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SHORT COMMUNICATION

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A single 24-hour plasma sample does not predict the carboplatin AUC from carboplatin-paclitaxel combinations or from a high-dose carboplatin-thiotepa-cyclophosphamide regimen

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Abstract *Purpose*: It has been observed that the area under the free carboplatin concentration in plasma ultrafiltrate versus time curve (AUC) is related to toxicity and tumour response. For this reason, it can be important to measure the carboplatin AUC and subsequently adjust the dose to achieve a predefined target AUC. The use of limited sampling strategies enables relatively simple measurement and calculation of actual carboplatin AUCs. *Methods*: We studied the performance of a limited sampling model, based on a single 24-h sample (the Ghazal-Aswad model), in 52 patients who received carboplatin in two different chemotherapy regimens (a carboplatin-paclitaxel combination and a high-dose carboplatin-thiotepa-cyclophosphamide combination). *Results*: The measured mean AUC in our population was 4.1 min · mg/ml (median 3.9, range 1.9–6.3, SD 1.0 min · mg/ml). With the limited sampling model, the predicted mean AUC was 4.4 min · mg/ml (median 4.2, range 2.4–8.4, SD 1.2 min · mg/ml). Statistical analysis revealed that the model was slightly biased (MPE%, 6.5%), but imprecise (RMSE%, 20.6%) in our study population. *Conclusion*: Although easy and attractive to use, the Ghazal-Aswad formula is not precise enough to predict the carboplatin AUC, and needs to be evaluated prospectively in other patient populations.

Key words Carboplatin · Limited sampling model · Pharmacokinetics · AUC

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Introduction

It is known that the area under the free carboplatin plasma concentration versus time curve (AUC) is a major determinant of toxicity and probably tumour response [6, 7, 10, 11, 25]. Therefore, it is important to estimate the carboplatin AUC, and to adjust the dose accordingly. Unfortunately, the exact quantification of the achieved AUC after dosing requires blood sampling at different time-points, which is inconvenient for the patient and is a time-consuming method. A relatively simple method which may allow the accurate estimation of the carboplatin AUC is to use a limited sampling strategy [22]. By concentration measurements at only one to three different time-points after the end of the infusion, the actually achieved carboplatin AUC can be calculated. Several limited sampling models have already been developed for carboplatin. However, those models are only valid for specific carboplatin infusion durations, combination regimens, or certain patients, e.g. children [15, 17, 20]. Recently, a unique limited sampling model using only a single 24-h plasma sample for the estimation of the free carboplatin AUC has been proposed [4]. The purpose of this study was to investigate this limited sampling model when applied retrospectively to different treatment combinations and infusion durations of carboplatin.

Patients and methods

Patient population

Patients participated in two clinical trials. The regimens and clinical details of these studies have been described previously [8, 24].

Patients in study A had locally advanced or metastatic stages IIIB or IV non-small-cell lung cancer (NSCLC). They had not received prior chemotherapy and participated in a dose-finding phase I trial. The treatment consisted of carboplatin 300 to 400 mg/m^2 administered as a 30-min intravenous infusion in combination with paclitaxel (100 to 250 mg/m^2) administered as a 3-h intravenous infusion [8].

The other patients participated in a phase II clinical trial (study B) and received high-dose intensities of alkylating agents followed by peripheral blood stem cell transplantation (PBSCT). In brief, carboplatin (400 mg/m^2 per day) was administered as a 1-h intravenous infusion followed by cyclophosphamide (1500 mg/m^2 per day) in a 1-h intravenous infusion and thiotepa (2 × 60 mg/m^2 per day) in a 30-min intravenous infusion (the second infusion given 12 h after the first). All agents were given daily for 4 consecutive days [24].

Pharmacokinetic studies

In study A, complete concentration-time curves were obtained for carboplatin in 36 patients. Samples were collected at 11 time-points: immediately before the infusion, at the end of infusion, and at 0.25, 0.5, 1, 2, 4, 8, 12, 24 and 48 h after the end of the 30-min infusion. In study B, blood samples were collected from 16 patients at 12 time-points on day 1 of the carboplatin infusion: immediately before, halfway through, and at the end of the infusion, and at 0.25, 0.5, 1.5, 2.75, 5, 8, 12, 18, and 24 h after the end of the 1-h infusion. Plasma was obtained by immediate centrifugation (5 min, 1500 *g*) of the samples. The plasma was then transferred directly into an Amicon micropartition system with a YMT-30 membrane (Amicon Division, WR Grace & Co, Danvers, Mass.) and centrifuged for 10 min at 1500 *g*. The plasma ultrafiltrate was stored at −20 °C until analysis. Platinum plasma and ultrafiltrate concentrations were quantitated using a validated method based on Zeeman flameless atomic absorption spectrophotometry and were recalculated as carboplatin concentrations [23]. The plasma ultrafiltrate concentration versus time curves of carboplatin were analysed using the pharmacokinetic software package MW/Pharm (MEDI\WARE BV, Groningen, The Netherlands) [16]. The actual carboplatin AUCs were determined as the exact integral of the fitted curves of the concentration versus time plots with extrapolation to infinity.

Statistical considerations

The carboplatin AUCs were also calculated using the formula of Ghazal-Aswad et al. [4]:

$$\text{AUC}(\text{min}\cdot\text{mg/ml}) = (\text{24-h total platinum concentration } (\mu\text{mol/l} + 0.3)/0.82$$

The performance of the prediction of the carboplatin AUCs was evaluated using the relative mean prediction error (MPE%), the relative root mean square prediction error (RMSE%), and their respective standard errors SE% [18, 22]. These parameters are defined as follows:

$$\text{MPE\%} = \left(N^{-1}\cdot\sum_{i=1}^{N}(\text{pe}_i)\right)\cdot 100\%$$

$$\text{SE\%} = \left[N\cdot(N-1))^{-1}\cdot\sum_{i=1}^{N}(\text{pe}_i - \text{MPE})^2\right]^{1/2}\cdot 100\%$$

$$\text{RMSE\%} = \left[N^{-1}\cdot\sum_{i=1}^{N}(\text{pe}_i)^2\right]^{1/2}\cdot 100\%$$

$$\text{SE\%} = [(N\cdot(N-1))^{-1}\cdot\sum_{i=1}^{N}[(\text{pe}_i)^2 - \text{RMSE})^2]^{1/2}\cdot 100\%$$

where N is the number of AUC pairs (i.e. pairs of predicted AUC values according to the limited sampling formula with the measured AUC values), and pe is the relative prediction error [$\ln(\text{AUC}_{\text{predicted value}}) - \ln(\text{AUC}_{\text{measured value}})$]. The MPE percentage, which is the mean difference between the natural logarithms of the measured and predicted concentrations, represents the systematically positive or negative error of a prediction. The RMSE percentage is a measure of the standard deviation of the model error. The smaller the RMSE% value, the better is the prediction. Statistical calculations were made using the computer programs NCSS (NCSS package, version 5.0; East Kaysville, Utah; J.L. Hintze, 1991).

Results

The pharmacokinetic data from 52 patients (36 from study A, and 16 from study B) were used in this study. The median age of the patients was 48 years (range 18 to 74 years), while the median administered carboplatin dose was 600 mg (range 450 to 840 mg). The measured AUC in study A was (mean ± SD) 3.8 ± 0.9 min · mg/ml (median 3.8, range 1.9–6.3 min · mg/ml), and in study B was 4.7 ± 1.0 min · mg/ml (median 4.2, range 3.2–6.1 min · mg/ml). These AUC values were significantly different from one another (*t*-test, $P < 0.001$), due to the generally higher carboplatin dose that was given in study B. The median measured total platinum concentration after 24-h was 3.2 μmol/l (range 1.7–6.6 μmol/l). The measured carboplatin AUCs were compared with the respective AUCs as calculated by the method of Ghazal-Aswad et al. (based on the total platinum plasma concentration 24-h after drug administration). Using this model, the predicted AUC in study A was (mean ± SD) 4.1 ± 1.2 min · mg/ml (median 4.0), and in study B (mean ± SD) 5.0 ± 1.1 min · mg/ml (median 5.0). The bias (MPE%) in study A was 6.2%, with an imprecision (RMSE%) of 21.8%, and in study B these parameters were 7.3% (MPE%) and 17.5% (RMSE%). Figure 1 shows the measured AUCs and the corresponding AUCs for studies A and B, as predicted by the formula of Ghazal-Aswad et al. The measured mean AUC in studies A and B together was 4.1 min · mg/ml (median 3.9, range 1.9–6.3, SD 1.0 min · mg/ml), and the predicted mean AUC was 4.4 min · mg/ml (median 4.2, range 2.4–8.4, SD

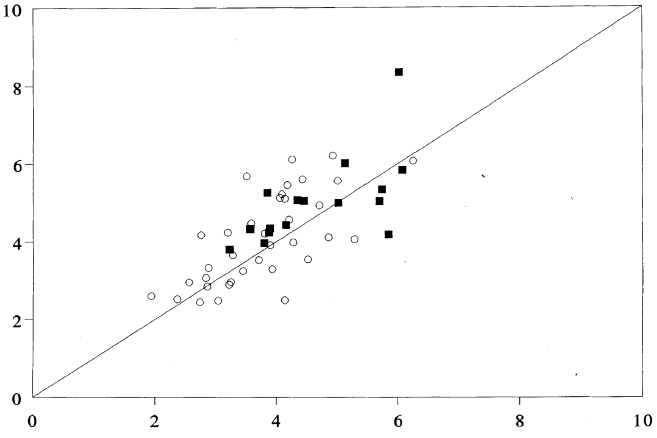

Fig. 1 Measured AUC (min · mg/ml) versus AUC as calculated by the single-sample model proposed by Ghazal-Aswad et al. [u] (○ study A, ■ study B; *solid line* $y = x$)

1.2 min · mg/ml). Overall, the equation of Ghazal-Aswad et al. systematically overestimated the actual AUC by 6.5% ± 2.7% (MPE% ± SE%); however, it gave an imprecision of 20.6% ± 2.4% (RMSE% ± SE%) in these patients.

Discussion

The relationship between the glomerular filtration rate (GFR) and the carboplatin clearance enabled Calvert et al. to develop the formula: carboplatin dose (mg) = target AUC (min · mg/ml) × (GFR + 25) (mL/min) [2]. Because the GFR assessment in this formula is based on the ^{51}Cr-EDTA clearance measurement, a precise but inconvenient method not available in every hospital, several authors have proposed alternative formulas. However, there is now accumulating data that these modified Calvert formulas are not accurate and precise enough and tend to overestimate the carboplatin AUC [1, 9, 13, 19]. This is important, since specific target AUCs in carboplatin dosing have been related to toxicity and the likelihood of response [10]. Therefore, it seems worthwhile to measure the achieved AUC after carboplatin dosing and to adjust the dose in following courses. One approach to achieving this easily is by using limited sampling models. Ghazal-Aswad et al. proposed a simple limited sampling model which uses only a single 24-h (plasma sample for the estimation of the free carboplatin AUC, irrespective of the infusion duration [4]. We evaluated this model by applying it to several combination schedules. However, this formula yielded slightly biased (MPE% 6.5%) and imprecise (RMSE% 20.6%) results. These values are higher than those reported by Ghazal-Aswad et al. (MPE%−4.2%, RMSE% 11.5%) [4].

The formula of Ghazal-Aswad et al. was developed in a population of patients who received carboplatin as a single agent. In the present study, carboplatin was given in combination with other cytostatic agents. However, challenging the possible influence of coadministered agents is that unbiased and precise limited sampling models have already been proposed for unbound carboplatin administered in combination with other antitumour agents [15, 20, 21]. In addition, no pharmacokinetic interaction has yet been observed between paclitaxel and carboplatin [8, 14]. For reasons of comparison, we also evaluated the target carboplatin AUCs and corresponding measured AUCs (based on the precise original Calvert formula with the GFR measured by ^{51}Cr-EDTA clearance) as predicted by the formula of Ghazal-Aswad et al. in 24 patients in another study [12]. Applying the same statistical methodology used here to those data resulted in a negligible MPE% of 2.4%, but yielded a RMSE% of 23.3%.

Recently, another group has also validated the Ghazal-Aswad limited sampling strategy in 14 patients. In this study, a median bias of 2% with a relatively high median imprecision of 21% was found. A poor correlation of 24-h total platinum plasma concentration with ultrafilterable platinum AUC ($r^2 = 0.34$) was also found [15]. There are relatively low levels of free carboplatin 24 h after administration since at that time the free drug has either been excreted or is protein-bound. The rate of this binding reaction over 24 h is dependent on the free platinum plasma concentration, and is thus related to the AUC. The observed imprecision of the formula of Ghazal-Aswad et al. may be explained by the fact that it does not take into account the non-renal excretion of platinum, for example via varying total amounts of proteins or other potential sites with platinum-binding affinity which may significantly differ between patients. After 24 h, this component may be more important than renal excretion, which only determines the clearance of unbound platinum. Furthermore, in patients with impaired renal function, both mechanisms can play a role, yielding even higher carboplatin AUCs.

We conclude that the limited sampling model proposed by Ghazal-Aswad et al., although very easy and attractive to apply, is not accurate enough to predict the carboplatin AUC reached with the chemotherapy regimens studied and thus is not universally applicable. In addition, it requires that the patient has to stay overnight or has to return to the hospital to provide a 24-h sample. Several other limited sampling strategies with good performance for the estimation of the carboplatin AUC have been established [15, 20]. These models have previously proven to be precise in patients of group B [21]. Unfortunately, limited sampling strategies suffer from a lack of flexibility in sampling time and infusion duration. Bayesian-based dose individualization methods circumvent this problem, although these also require blood samples, knowledge of the population pharmacokinetic parameters, special equipment and trained personnel [3, 5]. In the meantime, limited sampling models may be of great value, but prospective validation in other patient populations than used for the model development must precede the use of the models in those patient groups.

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