

3.1. Impact of the serum creatinine measurement method on carboplatin dosing

Individual carboplatin CL of the 40 patients were obtained by Bayesian analysis using POSTHOC option on NONMEM. Goodness-of-fit was good as shown by the comparison between adjusted and measured carboplatin concentrations (Fig. 1).

Table 1 shows the percentage of difference between optimal and calculated dose when Jaffé Scr is corrected (administered dose) and when Jaffé Scr is not corrected.

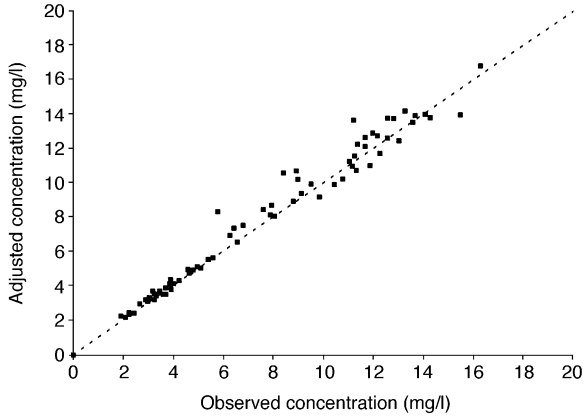

Fig. 1. Bayesian estimation of actual carboplatin clearance (CL) using POSTHOC option: individual model-predicted concentrations versus observed concentrations. Continuous line is the line of identity.

If the Jaffé value of Scr had not been corrected, the bias would have been significantly different from 0 ($P < 0.05$, one-side Student's t-test with 'use of Jaffé Scr value does not lead to carboplatin under-dosing' as the null hypothesis). In contrast, thanks to the correction of the Jaffé Scr, the bias between the optimal dose and administered dose was not significantly different from 0.

Fig. 2 shows the correlation between the actual carboplatin CL and value predicted by the Chatelut formula using the corrected Scr for the 40 patients of the present study among the overall population of our database.

3.2. Impact of the covariate 'Scr measurement method' on the population pharmacokinetic analysis

The prediction of carboplatin CL using Scr combined to other covariates according to the Chatelut formula was significantly improved by considering the covariate MET (for method of Scr measurement) as a weighting factor on Scr. By adding the covariate MET in the Chatelut formula as in the following equation, the objective function decreased by 9.4 showing a significant ($P < 0.01$) increase of goodness of fit:

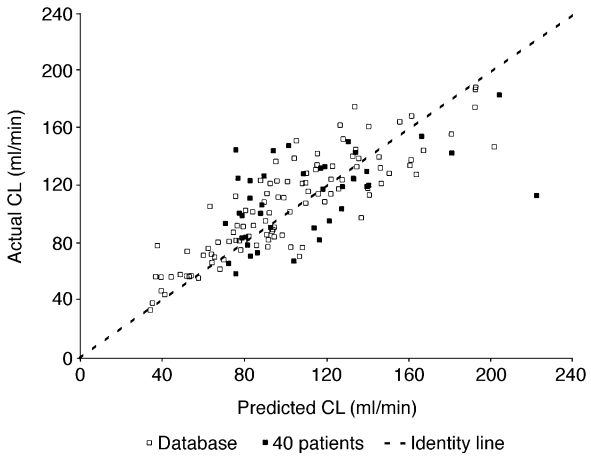

Fig. 2. Relationship between the actual carboplatin clearance (CL) and that predicted by the Chatelut formula in 143 patients including the 40 patients of the present study for whom the serum creatinine level was obtained by Jaffé method and corrected according to the equation: Scr = (Jaffé Scr − 1.6)/1.08.

Table 1
Percent errors between calculated and optimal dose by using corrected (i.e., Scr = (Jaffé Scr − 1.6)/1.08) or not corrected value of serum creatinine determined by Jaffé method in 40 patients

$(\text{Dose}_{\text{calc}} - \text{Dose}_{\text{opt}}) \times 100/\text{Dose}_{\text{opt}}$	Corrected Scr	Not corrected Scr
Bias, mse% (95% CI)	+1.1 (−7.6; +9.7)	−7.4 (−15.4; +0.6)
Precision, rmse% (95% CI)	27 (17; 35)	26 (19; 32)
Range of percent error	−48 to +96	−52 to +77
10th and 90th centiles	−31 to +27	−39 to +17

*Confidence Interval (α = 5%).

$$CL = 0.134.\text{weight (kg)} + \frac{218.\text{weight(kg)}.(1 - 0.00457.\text{age(y)}).(1 - 0.314.\text{sex})}{\text{Scr}(\mu\text{M}).(1 - \theta.\text{MET})}$$

where MET = 0 for the patients of the database ($n = 103$) for whom the enzymatic method was used, and MET = 1 for the patients ($n = 40$) of the present study for whom the Jaffé method was used. The final estimate (95% Confidence Interval (CI)) of the weighting factor on Scr, was: $\theta = +0.116$ (-0.014 to $+0.246$).

4. Discussion

The need for adjusting the serum creatinine level in the carboplatin formulae according to the type of biochemical assay used was expected. However, most of the routinely used methods are based upon only two main principles: the colorimetric Jaffé method and the enzymatic assay using creatinine amidohydrolase. For the enzymatic amidohydrolase assay, only two tests are widely commercially available. First is the Ortho-Clinical Diagnostics one-slide assay performed on Vitros® (formerly Ektachem®) analysers; this method was used in our institution when the Chatelut formula was established. Second is the Roche-Boehringer PAP assay performed on Hitachi® and Integra® analysers.

Ando and colleagues [13] proposed to add 2 mg l^{-1} (17.7 μmol/l) to the serum creatinine level (Scr) measured by the enzymatic PAP method when Scr is used to calculate creatinine clearance by Cockcroft–Gault equation as a surrogate for GFR in the Calvert formula. They also concluded that the adjusted serum creatinine level should be used in the Chatelut formula in order to avoid overdosing of carboplatin when the PAP method is used for creatinine measurement.

Wright and colleagues [14] have also shown that a potential source of variability in the GFR estimation arises from the serum creatinine assay and they propose two different formulae to estimate GFR in cancer patients, depending on the methodology used (PAP or kinetic Jaffé method).

In the present study, the impact of the methodology used for creatinine measurement is also clearly apparent, and the necessity to adjust Scr if determined by a kinetic Jaffé method in the Chatelut formula arises for the first time. This observation is of great importance due to the fact that the kinetic Jaffé assay is the most used method for creatinine measurement in the blood.

The results of this prospective clinical study are totally consistent with those of the previous analytical comparison made by us [8]. Correction of the Scr obtained by Jaffé method according to the equation inferred from this study led to an abolishment of the bias between the actual carboplatin CL and carboplatin clearance predicted by the Chatelut formula. Moreover, the analytical comparison showed that the kinetic Jaffé method overestimated the serum creatinine level by 13.9% on average, while the final estimate of the weighting factor on Scr obtained by population pharmacokinetic analysis of data combining Scr obtained by both methods was 11.6%. It is of interest to note that two completely independent analyses led to similar results. This confirms the power of population pharmacokinetics methodology.

Among the 40 patients, the worst prediction corresponded to a patient with a predicted carboplatin CL of 222 ml/min, while his actual value was 114 ml/min. This patient had a low creatinine level (i.e. 61 μM for a body weight of 73 kg). This overestimation (i.e. +96%) would have been limited to +63% if the following recommendation had been respected: to set the highest value we observed from our whole data set (i.e. 189 ml/min) as a superior boundary for the carboplatin CL when the estimation is performed according to patient covariates.

Adjustment of the Scr in the Chatelut formula when the Jaffé method is used may appear unnecessary regarding its small extent; as a matter of fact, a dose increase of 8% should not have significant clinical consequences. However, the general objective of population pharmacokinetics is to identify the covariates explaining the inter-individual variability in order to provide tools for decreasing this variability. Therefore, in this perspective, it is recommended to take into account this 'Scr assay' covariate in the carboplatin dosing.

References

1. Duffull SB, Robinson BA. Clinical pharmacokinetics and dose optimisation of carboplatin. *Clin Pharmacokinet* 1997, **33**, 161–183.
2. Calvert AH, Newell DR, Gumbrell LA, *et al*. Prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989, **7**, 1748–1756.
3. Cockcroft D, Gault M. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976, **16**, 31–41.
4. Calvert AH, Boddy A, Bailey NP, *et al*. Carboplatin in combination with paclitaxel in advanced ovarian cancer: dose determination and pharmacokinetic and pharmacodynamic interactions. *Semin Oncol* 1995, **22**, 91–100.
5. van Warmerdam LJ, Rodenhuis S, ten Bokkel Huinink WW, Maes RA, Beijnen JH. Evaluation of formulas using the serum creatinine level to calculate the optimal dosage of carboplatin. *Cancer Chemother Pharmacol* 1996, **37**, 266–270.
6. Chatelut E, Canal P, Brunner V, *et al*. Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst* 1995, **87**, 573–580.
7. Donahue A, McCune JS, Faucette S, *et al*. Measured versus estimated glomerular filtration rate in the Calvert equation: influence on carboplatin dosing. *Cancer Chemother Pharmacol* 2001, **47**, 373–379.

8. Jaudon T, Seronie-Vivien S, Chatelut E, Chanut C, Favre G. Comparison of jaffe method and enzymatic method for the measurement of serum creatinine: consequences of a method switch in an oncological clinical biochemistry laboratory. *Ann Biol Clin* 2000, **58**, 499–504.
9. Benezet S, Guimbaud R, Chatelut E, Chevreau C, Bugat R, Canal P. How to predict carboplatin clearance from standard morphological and biological characteristics in obese patients. *Ann Oncol* 1997, **8**, 607–609.
10. Chatelut E, Pivot X, Otto J, *et al*. A limited sampling strategy for determining carboplatin AUC and monitoring drug dosage. *Eur J Cancer* 1999, **36**, 264–269.
11. LeRoy AF, Wehling ML, Sponseller HL, *et al*. Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. *Biochem Med* 1977, **18**, 184–191.
12. Beal SL, Sheiner LB. Methodology of population pharmacokinetics. In Garrett ER, Hirtz J, eds. *Drug Fate and Metabolism,* vol. 5. New York, Marcel Decker, 1985, 135–183.
13. Ando M, Minami H, Ando Y, Saka H, *et al*. Multi-institutional validation study of carboplatin dosing formula using adjusted serum creatinine level. *Clin Cancer Res* 2000, **6**, 4733–4738.
14. Wright JG, Boddy AV, Highley M, Fenwick J, McGill A, Calvert AH. Estimation of glomerular filtration rate in cancer patients. *Br J Cancer* 2001, **84**, 452–459.