A Method for Accurate Estimation of Busulfan AUC and its Confidence Interval

Harukazu TSURUTA\textsuperscript{a,1}, Mariko FUKUMOTO\textsuperscript{b}, Leon BAX\textsuperscript{c}

\textsuperscript{a} Department of Medical Informatics, School of Allied Health Sciences, Kitasato University, Kanagawa, Japan
\textsuperscript{b} Division of Toxicology, Center for Clinical Pharmacy and Clinical Sciences, School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan
\textsuperscript{c} Pharsight Corporation, Sunnyvale, CA, USA

Abstract. We propose a new method for the estimation of the area under the curve (AUC) for plasma concentration time change, in which a curve that best approximates the measured data is searched for from a set of pre-generated theoretical concentration curves. We evaluated this estimation method and proved that it has virtually no bias. To calculate the confidence interval, we also developed a method for calculating the distribution of an AUC estimator based on the empirical distribution of within-patient errors using Monte Carlo simulation.

Keywords. busulfan, limited sampling strategy, AUC, confidence interval

1. Introduction

Busulfan (BU) is a bifunctional alkylating agent which is widely used for chemotherapy before allogeneic or autologous bone marrow transplantation. BU pharmacokinetic studies have suggested that individualization of BU doses based on the area under the curve (AUC) for plasma concentration time change of BU is necessary to secure optimal BU systemic exposure.

Because standard pharmacokinetic measurements require multiple blood samples and are therefore impractical in most usual clinical settings, various limited sampling strategies (LSSs) for the estimation of AUC have been proposed to reduce the number of blood samples. To develop LSSs, multiple linear regression (MLR) and the trapezium rule with approximation of the elimination phase by an exponential curve (TZE) are frequently used. We show that both of these methods have some biases, although many authors reported the accuracy of these LSSs by cross validation.

To solve this bias problem, we propose a new method for AUC estimation in which the most likely curve is selected from a set of pre-generated theoretical concentration time curves. We also introduce a method for calculating a bootstrap confidence interval based on the empirical distribution of within-patient errors.

\textsuperscript{1} Corresponding Author: Harukazu Tsuruta, PhD, Department of Medical Informatics, School of Allied Health Sciences, Kitasato University, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0373, Japan; E-mail: ts@med.kitasato-u.ac.jp
2. Methods

Blood samples were taken 11 times in 9 patients and 5 times in 69 patients both after the oral BU (1 mg/kg) intake following the clinical study plan. Using Akaike information criterion (AIC), we identified which pharmacokinetic model best fits our observations. We then obtained the distributions of model parameters using population pharmacokinetic analysis.

We generated a set of theoretical concentration time curves based on the identified model and the distribution of its pharmacokinetic parameters, then evaluated MLR and TZE using these virtual validation profiles. We also generated a more detailed set of 2,622 BU concentration time curves based on the identified model and by varying its parameters based on the possible ranges of the patients. These cases were thought to cover possible BU concentration changes. We subsequently searched a curve that best approximates the measured data from this set of model curves using a weighted least squares method.

To create a confidence interval for the AUC estimate, we first evaluated the distribution of within-patient errors. Then, for a theoretical concentration time curve, we added a random error based on the empirical distribution of within-patient errors and estimated the AUC using our new LSS. We repeated this procedure 5,000 times for each profile and thus obtained the distribution of estimated AUCs, from which we developed the 95% bootstrap percentiles.

3. Results and Conclusions

AIC showed that one compartment model with absorption from the intestinal compartment best fits our observed data. We then validated the existing LSSs using a set of simulated concentration time curves. The results revealed that both MLR and TZE have different but specific biases in the estimation of AUC and that they must be cautiously applied so as not to exceed the limitations of each estimation scheme.

We then evaluated our new estimation method and found that it has virtually no biases. We then systematically evaluated the coefficient of variation of the AUC estimator and found that our new method is more precise (<10%) than both MLR and TZE.

We conclude that our new LSS using the model concentration time curves and the weighted least squares method provides accurate and precise estimations of the AUC.

Acknowledgments: This work was partially supported by Grant-in-Aid for Scientific Research (C) 22500264.

References