Letters to the Editor

To the Editor:

We were excited to read the clinical case study recently published in Clinical Chemistry (1), because the dosing of busulfan is a topic of great interest; however, one of the authors’ Points to Remember was, “The therapeutic dose of intravenous busulfan is best predicted when the patient has achieved a Css” (1). We demonstrate that this statement is incorrect by addressing the question from both a theoretical and a practical point of view.

Busulfan pharmacokinetics are described by a 1-compartment model. Thus, with intravenous administration, the pharmacokinetics are described by the parameter’s clearance and volume of distribution. Because our aim is to achieve a constant area under the curve (AUC) for all patients, the clearance of busulfan is the most important parameter. The formula:

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\text{Clearance} = \frac{\text{Dose}}{\text{AUC}},
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demonstrates that if we know the clearance, we can adjust the dose to achieve a constant AUC. It does not matter if the patient is at steady state or not. Like other pharmacokinetic parameters, clearance displays some inter- and intraindividual variation, but other than a circadian rhythm, it does not change systematically with time over the 4 days of administration. Clearance may change when enzyme inducers or inhibitors are added to the medication, but the many published pharmacokinetic investigations of busulfan have not indicated nonlinear pharmacokinetics or autoinduction causing a change in clearance over time. Therefore, from a theoretical point of view, it does not matter when the blood sampling is done. From a practical point of view, it is appropriate to measure busulfan after the first dose to get the necessary information to be able to adjust the dose for subsequent administrations as quickly as possible. In previously published investigations on this 16-dose schedule, the therapeutic interval is always defined to the AUC from zero to infinity measured after the first busulfan dose (2).

We are not aware of how the mentioned therapeutic interval of 900–1350 \(\mu\text{mol} \cdot \text{L}^{-1} \cdot \text{min}^{-1}\) was defined. Fig. 2 of the case study by Johnson-Davis et al. suggests that the pharmacokinetic parameters do not change much over time. Rather, the authors appear to have calculated the AUC with noncompartmental methods and interpreted the AUC incorrectly by calculating the clearance from the AUC according to the above equation. However, this equation does not work correctly if the plasma busulfan concentration does not start at zero, i.e., if the patient had received previous busulfan doses. Therefore, the clearance values given in the authors’ Table 1 appear to be incorrect, except for the value after the first dose.

The 29.9% change in clearance from the first dose to the fifth dose is substantial (Table 1 in their case study), but it appears to be due to misinterpretation of the AUC. The values reported in the literature for intraindividual variation in clearance are not greater than

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References


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Therapeutic Drug Monitoring of Busulfan

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Fig. 1. Plasma concentrations (points) and pharmacokinetic model (line) for a patient receiving busulfan treatment (1 mg/kg every 6 h, for 16 administrations total).

13% (3) and are always lower than the interindivdual variation in busulfan clearance. From the clinical case study (1), the reader might infer that the changes in clearance and the volume of distribution are reduced with time, but previous pharmacokinetic investigations have found no indications for such a finding. The term “steady-state” was not used correctly, because all of the equations developed for steady-state conditions in pharmacokinetics imply constant pharmacokinetic parameters.

According to the known pharmacokinetic parameters of busulfan, the values for the maximum and minimum concentrations increase during the first 3 doses. Fig. 1 demonstrates this increase by showing the pharmacokinetic model and the data for a child undergoing a similar regimen (1 mg/kg every 6 h). The calculated pharmacokinetic parameters for this patient were as follows: AUC, 1375 μmol·L−1·min−1; clearance, 2.56 L/h; volume of distribution, 10.5 L; and t1/2, 2.85 h (4). Bayesian methods for dose adjustment are preferable because they can account for pharmacokinetic variation and have demonstrated their advantages in clinical practice (5).

One has to be aware of the pitfalls when analyzing pharmacokinetic data for dose calculation. Dose adjustment based on measurements of the plasma concentration can work only if values for the pharmacokinetic parameters remain relatively constant. Steady-state conditions during sample collection are not required for dose calculation and dose adjustment.

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References


In Reply

We appreciate the comments and concerns of Hempel and Trame relative to our Clinical Case Study published in the July 2010 issue of Clinical Chemistry (1). Hempel and Trame question the observed change in busulfan clearance described in the case report, which led them to hypothesize that first-dose pharmacokinetics may not be appropriate for predicting dose requirements in all patients (1). In particular, they question the method for calculating pharmacokinetic parameters and one of the Points to Remember (“The therapeutic dose of intravenous busulfan is best predicted when the patient has achieved aCss”).

For patients of typical body weight and at minimal risk of drug–drug interactions, interpatient and intrapatient consistency in pharma-