Cancer Chemother Pharmacol (1996) 37: 286–288

SHORT COMMUNICATION

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Effect of different mathematical methods on etoposide area under the curve estimations and pharmacodynamic response predictions

Received: 30 December 1994 / Accepted: 14 May 1995

Abstract Different methods to calculate interval area under the curve (AUC) data may produce substantial error. The purpose of this study was to compare methods of calculating etoposide AUC and determine the effect of these values on white blood cell (WBC) count nadir predictions calculated from a previously reported equation. Three AUC calculation methods were used: (1) the linear trapezoidal method, (2) a combination of the linear and logarithmic trapezoidal methods, and (3) the Lagrange method. Since none of the methods for determining the AUC could be considered the standard, the methods were evaluated by comparing differences between pairs of calculated AUC values by each method. The 95% CI for differences between all pairs of AUC values were greater than zero (no difference) indicating significance. Consistent with the smoother fitting function between data points, the Lagrange method tended to produce a larger AUC, lower clearance values, and lower WBC nadir count predictions than the other methods. The largest difference encountered was between the Lagrange and the linear-log AUC methods with a mean value of 16.9 μg h/ml (95% CI 9.4–24.3) This difference would account for approximately 11% of the total AUC. Using a previously published equation, where WBC nadir = −0.057 +0.048 × etoposide clearance, with clearance determined as dose/AUC, mean differences in calculated WBC nadir count values between the three AUC methods ranged from 80 to 220 cells/μl, which would be expected to be of little clinical consequence. The precision of this equation, using data derived from linear trapezoidal AUC calculations, had a mean absolute error of 0.93×10^3/μl (95% CI 0.53–1.32). Our findings suggest that any of the three mathematical methods studied would produce similar etoposide AUC values and pharmacodynamic predictions. Further, these findings also suggest that the major limitation in predicting etoposide leukopenia lies with the imprecision of the pharmacodynamic model more so than the ability to accurately determine the AUC. However, our findings may not be applicable if other factors intervene which dramatically alter the shape of the etoposide concentration-time curve.

Key words Etoposide · Pharmacokinetics · Area under the curve

Supported by National Institutes of Health grants numbers R01 CA 52168 and M01 RR 00070 (General Clinical Research Centers)

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Introduction

The area under the concentration time curve (AUC) for many antineoplastic drugs is useful describing a relationship to a pharmacodynamic effect, such as tumor response or toxicity [5]. For etoposide, Miller et al. [4] have derived an equation where the degree of hematologic toxicity can be estimated from clearance. Critical to the determination of clearance is the accurate determination of AUC, since clearance is derived from the ratio of the dose to the AUC.

Previous studies have indicated that different methods used to calculate interval AUC values may produce discordant results and errors of nearly 35% in the absorption phase and 80% in the post-absorption phase depending on the extent of curvature between data points and the span of time between data points [1]. Such errors could have a substantial impact on etoposide pharmacokinetic calculations and pharmacodynamic predictions. The degree of these errors in AUC determinations may be reduced by the use of the logarithmic trapezoidal methods for expo-

Table 1 Comparison of calculated values and differences between the methods of AUC determination

Method	Mean	95% CI
Calculatd AUC (μgh/ml)		
1. Linear	154.9	124.9–183.6
2. Linear/log	149.4	120.0–178.8
3. Lagrange	166.3	136.5–196.0
Differences		
1 vs 2	4.8	1.3– 8.2
1 vs 3	12.1	7.1– 17.2
2 vs 3	16.9	9.4– 24.3

Table 2 Comparison of values and differences between WBC nadir counts (WBC_n) determined by the methods for calculation of AUC

Method	Mean	95% CI
Calculated WBC_n ($\times 10^9/\mu l$)[a]		
1. Linear	1.80	1.47–2.07
2. Linear/Log	1.85	1.53–2.17
3. Lagrange	1.63	1.36–1.91
Differences:		
1 vs 2	0.08	0.02–0.08
1 vs 3	0.14	0.05–0.22
2 vs 3	0.22	0.08–0.35

[a] From Miller et al. [4] where $WBC_n = -0.057+0.048\ (E_{cl})$, where E_{cl} = dose/AUC (ml/min)

nential decay phase data or the use of cubic polynomial functions, such as the Lagrange and Spline methods [1, 9]. The purpose of this study was to compare three mathematical methods of calculating the AUC of etoposide and to determine the effect of these methods on white blood cell (WBC) count nadir (WBC_n) values based on the equation of Miller et al [4].

Patients and methods

The 16 patients evaluated in this study were part of a previously reported phase I trial conducted at Stanford University Medical Center [3, 8]. Etoposide (150 or 200 mg/m^2 daily for 3 days) was given as a 2-h infusion. Plasma samples were collected at ten time points: prior to and at the end of the infusion, and at 0.5, 1, 2, 4, 6, 12, 18, and 22 h after the end of the infusion. Etoposide was analyzed by HPLC as previously described [3]. The minimum level of quantitation was 1 μg/ml. The intraassay and interassay coefficients of variation at 10 μg/ml and 2.5 μg/ml were 9.2% and 9.7%, respectively. WBC_n values were obtained 10–14 days following treatment.

The AUC was calculated using three methods: (1) the linear trapezoidal method throughout the entire curve, (2) a combination where the linear method was used to calculate interval areas up to the end of the infusion and the logarithmic (log) method during the decay phase, and (3) the Lagrange method from the beginning of the infusion to the 12-h postinfusion time point and subsequent areas calculated by the log-trapezoidal method. All calculations were performed using the LAGRAN computer program [6] with the AUC extrapolated to affinity using a minimum of three data points to determine the elimination rate constant [3]. Etoposide clearance (E_{cl}) was calculated as dose/AUC and pharmacodynamic response predictions were calculated using the equation: $WBC_n = -0.057 + 0.048\ (E_{cl})$, [4]. As no method could be called the "standard", the methods were compared by analyzing differences between pairs of methods. Data are presented as the means and 95% confidence intervals (95% CI). To test the null hypothesis that these differences were significantly different than zero (no difference), 95% CI for the differences were presented and intervals with values greater than zero would thus indicate a significant difference [2]. Bias of the pharmacodynamic predictions was analyzed by calculating the mean error (actual WBC_n–predicted WBC_n) and precision by determining mean absolute error (absolute value of actual WBC_n–predicted WBC_n) [7].

Results

The calculated AUC values for each of the three methods had similar mean values and 95% CI (Table 1). Since none of the methods for determining the AUC could be considered the standard, differences between methods were evaluated by analyzing differences between pairs of calculated AUC values. All of the 95% CI for mean differences between pairs of methods were greater than a value of zero (no difference) indicating significance (Table 1). The linear and log AUC calculations produced similar results, with differences accounting for approximately 3% of the total AUC value. The largest difference encountered was between the Lagrange and the linear-log AUC methods with a mean value of 16.9 μg h/ml (95% CI 9.4–24.3; Table 1). This magnitude of difference would account for approximately 11% of the total AUC.

When AUC determinations from the three methods were used to calculate WBC_n counts, similar mean values were observed (Table 2). Mean differences in these values ranged from 0.08 to 0.22 ($\times 10^3/\mu l$) and 95% CI for all differences were greater than zero (no difference), indicating significance. Again, the largest difference observed was between values calculated from the log AUC method and the Lagrange AUC method, where the difference in the mean WBC_n predicted value by the Lagrange method was 0.22 ($\times 10^3$ cells/μl) lower than that predicted by the log AUC method. Mean error calculations of WBC_n predictions showed no bias, with 95% CI including zero. Precision was similar between all three methods, with mean absolute error WBC_n count values ranging from 0.93 to 0.97 ($\times 10^3$/μl) with similar 95% CI.

Discussion

Miller et al. [4] proposed an equation where the degree of etoposide-induced hematologic toxicity could be estimated from clearance. Critical to the determination of clearance is the accurate determination of AUC, since clearance is the ratio of dose to AUC. Previous data have indicated that various mathematical methods to calculate AUC may produce large errors in area estimates. For example, errors in interval AUC calculations using the linear trapezoidal method could range up to 84% depending on the length of the sampling interval and concavity of the curve [1]. This degree of error could substantially affect the accuracy of the pharmacodynamic predictions using the equation proposed

by Miller et al. [4]. Cubic polynomial methods, such as the Lagrange or Spline, have been reported to reduce the amount of error in AUC estimates as these functions providing a smoother non-straight-line fit between data points [9].

This is the first study to evaluate the theoretical advantages of these mathematical methods to calculate AUC and the resulting pharmacodynamic response for an antineoplastic drug. Consistent with the smoother fitting function between data points, the Lagrange method tended to produce a larger AUC, a lower clearance value, and lower WBC_n value predictions than the other methods. Similar to the results of previous mathematical studies [1, 10], all of the differences between pairs of AUC methods and WBC_n value predictions were statistically significantly greater than zero (no difference). However, these differences appeared to be of minor clinical relevance, since the mean predicted WBC_n values using values determined by the three methods ranged from 80 to 220 cells/μl.

This study also gave an opportunity to independently validate in part the pharmacodynamic predictor equation of Miller et al. [4]. The precision of the WBC_n equation using data from linear trapezoidal AUC calculations, was unbiased and had a mean absolute error of $0.93 \times 10^3/\mu l$ (95% CI 0.53–1.32). These values are similar to those reported in the original study, thus confirming the reproducibility of results using this equation. However, this degree of imprecision indicates the limited usefulness of this equation in clinical practice. For example, if one were to choose a target WBC_n value of $1.8 \times 10^3/\mu l$, predictions would fall in a range of $0.9 \times 10^3/\mu l$ to $2.7 \times 10^3/\mu l$, thus potentially overtreating or undertreating a proportion of patients. Miller et al. [4] also derived an equation to predict absolute neutrophil count which in the original study provided better results than the WBC_n equation ($r^2 = 0.74$ vs 0.34), but unfortunately absolute neutrophil count data were not available in our study to test the clinical utility of the better model. However, these observations underscore that the most significant problem in the prediction of leukopenia is the imprecision the pharmacodynamic model and not the ability to accurately determine the AUC to use in the model. Our data suggest that the three methods we studied to calculate etoposide AUC produce clinically similar results. However, our findings may not be applicable if critical factors for the determination of AUC change, such as the number and timing of plasma samples, the duration of infusion, or route of etoposide administration, so as to dramatically alter the shape of the concentration-time curve.

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