The platinum compound carboplatin is used in the treatment of several malignancies, often in combination chemotherapy regimens (1). Carboplatin is mainly eliminated by the kidneys. In patients with normal renal function, between 60% and 70% of an administered carboplatin dose is excreted into the urine within the first 24 hours of administration. The remainder of the drug binds irreversibly to proteins and tissue (1, 2). The free, ultrafilterable carboplatin fraction is considered pharmacologically active (3).

The use of carboplatin is mainly limited by myelosuppression. Carboplatin exposure, expressed as area under the plasma concentration versus time curve (AUC), has been related both concentration-time data of ultrafilterable platinum of 178 patients (280 courses, 3,119 samples) with different types of cancer receiving carboplatin-based chemotherapy in conventional and high doses were available. Data were described with a linear two-compartment population pharmacokinetic model. Relations between SCR-based formulae for estimating renal function and carboplatin clearance were investigated.

**Abstract**

**Purpose:** The Calvert formula is a widely applied algorithm for the a priori dosing of carboplatin based on patients glomerular filtration rate (GFR) as accurately measured using the $^{51}$Cr-EDTA clearance. Substitution of the GFR in this formula by an estimate of creatinine clearance or GFR as calculated by formulae using serum creatinine ($S_{CR}$; Cockcroft-Gault, Jelliffe, and Wright) is, however, routine clinical practice in many hospitals. The goal of this study was to validate this practice retrospectively in a large heterogeneous adult patient population.

**Conclusions:** Our data do not support the application of modifications of the Calvert formula by estimating GFR from $S_{CR}$ in the a priori dosing of carboplatin in patients with relatively normal renal function (creatinine clearance, 350 mL/min). For targeted carboplatin exposures, the original Calvert formula, measuring GFR using the $^{51}$Cr-EDTA clearance, remains the method of choice. Alternatively, in patients with normal renal function, a flat dose based on the mean population carboplatin clearance should be administered.

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**Grant support:** Dutch Cancer Society project NKI 2001-2420, 2005-3418. The Calvert formula, measuring GFR using the $^{51}$Cr-EDTA clearance, remains the method of choice.

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or the Jelliffe formula (18). These formulae are based on measured serum creatinine (SCR) in μmol/L, age in years, gender (1 if female, 0 if male), and BSA in m² or weight in kg.

Cockcroft-Gault (17):

\[
\text{Cl}_{\text{Cr}} = \frac{(140 - \text{Age}) \times \text{Weight} \times 1.23 \times (1 - 0.15 \times \text{Gender})}{\text{SCR} \times 0.742}
\]

Jelliffe (18):

\[
\text{Cl}_{\text{Cr}} = \frac{[98 - 0.8 \times (\text{Age} - 20)] \times (1 - 0.1 \times \text{Gender}) \times \text{BSA}}{\text{SCR} \times 0.0113}
\]

Recently, Wright et al. (19) developed a method for estimating GFR based on the same variables.

Wright (19):

\[
\text{GFR} = \frac{(6.580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Gender})}{\text{SCR}}
\]

To evaluate the dosing accuracy of the Calvert formula using the above described substitutions of the GFR and to define patient characteristics influencing carboplatin pharmacokinetics, we did a large population pharmacokinetic study. We pooled pharmacokinetic data of carboplatin obtained from several studies, including both conventional as well as high-dose chemotherapy regimens. The intention was to use as much data available of many different populations with various types of cancer treated with different schedules of carboplatin. The performance of a formula calculating carboplatin clearance

<table>
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<tr>
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<th>Number</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
</tr>
<tr>
<td>Age (y)</td>
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<tr>
<td>BSA (m²)</td>
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<tr>
<td>Weight (kg)</td>
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<td>46-170</td>
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<tr>
<td>Length (cm)</td>
<td>171</td>
<td>153-210</td>
<td></td>
</tr>
</tbody>
</table>

Protocol

Non-small cell lung cancer (20)
- 2-6 × PC (dose carboplatin AUC = 6 mg/mL min administered in 30 min)
- 6-10 plasma samples per patient per course
- t = 0.5, 4.5, 8.5, and 23.5 h

Non-small cell lung cancer (21, 22)
- PC (dose carboplatin 300-400 mg/m²/30 min)
- 6-10 plasma samples per patient per course
- t = 0.5, 1.5, 2.5, 4.5, 8.5, 12.5, 24.5, and 48.5 h

Ovarian (21, 23)
- PC (dose carboplatin 300-600 mg/m²/30 min)
- 8-12 plasma samples per patient per course
- t = 0.5, 1.5, 2.5, 4.5, 8.5, 12.5, 24.5, and 48.5 h

High-risk primary breast cancer (6)
- CTC* (dose carboplatin 400 mg/m²/d or AUC 20 mg/mL min administered in 1 h for 4 d)
- 15-20 plasma samples per patient per course
- t = 0.5, 1.5, 2.5, 4.5, 8.5, 12.5, 24.5, and 48.5 h
- Days 1 and 3

Metastatic breast cancer (ref. 6, and 17 pat’s added)
- tCTC (dose carboplatin 267 mg/m²/d or AUC 13.3 mg/mL min administered in 1 h for 4 d)
- 15-20 plasma samples per patient per course
- t = 0.5, 1.5, 2.5, 3.75, 5.5, 10, and 24 h
- Days 1 and 3

Refractory germ cell cancer (ref. 6, and 8 pat’s added)
- CTC (dose carboplatin 400 mg/m²/d or AUC 20 mg/mL min administered in 1 h for 4 d)
- 15-20 plasma samples per patient per course
- t = 0.5, 1.5, 2.5, 3.75, 5.5, 10, and 24 h
- Days 1 and 3

Refractory germ cell cancer (ref. 6, and 3 pat’s added)
- tCTC (dose carboplatin 267 mg/m²/d or AUC 13.3 mg/mL min administered in 1 h for 4 d)
- 15-20 plasma samples per patient per course
- t = 0.5, 1.5, 2.5, 3.75, 5.5, 10, and 24 h
- Days 1 and 3

Metastatic ovarian cancer (6)
- tCTC (dose carboplatin 267 mg/m²/d or AUC 13.3 mg/mL min administered in 1 h for 4 d)
- 15-20 plasma samples per patient per course
- t = 0.5, 1.5, 2.5, 3.75, 5.5, 10, and 24 h
- Days 1 and 3

Biochemical variables

| Serum creatinine (μmol/L) | 51     | 18-124 |
| ClCR [calculated with the Cockcroft-Gault formula (mL/min; ref. 17)] | 141    | 55-451 |
| Albumin (g/L)             | 40     | 18-52  |

Abbreviation: PC, paclitaxel and carboplatin.
*CTC, high-dose cyclophosphamide (1-hour infusion), carboplatin (1-hour infusion), and thiotepa (2× 0.5-hour infusion) everyday during 4 days.
Materials and Methods

Patients. Pharmacokinetic data of ultrafilterable platinum were used as obtained in several previously published studies in which patients received carboplatin both in high-dose as well as in conventional-dose regimens in combination with other chemotherapeutic agents (6, 20–23). Data were available of 178 patients (280 courses) of carboplatin (in total 3,119 samples). Of all patients in the data set, baseline patient characteristics and biochemical variables were available as summarized in Table 1. All protocols were approved by the Committee of Medical Ethics of the Netherlands Cancer Institute, and written informed consent was obtained from all patients.

Pretreatment SCR levels were estimated by the kinetic Jaffe method (Hitachi systems, Roche Diagnostics, Almere, the Netherlands) in three (24). Therefore, the noncompensated SCR values in our data set were retroactively adjusted by subtracting 26 \mu mol/L from the initial values.

Sampling and analyses. In all studies, the ultrafilterable plasma fraction was prepared immediately after blood sampling using the Amicon micropartition system with a YM-14 membrane (30 kDa; Millipore Corp., Bedford, MA). A volume of 0.5 mL plasma was transferred in the micropartition system and centrifuged at 2,500 \times g for 20 minutes. Ultrafiltrate was stored at −20°C until analyses. Analyses of platinum in ultrafiltrate were done using flameless atomic absorption spectrometry as described previously (25).Accuracy and day-to-day precision of this method were 93.9% to 103.3% and 1.5% to 10.2%, respectively. The number and time points of samples withdrawn in each study protocol are depicted in Table 1.

Population pharmacokinetics. A population pharmacokinetic model of carboplatin (measured as free platinum) was developed using the nonlinear mixed effect modeling program NONMEM (version V 1.1; Globomax LLC, Hanover, MD; ref. 26). The first-order conditional estimate method with INTERACTION was used after log transformation of the data (27).

Both interindividual variability (IV) and interoccasion variability (IOV) were modeled with an exponential function. For example, variability in clearance Cl was estimated using the following: $Cl_{ij} = Cl_{pop} \times exp(\eta_i + \kappa_j)$, where $Cl_{ij}$ represents Cl of the $i^{th}$ individual on the $j^{th}$ occasion, $Cl_{pop}$ is the population value of Cl, $\eta$ is the interindividual random effect with mean 0 and variance $\sigma^2$, and $\kappa$ is the interoccasion random effect with mean 0 and variance $\tau^2$ (28).

The difference between observed concentrations and their respective predictions resulting from measurement error and model misspecification (i.e., the residual or unexplained variability) was modeled with an exponential error model: $\ln(C_{obs\ j}) = \ln(C_{pred\ j}) + \epsilon_{ij}$ where $\epsilon_{ij}$ is the residual error with mean 0 and variance $\sigma^e$, representing the difference between the natural logarithm of the $j^{th}$ observed concentration in the $i^{th}$ individual $[\ln(C_{obs\ ij})]$ and its respective prediction $[\ln(C_{pred\ ij})]$.

Four different models describing the possible relation between carboplatin clearance and SCR were tested:

1. $Cl_{pop} = \theta(1)$
2. $Cl_{pop} = GFR + 25$
3. $Cl_{pop} = GFR + \theta(1)$
4. $Cl_{pop} = \theta(1) + (140 - age) \times \theta(2) \times weight \times \theta(3) /SCR$

(in which GFR was calculated using the Wright formula or replaced by ClCR using the Cockcroft-Gault and the Jelliffe formula).

In model 1, no relation between SCR and carboplatin clearance was assumed and this model was used as reference for the other models. Model 2 is the regularly applied Calvert formula in which the GFR is approximated by different SCR-based formulae. In model 3, the variable from the Calvert formula was reestimated on our data set. Model 4 was used to further analyze the possible relation between SCR, determinants of SCR (i.e., age, gender, and body size), and carboplatin pharmacokinetics in our data set. In this model, some of the variables of the Cockcroft-Gault formula were reestimated. This model was used to test whether any relation between SCR and carboplatin clearance existed in our data set after compensation for known determinants of creatinine production (age, body size, and gender).

Estimated values of ClCR >150 mL/min based on the different formulae used are physiologically unlikely. Therefore, we tested the unadjusted ClCR as covariate but also values >150 mL/min and >250 mL/min truncated to these values (29). We also tested for possible other determinants of carboplatin pharmacokinetics in our data set as...
pretreatment regimen (cisplatin- or noncisplatin-containing regimen), study protocol, and the administration of multiple doses. A covariate was considered significantly associated with the pharmacokinetic variable of interest when the objective function value (OFV) decreased >7.8 (P < 0.005).

Results

Data were best described with a two-compartment model estimating first-order elimination (Cl), volume of distribution (Vd), and the distribution rate constants $k_{12}$ and $k_{21}$. IIV was estimated for Cl, Vd, $k_{12}$, and $k_{21}$, whereas IOV was estimated for Cl and $k_{12}$.

The observed carboplatin concentration was accurately predicted by the model (Fig. 1). Furthermore, the weighted residuals did not vary according to the predicted concentration or time (Figs. 2 and 3), indicating that the model accurately described the data. Covariance between Cl and Vd was estimated. Population pharmacokinetic variables obtained from the total carboplatin data set are summarized in Table 2.

Of the four models tested, model 1 in which no relation between SCR and carboplatin clearance was assumed showed a better fit than models 2 and 3 (the original Calvert formula in which GFR is estimated by SCR-based formulae and a model in which the variable of the Calvert formula was reestimated on our data set; Table 3). Model 4 (the Calvert formula with GFR estimated by the Cockcroft-Gault formula and all variables reestimated on our data set) showed a significant improvement of fit (ΔOFV = -24.6; df, 2; P < 0.001). This model yielded the following equation:

$$\text{Cl}_{\text{carb}}(\text{mL/min}) = 115.5 + 0.212 \times (140 - \text{age}) \times \frac{\text{weight}}{0.73\text{gender}/S_{\text{CR}}}$$

whereas the original Calvert formula (using Cockcroft-Gault to calculate $\text{Cl}_{\text{CR}}$) was

$$\text{Cl}_{\text{carb}}(\text{mL/min}) = 25 + 1.23 \times (140 - \text{age}) \times \frac{\text{weight}}{0.85\text{gender}/S_{\text{CR}}}$$

This shows that, in the reestimated equation, the intercept is 4.6 times higher and the slope is six times smaller than in the Calvert formula (using Cockcroft-Gault to calculate $\text{Cl}_{\text{CR}}$), indicating that the relation between carboplatin pharmacokinetics and $S_{\text{CR}}$ and determinants of $S_{\text{CR}}$ is much weaker than suggested by substituting the Cockcroft-Gault estimate of $\text{Cl}_{\text{CR}}$ in the original Calvert formula. This is also shown in Fig. 4A-C.

No differences in pharmacokinetics could be shown between the different study protocols and treatment regimens. A total of 16 patients with refractory germ cell cancer (35 courses) had received cisplatin pretreatment of daily 20 mg/m$^2$ cisplatin during 5 days for four courses (6). In addition, one patient with metastatic ovarian cancer (6) had been pretreated with cisplatin. Pretreatment with platinum-based therapy, however, had no significant effect on carboplatin clearance. In addition, no difference in carboplatin clearance was found after multiple courses of carboplatin. Evaluation of relations between pretreatment regimen, protocol and multiple courses, and pharmacokinetic variables using a univariate procedure did not result in a significant correlation.

Figure 4A-C shows that the expected relation between carboplatin clearance and $\text{Cl}_{\text{CR}}$ (as calculated using the Cockcroft-Gault or the Jelliffe formula) or GFR (as calculated using the Wright formula) using truncation to 250 mL/min was not significant. Similar results were obtained when the upper limits were not truncated or truncated to 150 mL/min. In addition, no relation was found between carboplatin clearance and SCR (Fig. 5) not even when only the patients with physiologic values of $\text{Cl}_{\text{CR}}$ were included in the analyses. The performance of the Chatelut formula in predicting carboplatin clearance in our population was also poor as shown in Fig. 6.

Table 2. Population pharmacokinetic variables of carboplatin using the full data set

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (% RSE)</th>
<th>IIV, % (% RSE)</th>
<th>IOV, % (% RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (L/h)</td>
<td>8.33 (1.66)</td>
<td>19.1 (19.3)</td>
<td>9.52 (20.1)</td>
</tr>
<tr>
<td>Volume of distribution (L)</td>
<td>16.3 (2.18)</td>
<td>17.0 (17.0)</td>
<td>ND</td>
</tr>
<tr>
<td>Distribution microconstant $k_{12}$ (h$^{-1}$)</td>
<td>0.104 (10.0)</td>
<td>37.8 (45.5)</td>
<td>33.8 (38.2)</td>
</tr>
<tr>
<td>Distribution microconstant $k_{21}$ (h$^{-1}$)</td>
<td>0.171 (8.42)</td>
<td>49.2 (35.6)</td>
<td>ND</td>
</tr>
<tr>
<td>Correlation coefficient ($\rho$) of Cl and Vd</td>
<td>0.594</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariance of Cl and Vd</td>
<td>0.0193 (23.5)</td>
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<td></td>
</tr>
<tr>
<td>Proportional residual error (%)</td>
<td>21.8 (5.00)</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: RSE, relative SE of estimate; ND, not determined.
These results question the value of the variables SCR, weight, BSA, gender, and age in predicting individual pharmacokinetics of carboplatin in our population. Carboplatin dosing formulae based on these patient characteristics are thus not predictable of carboplatin exposure in this population.

### Discussion

In our study, no significant relation between carboplatin pharmacokinetics and patient characteristics could be detected with a population pharmacokinetic analysis in a large patient population. Because carboplatin dosing based on patients’ SCR, age, gender, weight, and height is widely applied in clinical oncology, the accuracy of this practice should be questioned.

The predominant determinant of carboplatin clearance is the GFR. It has been shown that, when GFR was estimated using radioisotopes, a strong relation with carboplatin clearance exists (12). However, these methods are expensive, inconvenient, and not universally available. ClCR is widely accepted as a simple measure of GFR, although it systematically overestimates GFR because creatinine is not solely filtered by the glomerulus but is also secreted by the proximal tubule. ClCR can be measured by collection of timed urine, which is also labor intensive and often prone to error. Therefore, simple formulae have been introduced to estimate ClCR based on SCR, age, gender, weight, and length (17, 18). It has, however, also been shown that SCR as used in these formulae, is a poor indicator of glomerular function and, thus, carboplatin clearance. It is an insensitive measure of early glomerular impairment and is also dependent on nonrenal factors, especially creatinine production, which itself is dependent on muscle mass. Fluctuations in the endogenous creatinine production may therefore cause erroneous results in estimation of renal function. In addition, the methodologic difficulties inherent in the measurement of SCR reduce the accuracy of the method (30). The enzymatic methods of SCR have been shown to give more reliable results than the widely used Jaffé alkaline picrate colorimetric methods, which are complicated by the measurement of noncreatinine chromogens (19). The use of different assays

<table>
<thead>
<tr>
<th>Model</th>
<th>Model description</th>
<th>OFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clpop = theta(1)</td>
<td>No relation between creatinine and Cl</td>
<td>4,764.722</td>
</tr>
<tr>
<td>Clpop = GFR + 25</td>
<td>Calvert formula</td>
<td>4,457.087</td>
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<tr>
<td>Clpop = GFR + theta(1)</td>
<td>Calvert formula, variable reestimated</td>
<td>4,460.216</td>
</tr>
<tr>
<td>Clpop = theta(1) + (140 - age) x weight x theta(3) / S_Cr</td>
<td>Full model for relation between S_Cr and Cl</td>
<td>4,789.303</td>
</tr>
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</table>

Abbreviations: OFV, objective function value; Clpop, population value of clearance.
for S_{CR} may therefore result in systematically different results between studies.

In contrast to our results, many authors have reported relations between S_{CR}, age, gender, weight, height, and carboplatin pharmacokinetics (11, 13, 31–33). In the studies in which a correlation was found between S_{CR} and carboplatin clearance (13, 31), also patients with (moderate) renal insufficiency were included while in our study, renal function was adequate in all patients (Cl_{CR} > 50 mL/min, as calculated using the Cockcroft-Gault formula), which is the result of the inclusion criteria of the different protocols. This is probably an important explanation for our different results. Variability in carboplatin clearance in our population was small (IIV, 19.1% and IOV, 9.52%; Table 2), which may also be caused by the inclusion of patients with relatively normal renal function.

Without a clear correlation between S_{CR} and carboplatin clearance, substituting GFR in the Calvert formula with an estimation of Cl_{CR} or GFR based on S_{CR} measurements (using the Cockcroft-Gault, the Jelliffe, or the Wright equations) is therefore also prone to errors. This may explain the lack of relation between Cl_{CR} or GFR and carboplatin clearance in our study. Moreover, it should be questioned whether these equations should be applied in our patient population because of the large number of patients with very low measured S_{CR} values (Fig. 5) and concomitant extremely high physiologic unlikely estimated Cl_{CR} or GFR values (Fig. 4A-C) seen in our population. In the work of Kirkpatrick et al. (29), S_{CR} values < 60 µmol/L were set at 60 µmol/L in patients receiving gentamicin because it was thought that low values of S_{CR} may reflect decreased production rather than enhanced clearance. In our population, S_{CR} values were < 60 µmol/L in more than half the patients probably due to the disease condition of these patients. In these patients, estimated Cl_{CR} or GFR values were therefore above the physiologic meaningful upper limit of 150 mL/min. Applying the Calvert formula with these estimates of Cl_{CR} or GFR may result in inaccurate predictions of the carboplatin exposure.

These low S_{CR} values were not only the result of the subtraction of 26 µmol/L but were also directly observed. Moreover, these low S_{CR} values were seen in samples from all the different study protocols. Therefore, the observed low S_{CR} values are not due to the different protocols used to measure S_{CR}.

Substitution of the Cl_{CR} estimates of GFR from the Cockcroft-Gault formula and the Jelliffe formula into the Calvert formula has become routine practice in many centers. Although the Calvert formula, with GFR calculated using the $^{51}$Cr-EDTA clearance, is a superior method of dosing carboplatin than the traditional BSA method (34), the use of this formula with inaccurate substitutions of the GFR is not. The same is true for the application of the Chatelut formula. Studies evaluating the performance of the Chatelut formula (35, 36) or the Calvert formula using the Cockcroft-Gault (13, 35–39), Jelliffe (35, 37), or Wright (37) equations in predicting carboplatin exposures indeed reported poor precisions (percentage root mean squared error, 17–43%). The authors, however, did not establish the dosing precision if doses would have been based on BSA or if a flat dose would have been administered. The variation in carboplatin exposure in our population after administration of a flat dose would be ~ 21% ($\sqrt{1.912 + 9.522}$) calculated from the observed variation in carboplatin clearance within our patient population (IIV, 19.1% and IOV, 9.52%; Table 2). Therefore, in our population, the performance of the dosing formulae in approaching a fixed carboplatin exposure is not better than of a flat dose based on the mean carboplatin population clearance.

In summary, the current data do not support the general use of estimates of renal function by the Cockcroft-Gault, Jelliffe, or Wright formulae, based on S_{CR} measurements, to select the dose of carboplatin using the Calvert formula for patients with relatively normal renal function. The original Calvert formula, using the clearance of $^{51}$Cr-EDTA as an accurate measure of the GFR, remains the method of choice. When targeted carboplatin exposures are desired and radioisotope methods are not available, we propose to base the carboplatin dose in patients with a Cl_{CR} > 50 mL/min (as calculated with the Cockcroft-Gault formula, with S_{CR} measured using the compensated Jaffe method) on the mean carboplatin population clearance of this study (8.33 L/h = 138.8 mL/min) using the following general formula:

$$\text{carboplatin dose} = \frac{\text{desired carboplatin AUC} \times \text{carboplatin population clearance}}{\text{desired carboplatin AUC} \times \text{carboplatin population clearance}}$$

Thus, in case an AUC of 5 mg/mL min is desired, the appropriate dose for carboplatin would be 5 mg/mL min × 138.8 mL/min = 694.2 mg (=695 mg). In the future, alternative approaches for estimating renal function using promising markers of GFR, such as cystatin C, may prove suitable and applicable in routine clinical practice for estimating accurate a priori carboplatin doses (40).

References
Flat Dosing of Carboplatin Is Justified in Adult Patients with Normal Renal Function

Corine Ekhart, Milly E. de Jonge, Alwin D.R. Huitema, et al.


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