Multi-Institutional Validation Study of Carboplatin Dosing Formula Using Adjusted Serum Creatinine Level

Masahiko Ando, Hironobu Minami, Yuichi Ando, Hideo Saka, Shuzo Sakai, Masashi Yamamoto, Yasutsuna Sasaki, Kaoru Shimokata, and Yoshinori Hasegawa

Japanese Red Cross Nagoya First Hospital, Nagoya 453-8511 [M. A., S. S.]; National Nagoya Hospital, Nagoya 460-0001 [H. S.]; Nagoya Ekisaikai Hospital, Nagoya 454-8502 [M. Y.]; First Department of Internal Medicine [M. A., Y. A., Y. H.] and Clinical Preventive Services, Nagoya University School of Medicine, [K. S.], Nagoya 466-8550; and National Cancer Center Hospital East, Kashiwa 277-0882 [H. M., Y. S.], Japan

ABSTRACT

Creatinine clearance (Ccr) is widely used as a practical substitute for glomerular filtration rate (GFR) in the Calvert formula: carboplatin dose (mg) = target area under the concentration versus time curve (AUC, mg ml⁻¹ min) × [GFR (ml min⁻¹) + 25]. However, it causes systematic overdosing when the creatinine levels are measured by an enzymatic peroxidase-antiperoxidase method (PAP-Cr). We previously suggested an amended dosing formula to adjust this overdosing: carboplatin dose (mg) = AUC (mg ml⁻¹ min) × [adjusted Ccr (ml min⁻¹) + 25], where the Ccr was adjusted by adding 0.2 (mg dl⁻¹) to serum PAP-Cr. In this study, we prospectively validated this formula in 55 patients from six institutions. Target AUC ranged from 3 to 7 mg ml⁻¹ min, and Ccr was measured by 24-h urine collection. Estimation of carboplatin clearance with the amended formula was unbiased [mean prediction error (MPE) ± SE = 2.9 ± 3.4%] and acceptable precise [root mean squared error (RMSE) = 24.7%], whereas the Calvert formula using non-adjusted Ccr overpredicted carboplatin clearance systemat-ically by 24.7%, whereas the Calvert formula using non-adjusted Ccr overpredicted carboplatin clearance systematically (MPE ± SE = 24.9 ± 4.9% and RMSE = 36.1%). The improvement in the bias and precision of the estimation was seen in all of the participating institutions as shown by decrease in the absolute value of MPE and RMSE for each institution. The Chatelut formula also highly overestimated carboplatin clearance when PAP-Cr was used, but the adjustment of PAP-Cr yielded a decrease in MPE by 30.4% and in RMSE by 21.3%. These results confirmed the necessity of adjusting the serum PAP-Cr in carboplatin dosing formulas.

INTRODUCTION

Carboplatin, a second-generation platinum-containing compound, has proven activity against a range of malignancies and is much less nephrotoxic, neurotoxic, and emetogenic than its parent compound cisplatin (1). Thrombocytopenia is the major dose-limiting toxicity of carboplatin and is highly correlated with AUC [2], which is the ratio of dose:clearance. Carboplatin clearance depends on each patient’s renal function, and therefore individualized carboplatin dosing is generally determined using the following formula (the Calvert formula; Ref. 3):

Dose (mg) = Target AUC (mg ml⁻¹ min) × [GFR(ml min⁻¹) + 25] (A)

A measurement of GFR in this formula primarily requires the [³¹Cr]-EDTA method, which is not always available in every clinical center or hospital. Thus, the use of Ccr as a substitute for GFR in the formula is practical and is now widely accepted in clinical practice (4–6). However, creatinine is not an ideal filtration marker because it is both filtered by glomeruli and secreted by renal tubules (7–9). Accordingly, Ccr theoretically exceeds GFR by >12% in subjects with normal renal function (9). Two methods are available for measuring creatinine levels, a kinetic Jaffé method (7, 10) and an enzymatic PAP method (11, 12). The Jaffé method is known to cross-react with non-creatinine chromogens in serum and overestimate creatinine level by 5 to 15% in serum (7) but not in urine (13). As a result, the calculated Ccr can be accepted as a good approximation of GFR because this error coincidentally offsets the excess of Ccr over GFR (9, 14). In contrast, the new enzymatic PAP method is more specific and ensures better interlaboratory agreement than the Jaffé method (11, 12). Because the PAP method is not influenced by chromogens, the serum creatinine level is lower than that measured by the Jaffé method and the corresponding Ccr is increased close to its true value, which is higher than GFR (11, 12). Therefore, when serum creatinine level is measured by the PAP method, the Calvert formula using Ccr instead of GFR causes overestimation of carboplatin clearance, resulting in overdosing of the drug (15). The majority of clinical laboratories use the PAP method in Japan, whereas the Jaffé method has been widely accepted in the United States (16).

We previously found that the observed carboplatin clear-

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2 To whom requests for reprints should be addressed, at First Department of Internal Medicine, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. Phone: 81-52-744-1974; Fax: 81-52-744-2157; E-mail: yhasega@med.nagoya-u.ac.jp.

3 The abbreviations used are: AUC, area under the concentration versus time curve; GFR, glomerular filtration rate; Ccr, creatinine clearance; PAP, peroxidase-antiperoxidase; MPE, mean prediction error; RMSE, root mean squared error.
ance is, as expected, lower than that calculated by the Calvert formula in which 24-h urinary \( C_{cr} \) with the PAP method was directly substituted for GFR (17). To adjust this overdosing, we proposed an amended dosing formula in which the \( C_{cr} \) was adjusted by adding 0.2 (mg dl\(^{-1}\)) to the serum creatinine level measured by the PAP method in its calculation (18). On the contrary, investigators at another institution reported that the Calvert formula using 24-h urinary \( C_{cr} \), in which serum creatinine levels were determined with the PAP method, predicted carboplatin clearance well (19). We considered that it was necessary to investigate whether or not there is any variability among different institutions in the predictive accuracy of carboplatin dosing formulas.

In this study, we prospectively validated the adjusted carboplatin dosing formula using the serum creatinine level that had been measured by the PAP method and compared its predictive accuracy among institutions. Additionally, the effect of this adjustment of the serum creatinine levels measured by the PAP method was evaluated in the Chatelut formula (20) and the Cockcroft-Gault equation (21). The former formula directly predicts carboplatin clearance, and the latter equation estimates \( C_{cr} \) from the patient’s demographic characteristics. Both require a single sampling for serum creatinine measurement without urine collection and are frequently used for outpatient chemotherapy in clinic (22–24).

**PATIENTS AND METHODS**

Patients were eligible for entry if they met the following criteria: (a) diagnosis of solid tumors; (b) age, >20 years; (c) WHO performance status, 0–2; (d) no chemotherapy with antineoplastic agents within 4 weeks; and (e) adequate bone marrow function (WBC, >3,000/µl; platelet count, >100,000/µl). Patients who received cisplatin-containing chemotherapy within 12 weeks were ineligible because \( C_{cr} \) does not give satisfactory estimates of renal function during this period (25). This study was approved by the ethics committee at each institution, and written informed consent was obtained from all patients.

The participating institutions were National Cancer Center Hospital East (Kashiwa, Japan), and National Nagoya Hospital, Nagoya Ekisaikai Hospital, and Japanese Red Cross Nagoya First Hospital in Nagoya, Japan. Two other institutions participated in the study, but the data from these two were combined for analysis because of the small number of patients (a total of four patients). In all of the institutions, creatinine values were determined using the PAP method at their own laboratories (11, 12). The specific test kits were as follows: Serotec CRE-L kit (Serotec Co., Sapporo) at institution A, Kainos CRE-L kit (Kainos Co., Tokyo) at institutions B and D, and Wako CRE-L kit (Wako Junyaku Co., Osaka) at institution C. All of the kits are based on the enzyme catalytic sequence, where creatinase, creatinase, and sarcosine oxidase are coupled to convert creatinine to hydrogen peroxide, which is colorimetrically detectable. The different quinone dye was measured in the colorimetric assay among the kits. Carboplatin was given by 1-h infusion as a monotherapy or in combination with other antineoplastic agents. The target AUC of carboplatin was 7 mg ml\(^{-1}\) min with the monotherapy and 3 to 6 mg ml\(^{-1}\) min with the combination therapy. The dose of carboplatin was determined using the formula (18):

\[
\text{Dose (mg)} = \frac{\text{Target } AUC (\text{mg } \text{ml}^{-1} \text{ min}) \times [\text{adjusted } C_{cr} (\text{ml min}^{-1}) + 25]}{B}
\]

Adjusted \( C_{cr} = C_{cr} \)

\[
\times \frac{\text{Serum creatinine (mg dl}^{-1}\text{)}}{\text{Serum creatinine (mg dl}^{-1}\text{)} + 0.2(\text{mg dl}^{-1})}
\]

\( C_{cr} \) was measured by 24-h urine collection. We used only the data from >800 ml/day of urine to obtain an accurate estimation of \( C_{cr} \). The average of two measurements, which were obtained on separate days within a week, was used for dosing.

\[
\text{Observed } C_{cr} (\text{ml min}^{-1}) = \frac{\text{Urine volume (ml min}^{-1}) \times \text{urine creatinine (mg dl}^{-1})}{\text{Serum creatinine (mg dl}^{-1})}
\]

A pharmacokinetic study was performed during the first cycle of the chemotherapy. Heparinized blood samples were obtained at the end of infusion and at 0.25, 0.5, 1, 2, 4, 8, and 24 h after the end of infusion. The plasma was immediately separated by centrifugation. Ultrafiltrate of plasma was obtained using Amicon MPS micropartition system with YMT membranes (Grace Japan KK, Amicon, Tokyo) and stored at -20°C until analysis. The ultrafiltered platinum level was measured by flameless atomic absorption spectrometry (26). The lower limit of measurement was 25 ng ml\(^{-1}\). The intra- and interassay coefficient of variation was 2.6 and 4.1%, respectively. The carboplatin level was calculated on the basis of the molar ratio of platinum:carboplatin.

The observed AUC of carboplatin was calculated using the trapezoidal method with extrapolation to infinity, using WINNONLIN version 1.1 software (Scientific Consulting Inc., Apex, NC), and the observed clearance was calculated as follows:

\[
\text{Observed carboplatin clearance (ml min}^{-1}) = \frac{\text{Dose (mg)}}{\text{Observed } AUC (\text{mg } \text{ml}^{-1} \text{ min})}
\]

The observed clearance was compared with the estimated clearance, which was calculated as follows: estimated clearance (ml min\(^{-1}\)) = adjusted \( C_{cr} \) (ml min\(^{-1}\)) + 25. Furthermore, estimations of clearance by the various methods were evaluated for their accuracy, which were calculated using the following formulas: (a) \( C_{cr} + 25 \) (the Calvert formula using nonadjusted \( C_{cr} \); (b) the Calvert formula using the Cockcroft-Gault equation; (c) the Calvert formula using the Cockcroft-Gault equation with the adjustment of serum creatinine by adding 0.2 mg dl\(^{-1}\); (d) the Chatelut formula; and (e) the Chatelut formula with adjustment of serum creatinine by adding 0.2 mg dl\(^{-1}\). The Cockcroft-Gault equation was used to estimate \( C_{cr} \) as follows (21):

\[
\frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times (1 - 0.15 \times \text{gender})}{72 \times \text{serum creatinine (mg dl}^{-1})}
\]
The Chatelut formula was as follows (20):

\[
\text{Carboplatin clearance (ml min}^{-1}\text{)} = 0.134 \times \text{weight (kg)}
\]  
\[
+ \frac{218 \times \text{weight (kg)} \times [1 - 0.00457 \times \text{age (years)}]}{88.5 \times \text{serum creatinine (mg dl}^{-1}\text{)}} \times (1 - 0.314 \times \text{gender})
\]

where gender = 0 for male and 1 for female subjects.

The accuracy of the estimation was evaluated with MPE ± SE and RMSE (27).

\[
MPE = \frac{1}{n} \sum \left( \frac{\text{estimated clearance} - \text{observed clearance}}{\text{observed clearance}} \times 100 \right) \%
\]

\[
\text{RMSE} = \sqrt{\frac{1}{n} \sum \left( \frac{\text{estimated clearance} - \text{observed clearance}}{\text{observed clearance}} \times 100 \right)^2} \%
\]

The MPE and its 95% confidence interval was calculated for the overall population and for each institution separately. Whether the adjustment of the serum creatinine level improved the estimation of the carboplatin clearance was analyzed using Wilcoxon signed-rank test. An ANOVA was used to analyze the difference in the MPE among institutions. An analysis of covariance was used to evaluate the interinstitutional difference in the MPE taking age, gender, body weight, history of previous chemotherapy, adjusted Ccr, percentage range of the values of adjusted Ccr derived from the two measurements, and time interval between the two measurements into consideration. Demographic and biological characteristics of patients were compared among the institutions by the \(\chi^2\) test or Kruskal-Wallis test. Statistical analyses were performed by SAS version 6.12 software (SAS Institute Inc., Cary, NC).

RESULTS

Fifty-five patients from the six institutions were entered into the study (Table 1). The demographic characteristics of patients were similar among the institutions except for age (\(P = 0.030\)), the value of adjusted Ccr (\(P = 0.006\)), time interval between the two measurements of adjusted Ccr (\(P = 0.015\)), and the previous chemotherapy (\(P = 0.001\)). A total of five patients had received cisplatin-containing chemotherapy before entry into this study, with no difference in the distribution among institutions. The percentage range of the two measurements of adjusted Ccr was <25% in 48 of the 55 patients. No association was observed between the time interval and the percentage range between the measurements (\(r = 0.150\); \(P = 0.274\)).

The Calvert formula with nonadjusted Ccr used as a substitute for GFR overestimated the carboplatin clearance as shown by 24.9% of MPE. This was improved to 2.9% by adjusting the serum creatinine level by adding 0.2 mg dl\(^{-1}\) (\(P < 0.001\)). The adjustment of the serum creatinine level also im-

<table>
<thead>
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<th>Characteristics</th>
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<tr>
<td>Gender</td>
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<tr>
<td>Female/Male</td>
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<tr>
<td>Age (yr)</td>
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<td>Serum creatinine (mg dl(^{-1}))</td>
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<td>Adjusted creatinine clearance (ml min(^{-1}))</td>
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<tr>
<td>Interval between the two measurements of adjusted Ccr (days)</td>
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<tr>
<td>Weight (kg)</td>
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<td>Body surface area (m(^2))</td>
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<td>Previous chemotherapy</td>
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</table>

Table 1 Demographic characteristics of patients according to institution

The accuracy of the estimation was evaluated with MPE ± SE and RMSE (27).

\[
MPE = \frac{1}{n} \sum \left( \frac{\text{estimated clearance} - \text{observed clearance}}{\text{observed clearance}} \times 100 \right) \%
\]

\[
\text{RMSE} = \sqrt{\frac{1}{n} \sum \left( \frac{\text{estimated clearance} - \text{observed clearance}}{\text{observed clearance}} \times 100 \right)^2} \%
\]

The MPE and its 95% confidence interval was calculated for the overall population and for each institution separately. Whether the adjustment of the serum creatinine level improved the estimation of the carboplatin clearance was analyzed using Wilcoxon signed-rank test. An ANOVA was used to analyze the difference in the MPE among institutions. An analysis of covariance was used to evaluate the interinstitutional difference in the MPE taking age, gender, body weight, history of previous chemotherapy, adjusted Ccr, percentage range of the values of adjusted Ccr derived from the two measurements, and time interval between the two measurements into consideration. Demographic and biological characteristics of patients were compared among the institutions by the \(\chi^2\) test or Kruskal-Wallis test. Statistical analyses were performed by SAS version 6.12 software (SAS Institute Inc., Cary, NC).
proven the precision in the estimation of carboplatin clearance ($P = 0.003$), so that the prediction of carboplatin clearance with the amended formula based on adjusted Ccr was unbiased and acceptably precise (Table 2 and Fig. 1). The improvement in the estimation of carboplatin clearance was seen in every participating institution; the absolute value of MPE was decreased by a median of 11.8% (range, 0.1–26.3%) and RMSE decreased by 6.1% (1.7–22.1%; Fig. 2). The difference in the MPE was significant among the institutions ($P = 0.031$ with and $P = 0.009$ without the adjustment (Figs. 2, A and B, respectively)).

The interinstitutional difference remained significant in the analysis of covariance (Table 3), with a significant overestimation of carboplatin clearance by 17% in the patients treated at institution B ($P = 0.025$). The differences in age, adjusted Ccr, the time interval between the two Ccr measurements, and the previous chemotherapy did not explain the interinstitutional difference in the MPE. The interinstitutional difference in the MPE did not change after the exclusion of the seven patients whose percentage range of adjusted Ccr exceeded 25% ($P = 0.031$).

The Chatelut formula also highly overestimated carboplatin clearance when the serum creatinine level measured by the PAP method was used in its calculation, and the adjustment by adding 0.2 mg dl$^{-1}$ to the serum creatinine level decreased MPE and RMSE by 30.4 and 21.3%, respectively (Table 2). Similar results were obtained when the Cockcroft-Gault equation was used in the Calvert formula; the bias became nonsignificant after the adjustment of the serum creatinine level, with an improvement in RMSE by 3.8%.

**DISCUSSION**

We proved that the formula using Ccr calculated with the creatinine level measured by the PAP method and adjusted by adding 0.2 mg dl$^{-1}$ was reliable for carboplatin dosing in this multi-institutional prospective evaluation. The amended formula successfully corrected the systematic overestimation of carboplatin clearance by the Calvert formula using nonadjusted Ccr with the PAP method, so that the estimated carboplatin clearance by this formula was unbiased and acceptably precise. The improvement in the bias and precision of the estimation was discernible throughout the participating institutions as shown by the reduction in the absolute value of MPE and RMSE in every institution. These results reinforce the usefulness of this carboplatin dosing formula and suggest its high acceptability in clinical practice. It remains to be studied whether more precise individualized dosing in carboplatin chemotherapy should improve the therapeutic outcome of the drug.

This is the first study evaluating interinstitutional variability in the validity of the estimated carboplatin clearance by uniform dosing formula using serum creatinine levels measured by the PAP method. In the analysis of covariance, we found a significant overestimation in the patients treated at institution B. The demographic and biological characteristics of the patients treated at this institution were comparable with those in the other institutions. We had evaluated an interinstitutional variability in measuring creatinine levels by assaying identical serum samples of three different concentrations among institutions B, C, and D. Each sample was measured in triplicate, and we confirmed that there was no difference in measured creatinine values among institutions. In the present study, the analysis of covariance also found a significant difference in the MPE of carboplatin clearance between institutions B and D, where the same kit for creatinine measurement was used ($P = 0.048$). Therefore, we consider that the interinstitutional variability in prediction of carboplatin clearance should not be caused by the difference in the method of creatinine measurement.

Several pharmacokinetic studies have reported controversial results about the predictive accuracy of the Calvert formula using 24-h urinary Ccr (6, 19, 28). Some studies that underestimated the carboplatin clearance provided little explanation about the completeness of urine collection and the method of creatinine measurement (6, 28). Inadequate urine collections would cause underestimation of carboplatin clearance. Other investigators in Japan recently observed a good concordance of carboplatin clearance with the corresponding predicted value in their study (19). We consider that the discrepancy between our result and ours might be caused by a low dose (25 mg m$^{-2}$) of carboplatin in about half of their patients and by some technical problems concerning the pharmacokinetic study, especially a lack of sampling shortly after the infusion in their study. Indeed, their concentration versus time data were fitted to a monoeponential curve, leading to underestimation of AUC, whereas the pharmacokinetics of carboplatin are usually fitted well by a two-compartment model (29). In addition, the possibility of inadequate urine collections cannot be ruled out.

The Chatelut formula overpredicted carboplatin clearance when serum creatinine levels measured by the PAP method were used in the calculation. The Ektachem method was used for serum creatinine measurement in developing the formula, which generally gives higher values than those measured by the PAP method (30, 31). The difference in the method of creatinine measurement, therefore, explains the overestimation of carboplatin clearance by the Chatelut formula with the PAP method (32). The present study showed that the adjustment of the serum creatinine value is reasonable for the Chatelut formula. In other studies, the Chatelut formula using the serum creatinine value measured by the Jaffé method predicted carboplatin clearance acceptably (24, 33). These observations were consistent with our results. The adjustment of serum creatinine also improved the predictive accuracy of the Calvert formula in which Ccr, as a substitute for GFR, was calculated using the Cockcroft-Gault equation. Considering that the Cockcroft-Gault equation was originally developed using serum creatinine measured by the

<table>
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<th>Estimated carboplatin clearance</th>
<th>MPE ± SE (%)</th>
<th>RMSE (%)</th>
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<tr>
<td>Ccr$_{adj}^a$ + 25</td>
<td>24.9 ± 4.9</td>
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<tr>
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<td>Chatelut formula</td>
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<td>Chatelut formula using adjusted serum creatinine</td>
<td>8.9 ± 4.0</td>
<td>29.6</td>
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<tr>
<td>Ccr$_{CG}^a$ + 25</td>
<td>13.4 ± 3.7</td>
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<tr>
<td>Adjusted Ccr$_{CG}^b$ + 25</td>
<td>−6.4 ± 3.3</td>
<td>23.5</td>
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$^a$ Ccr$_{adj}$ creatinine clearance based on 24-h urine collection.

$^b$ Ccr$_{CG}$ creatinine clearance calculated from the Cockcroft-Gault equation.
Jaffe’s method, it is reasonable to use the adjusted serum creatinine in the Cockcroft-Gault equation (21, 34).

We calculated the AUC of carboplatin on the basis of the trapezoidal method in this analysis because the method was used in the development of the original Calvert formula (3). Because the trapezoidal method may overestimate the AUC after the end of the infusion, we also calculated the AUC using the log-trapezoidal method. Overall, the MPE was improved from $19.4^{\pm}4.3\%$ without the adjustment to $21.7^{\pm}6.3\%$ with the adjustment, suggesting the robustness of our conclusion.

We confirmed the necessity of adjusting Ccr by adding 0.2 mg dl$^{-1}$ to the serum creatinine level when Ccr was used as a surrogate for GFR in the Calvert formula. This is true whether Ccr is measured by collecting 24-h urine or estimated by the Cockcroft-Gault equation. Likewise, when the PAP method is used for creatinine measurement in the Chatelut formula, the adjusted serum creatinine level should be used to avoid overdosing of carboplatin.

Considering moderate interinstitutional variability in predicting carboplatin clearance, preliminary pharmacokinetic examinations at each institution should be useful to evaluate the predictive accuracy of carboplatin dosing formulas before they are applied to clinical use.

**REFERENCES**


**Table 3**

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$^a$ F, variance ratio.
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