Cancer Chemother Pharmacol (1993) 31: 324–327

Cancer Chemotherapy and Pharmacology

A limited sampling method for estimation of the carboplatin area under the curve*

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Received 9 August 1991/Accepted 7 September 1992

Summary. A limited sampling method for estimation of the carboplatin area under the curve (AUC) from one or two plasma concentration determination is presented. The model was conceived and developed using 43 pharmacokinetic studies in 15 patients with ovarian cancer (model data set) who received carboplatin in combination with cyclophosphamide. Linear regression analyses comparing the AUC and the drug concentration at a single time point (0.25–10 h after the end of the infusion) as calculated from the fitted exponential equations gave correlation coefficients as high as 0.97, with maximal correlations falling within the interval of 2–3.25 h. The model was validated prospectively in 9 patients with ovarian cancer (validation data set) who received the same treatment as did the model data set (21 pharmacokinetic studies), testing the equation $AUC = 0.52 \times C_{2.75\,h} + 0.92$. Observed and estimated AUCs were correlated in the validation data set ($r = 0.91$). The mean predictive error (MPE% ± SE) was $-4.4\% \pm 3.1\%$ and the root mean squared error (RMSE%) was 13.9%. Multiple regression analysis revealed that adding a second sample drawn at 0.25 h ($AUC = 0.053 \times C_{0.25\,h} + 0.401 \times C_{2.75\,h} + 0.628$) improved the MPE% to $-2.2\% \pm 2.1\%$ and the RMSE% to 9.4% ($r = 0.96$). We conclude that the carboplatin AUC can be estimated from a single plasma sample at 2.75 h or, more precisely, from two plasma samples at 0.25 and 2.75 h. The methods described may prove to be a handy tool for the calculation of approximate AUCs in trials of a size that would discourage detailed pharmacokinetic studies.

* This work was supported by grants from the Lundbeck Foundation and the Danish Cancer Society

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Introduction

Most cytostatic agents are characterized by a very narrow therapeutic margin, and their clinical application therefore obviously invites close therapeutic drug monitoring (TDM). TDM has demonstrated its usefulness with regard to improved therapy (increased effect and/or diminished side effects) in numerous drugs with narrow therapeutic indices, e.g., aminoglycosides, theophylline, digoxin, and lithium.

TDM has thus far played a minor role in clinical oncology, although it may offer important improvements in cytostatic treatment. A classic example of TDM in cancer chemotherapy is the pharmacokinetic monitoring in high-dose methotrexate treatment, whereby leucovorin is given until the methotrexate plasma concentration has fallen below a certain level [23]. This strategy has undoubtedly reduced the toxicity of the treatment. However, it remains to be fully established whether high-dose methotrexate treatment is superior to treatment with conventional doses.

Santini et al. [20] treated patients presenting with head and neck cancer with a combination of 5-fluorouracil (5-FU) and cisplatin. Their study indicates that 5-FU dose adjustments based on 5-FU plasma concentrations can improve the complete response rate and reduce the toxicity of 5-FU. Another example of pharmacokinetic monitoring has been reported from a phase I study of hexamethylene bisacetamide (HMBA) by Conley et al. [5]. These authors describe a method for adaptive control dosing of HMBA based on a relationship between the HMBA area under the plasma concentration versus time curve (AUC) and the percentage of change in the platelet count from the baseline value. Such detailed studies of pharmacokinetic and pharmacodynamic relationships are clearly important in the evaluation of new experimental drugs. For a number of older drugs that are routinely used in the clinical setting, pharmacokinetics and pharmacodynamic studies are also indicated, as the knowledge in this area is sparse.

A prerequisite for TDM is the existence of a relationship between pharmacokinetic parameters and clinical effect. Recent studies in cytostatics have demonstrated that

the AUC is the pharmacokinetic parameter that shows the best correlation with the pharmacodynamics of drugs [7, 8, 16].

The platinum analogue carboplatin has attracted considerable interest in recent years because it lacks the nephro- and neurotoxicity that are dose-limiting for cisplatin [3, 15]. On the other hand, carboplatin is myelotoxic, with thrombocytopenia being the most prominent side effect. It has been demonstrated that the carboplatin AUC is closely correlated with the thrombocytopenic effect of the drug [7, 22].

A study by Horwich et al. [12] has indicated that the antitumour effect of carboplatin in teratoma patients is related to the carboplatin AUC calculated as [(GFR + 25)/dose in milligrams], as the patients who experienced a relapse of their disease were those who had exhibited a carboplatin AUC of less than 4 mg min ml^{-1}. However, the exact relationship between the carboplatin AUC and the antitumor effect in different tumour types remains to be established, and investigation of this issue necessitates large-scale pharmacokinetic/pharmacodynamic studies. One major obstacle to such studies is the inconvenience and high cost involved in the exact measurement of AUC, which requires multiple blood sampling. A method for solving this problem would be a limited sampling strategy, which has been described for a few other cytostatic drugs [1, 9, 13, 14, 17–19]. The present study was undertaken to develop a limited sampling method for estimation of the carboplatin AUC.

Materials and methods

Sampling models. The sampling models were developed using 43 pharmacokinetic studies in 15 patients with ovarian cancer (model data set) who were treated with a combination of carboplatin and cyclophosphamide. Validation of the sampling strategies was undertaken in 9 patients with ovarian cancer (validation data set, 21 pharmacokinetic studies) who received the same treatment as given to the patients in the model data set.

Before each treatment, the glomerular filtration rate (GFR) was determined by [^{51}Cr]-ethylenediaminetetraacetic acid (EDTA) clearance [2]. The GFRs ranged between 49.3 and 119.8 ml/min (mean, 87.0 ml/min) in the model data set and between 65.1 and 111.3 ml/min (mean, 86.5 ml/min) in the validation data set.

Treatment plan. The patients, all of whom received 500 mg/m^2 cyclophosphamide, were randomized to one of three carboplatin dose levels: 250, 375, and 500 mg/m^2. Cyclophosphamide was diluted in 75 ml isotonic saline and given as a 15-min i.v. infusion. Carboplatin was diluted in 300 ml isotonic saline and infused over 1 h immediately after the cyclophosphamide infusion. The infusion rate was held constant by an IVAC infusion pump (model 281; IVAC Corporation, San Diego, Calif.). Treatment was repeated every 4 weeks for 4 months.

Blood sampling. Blood samples were collected in heparinized tubes at the following approximate time points after the carboplatin infusion: 0.05, 0.25, 0.75, 2.75, 3.75, 4.75, 6.75, 8.75, and 22 h.

Pharmacokinetic analysis. The carboplatin level in plasma ultrafiltrate was determined using the high-performance liquid chromatographic (HPLC) method described by Duncan et al. [6]. Intra- and inter-day coefficients of variation were determined to be 5.3% and 7.7%, respectively, at 10 μg/ml. The detection limit was 0.2 μg/ml, with the coefficient of variation being less than 25%.

Postinfusion carboplatin plasma concentration versus time curves were fitted by the computer program GraphPad Inplot (GraphPad Software, San Diego, Calif.) to a biexponential equation, assuming a two-compartment model for the distribution and elimination of carboplatin [10]:

$$C(t) = A' \times e^{-\alpha t} + B' \times e^{-\beta t},$$

where C is the concentration at time t, A' and B' are concentration constants, and α and β are rate constants. The AUC from the beginning of the carboplatin infusion to infinity was calculated using the following equation [11]:

$$AUC_{0-\infty} = \frac{A'T}{1 - \exp(-\alpha T)} + \frac{B'T}{1 - \exp(-\beta T)},$$

where T represents the infusion time. Fitted carboplatin concentrations at multiple time points were calculated using the following equation:

$$C(t) = A' \times e^{-\alpha t} + B' \times e^{-\beta t}.$$

Linear regression analyses were performed to find an optimal single sampling time, correlating the fitted carboplatin concentrations (0.05–10 h postinfusion) with the corresponding AUC.

To disclose whether the addition of another sampling time point would improve the model, multiple regression analyses (SOLO statistical system, version 3.1; BMDP Statistical Software Inc., Los Angeles, Calif.) were performed using the AUC as the dependent variable and fitted concentrations at different time points as the independent variables. The models created were validated on the validation data set. From the concentrations measured, an estimate of the AUC was calculated, and this was correlated with the AUC determined from the fitted curve. The precision of the model was assessed by the root mean squared error (RMSE%) and bias was assessed by the mean predictive error (MPE%) [21].

Results

Figure 1 depicts the regression coefficients obtained for the model data set of carboplatin concentration versus AUC at different time points. Maximal and essentially equivalent correlations were found between the fitted concentrations and the AUCs during the interval of 2–3.25 h after the infusion. An optimal single sampling time point would therefore lie somewhere within this interval. Figure 2 shows the regression lines constructed for the carboplatin AUC versus the carboplatin concentration at 2.0, 2.25, 2.5, 2.75, 3.0, and 3.25 h.

The estimated AUCs were calculated from the equation based on carboplatin concentrations measured at 2.75 h in the validation data set ($AUC = 0.52 \times C_{2.75\,h} + 0.92$; see Fig. 2). The estimated AUCs were correlated with the observed AUCs by linear regression analysis ($r = 0.91$, Fig. 3). The slope of the regression line did not differ significantly from unity. The bias of the model (MPE% ± SE) was $-4.4\% \pm 3.1\%$ and the precision (RMSE%) was 13.9%.

The multiple regression analysis of the carboplatin AUCs versus the plasma concentrations at different sampling time points in the model data set indicated that an additional plasma sample taken at 0.25 h postinfusion would improve the precision of the estimation of AUC. The optimal two-sample model was:

$$AUC = 0.053 \times C_{0.25\,h} + 0.401 \times C_{2.75\,h} + 0.628,$$

where $C_{0.25\,h}$ and $C_{2.75\,h}$ represent the carboplatin plasma concentrations at 0.25 and 2.75 h, respectively ($r = 0.98$).

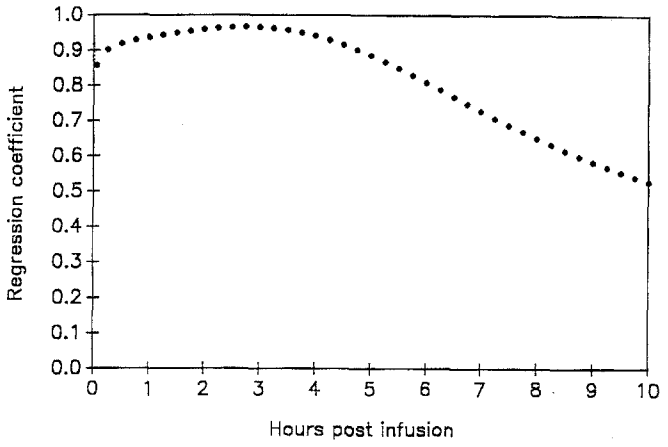

Fig. 1. Regression coefficients for the model data set at different time points

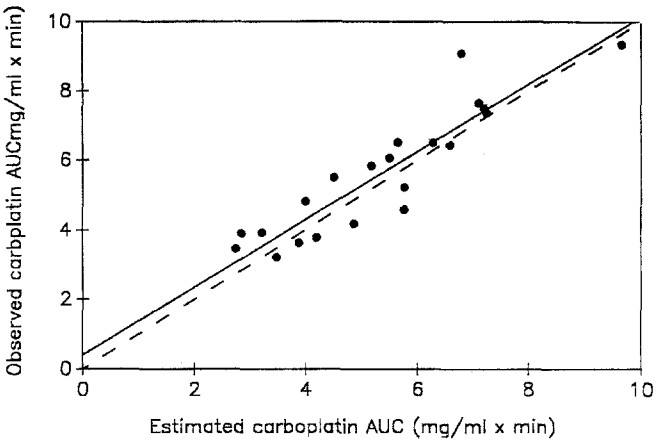

Fig. 3. Observed carboplatin AUCs versus AUCs estimated from one plasma sample (2.75 h). The line of unity (– – – –) and the linear regression line (———) are shown. The mean value ± SE for the slope is 0.95 ± 0.10, and that for the intercept is 0.56 ± 0.56 ($r = 0.91$)

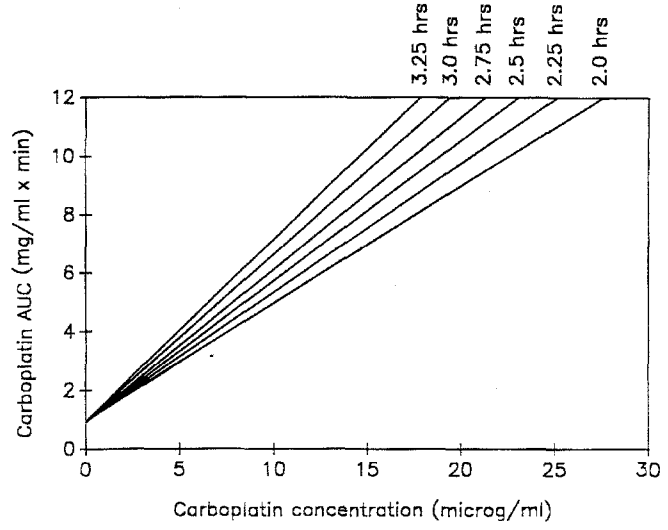

Fig. 2. Regression lines for carboplatin AUC versus carboplatin concentration at 2, 2.25, 2.5, 2.75, 3, and 3.25 h. 2 h, $y = 0.40x + 0.97$; 2.25 h, $y = 0.44x + 0.94$; 2.5 h, $y = 0.48x + 0.93$; 2.75 h, $y = 0.52x + 0.92$; 3 h, $y = 0.57x + 0.94$; 3.25 h, $y = 0.62x + 0.95$

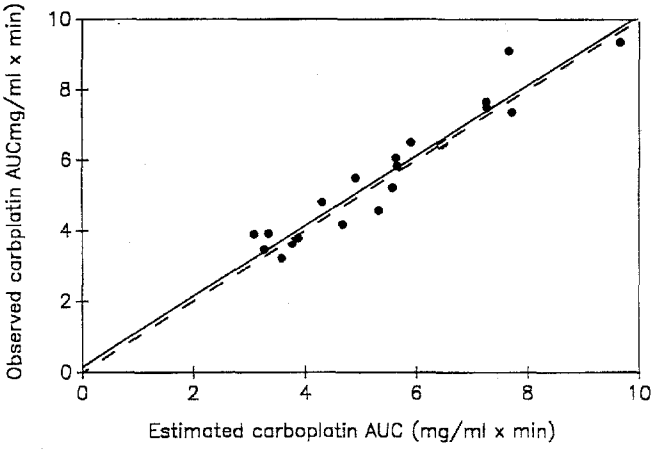

Fig. 4. Observed carboplatin AUCs versus AUCs estimated from two plasma samples (0.25 and 2.75 h). The line of unity (– – – –) and the linear regression line (———) are shown. The mean value ± SE for the slope is 0.99 ± 0.06, and that for the intercept is 0.19 ± 0.39 ($r = 0.96$)

From the concentrations measured at 0.25 and 2.75 h, an AUC estimate was calculated and correlated with the AUC determined from the multiple plasma sampling in the validation data set. The relationship between estimated and observed AUCs (Fig. 4) had a correlation coefficient of 0.96 and was unbiased (MPE% ± SE, –2.2% ± 2.1%) and precise (RMSE%, 9.4%).

Discussion

The results of the present study show that a single sample taken at 2.75 h postinfusion produces an acceptable estimate of the carboplatin AUC (RMSE%, 13.9%). The model data suggest that single sampling can be performed during the interval of 2–3.25 h, with the corresponding equation being chosen to calculate the AUC (Fig. 2). There is no doubt that the two-sample approach (RMSE%, 9.4%) is superior as regards the precision of estimation of the AUC (Figs. 3, 4). In large-scale studies, however, it can be difficult to obtain the number of plasma samples required for an optimal limited sampling method. Therefore, the single-sample approach is currently being used in a Danish multicenter study to evaluate the exposure-effect relationship in patients with ovarian cancer who are being randomized on the basis of two different target AUCs (4 and 8 mg min ml^{-1}) according to the dosage formula suggested by Calvert et al. [4].

Limited sampling strategies have been developed for a few other cytostatic agents [1, 9, 13, 14, 17–19]. In some of these strategies, the dose level as measured in milligrams per square meter of body surface area is included in the AUC estimate. To test whether this parameter would improve the validity of the method, we tried to include the dose in milligrams per square meter in the single- and two-sample models using multiple regression analysis. For the single-sample approach, the model improved slightly

(the correlation coefficient remained unchanged at 0.97 and the RMSE% decreased from 7.3% to 7.2%). On validation, however, the RMSE% increased from 13.9% to 16.7%, the correlation coefficient decreased from 0.91 to 0.89, and the MPE% remained unchanged. For the two-sample approach, the model as well as the validation deteriorated. In the model, the correlation coefficient remained unchanged at 0.98 and the RMSE% increased from 6.3% to 6.4%. In the validation, the correlation coefficient decreased from 0.96 to 0.94, the RMSE% increased from 9.4% to 12.1%, and the MPE% decreased slightly from –2.2% to –1.5%. We conclude that for carboplatin at the doses examined, the dose expressed in milligrams per square meter does not contribute significantly to estimation of the AUC using a limited sampling strategy. This finding is in accordance with the current knowledge about carboplatin [3], showing that carboplatin shows linear and dose-independent pharmacokinetics within the dose interval examined in the present study.

It is noteworthy that when fitted concentrations are used in the model development, model validation based on the concentrations actually measured is necessary before the model can be recommended for general use. This has been done in the present investigation and in one other study [19].

A prerequisite for the use of the present limited sampling methods is that the infusion time be 1 h and that the infusion rate be held constant. Furthermore, use of the model in chemotherapy regimens other than the one investigated in the current study should be made with caution, as the possibility of pharmacokinetic interactions between carboplatin and other cytostatic drugs cannot be excluded.

In carboplatin treatment there is a close relationship between drug exposure and myelotoxicity (thrombocytopenia) [7, 22]. The relationship between drug exposure and tumour response may be investigated using a limited sampling method for estimation of the carboplatin AUC, especially in studies involving larger patient populations, in which the multiple blood sampling required for accurate pharmacokinetic analysis is not feasible.

Acknowledgements. We wish to thank Prof. E. Steiness for helpful discussions during the study. Furthermore, we are grateful to laboratory assistants Ms. K. Busch, Ms. E. Hornemann, and Ms. H. Alfang Hansen for excellently performing the carboplatin analyses as well as to research nurse Ms. K. Østergaard Nielsen for her invaluable assistance during the study and for her careful nursing of the patients.

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