Calvert’s Formula for Dosing Carboplatin: Overview and Concerns of Applicability in High-Dose Setting

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The uniqueness of carboplatin as a chemotherapy drug is in the fact that the systemic drug exposure produced by any dose in a patient can be reasonably estimated on the basis of his or her renal function. Calvert’s formula (1) of delivering a calculated dose in terms of target carboplatin area under the time–concentration curve (AUC) and a measured or estimated glomerular filtration rate (GFR) has been widely used. Here, we describe the derivation of Calvert’s formula and point out some limitations in its development, including violation of an underlying assumption of linear regression theory. We also discuss the related published literature and recommend practicing caution in its use for a high-dose setting.

Calvert et al. (1) derived the dosage formula in three stages. Analysis at stage I involved a retrospective look at data from pharmacokinetic studies and produced a preliminary dosing relationship as

\[\text{dose}/\text{AUC} = [1.21(\pm 0.19) \times \text{GFR} + 23(\pm 16)].\]  

The error terms given in the parentheses represent the standard errors of estimates of slope (i.e., 1.21) and the intercept (i.e., 23). The correlation between dose/AUC and GFR was high \((r = 0.851;\) two-sided \(P<0.0001, t\) test). The formula is simplified in the equation as:

\[\text{dose} = \text{AUC} \times [1.2 \times \text{GFR}] + 20.\]  

In stage II, the authors used this formula to dose 31 patients for target AUCs of 3–8 mg/mL per minute. The model was reported to underpredict AUC by about 20\% (1). In stage III, the authors attempted to improve on the underprediction by using the data from stage II and revising the dosing formula as follows (with the error terms given in the parentheses representing the standard errors of estimates of slope [i.e., 0.93] and the intercept [i.e., 26] given below):

\[\text{dose} = \text{AUC} \times [0.93(\pm 0.08) \times \text{GFR} + 26(\pm 6)].\]  

The formula was then simplified to

\[\text{dose} = \text{AUC} \times (\text{GFR} + 25)\]  

and was widely used in the next decade (1989–1999) for dosing carboplatin.

There are two limitations in this development process. First, the use of the rounded parameter estimates introduces an unnecessary bias, even though one can justify the rounding as a matter of simplification. The second and more serious flaw is rooted in the underlying assumption of linear regression theory. Suppose the linear model under consideration is

\[y_i = a + b \times x_i + e_i,\]  

where \(y_i\) and \(x_i\) are the values of the dependent and independent variables, respectively, for the \(i^{th}\) patient, \(a\) and \(b\) are the intercept and slope parameters, respectively, and \(e_i\) is the random error following a normal distribution with mean zero and constant variance \(\sigma^2\) (2). Error terms for any two subjects are not correlated. Based on a sample of size \(n\), estimates of \(a\) and \(b\) can be obtained with the use of the least-squares theory, and the fitted equation can be used for predicting the mean response of \(y\) for a new value of \(x = x_{\text{new}}\). The point estimator of the predicted \(y\) is

\[\hat{y}_{\text{new}} = \hat{a} + \hat{b} \times x_{\text{new}}\]  

and is associated with a variance of

\[\sigma^2 \left[ \frac{1}{n} + \frac{\sum_{i=1}^{n} (x_i - \bar{x})^2}{n} \right],\]  

where \(\bar{x}\) is the average of \(x_i\)’s. In the study by Calvert et al. (1),

\[y_i = \frac{\text{dose}_i}{\text{AUC}_i}\]  

and \(x_i = \text{GFR}_i\). The dose and the AUC for each patient were varying in stage I; hence, the composite variable \(y_i\) is a random variable.

But when the model is applied for dosing, it is used as

\[\text{dose}_i = \hat{a} \times \text{AUC}_i + \hat{b} \times \text{GFR}_i \times \text{AUC}_i,\]  

so that the dependent random variable is dose, and not \(\frac{\text{dose}_i}{\text{AUC}_i}\). In this context, AUC is not a part of the dependent random variable but is an independent random variable. As a result, the variance of the random error term changes to AUC \(\sigma^2\) rather than \(\sigma^2\) violating the assumption of constant variance. The variability of the predicted \(y\) as given in equation 7 with \(\sigma^2\) replaced by AUC \(\sigma^2\) will increase as higher AUC is targeted. In other words, the impact of this violation is expected to be more severe for higher values of AUC.

We conducted a MEDLINE® search with key words of “Calvert’s Formula,” in an attempt to examine the range of its application. Forty-five studies were found between 1989 through 1999. The majority (31 of 45) involved a fixed dose for carboplatin. Most of the trials involved target AUCs between 4 and 7.5, with only five trials (3–7) proposing AUCs above 7.5 (fixed AUCs of 9, 11, 12, and 16 mg/mL per minute). Unfortunately, only 22\% (10 of 45 studies) compared the target AUC and measured AUC (6–15). Most of these 10 studies (eight of the 10) have indicated a 10–20\% underprediction. While modifications of GFR measurement have been proposed, no alternative or updated dosing formula has been found.

Based on a retrospective analysis in a previous study (16), it has been suggested that the same dosing formula should also be of value in studies of high-dose carboplatin. That analysis used data obtained from eight patients treated with 800–1600 mg/m² of carboplatin and indicated that the AUCs predicted by the dosage formula stayed

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See “Notes” following “References.”
within 20% of the observed AUC, with 28 mg/mL per minute being the highest AUC achieved. Our experience had been problematic with prediction (17).

In our phase I study, the carboplatin dose was escalated with the use of AUCs of 12, 15, 18, 21, 24, 28, and 32 mg/mL per minute. All patients had prior chemotherapy. GFR was measured by the Tc-DTPA (i.e., diethylenetriamine penta-acetic acid) method and ranged from 44.6 to 223 mL/minute, with only two patients falling much outside the range of GFR in the study by Calvert et al. (1). The data presented in Fig. 1 provide evidence of large discrepancies between target and measured AUCs. This situation is reflected in a low correlation of $r = .27$ ($r = .37$ without the one outlying observation). Possible causes for lower measured AUC include error during sampling, assay analysis, GFR determination, and AUC calculation. Other factors that could have resulted in lower AUC of carboplatin include increased volume of intravenous fluid administered and saturation of renal reabsorption mechanism (21–23). However, since the discrepancy worsens with higher target AUCs, saturation of renal absorption and our statistical argument seem to be the two primary issues that could account for this phenomenon.

In this brief communication, we draw attention to the fact that linear regression is easy to fit, but we suggest that some caution should be practiced in its use for prediction. First, it is important to remember that the validity of the regression application depends on whether the study population and outcomes measured are truly comparable to those employed in the trial on which the original regression analysis was based. Hence, patient characteristics (such as exposure to prior therapy and age) and data acquisition (such as blood-sampling intervals and methods of measuring AUC and calculating GFR) need to be in concordance to ensure the correctness of the basic reasoning that any dose of carboplatin administered to a patient can be estimated in terms of his or her renal function with any specific regression equation. Another caution deals with inference pertaining to the levels of the independent variable that fall outside the range of original observations. If the observed GFR of a patient were to fall far beyond the range of those observed in the study by Calvert et al. (1), one cannot be sure about the accuracy of that patient’s dosing based on this formulation.

Other than the above cautions related to usual linear regression theory, the most important deviation involves the formulation of a model for a specific response (dose/AUC by GFR) and then using it differently in prediction (dose by AUC and GFR). This approach does not satisfy the underlying assumptions of a linear model and could greatly affect prediction. To avoid this situation, a new model could be devised with AUC as an independent variable:

$$
dose_i = a \cdot \text{AUC}_i + b \cdot \text{GFR}_i + c \cdot \text{GFR}_i \cdot \text{AUC}_i + \varepsilon_i
$$

where $\varepsilon_i$ is a random error term with mean zero and variance $\sigma^2$. This model will have constant error variance for all levels of AUC. Data from a new clinical trial with patients dosed by their body surface area will be needed for this modeling. More studies of quantification of renal absorption are also necessary.

The limitations in the development of the statistical model, along with the unfavorable experience (17) for high AUC, prompt us to recommend that future investigators be careful in employing Calvert’s dosing formula, particularly for high target levels of AUC.

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NOTES

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