Which Dose of Busulfan Is Best?

Kamisha L. Johnson-Davis,[1] Gwendolyn A. McMillin,[1*] JoEtta M. Juenke,[3] Clyde D. Ford,[2] and Finn B. Petersen[2]

[1] Department of Pathology, University of Utah Health Sciences Center, Salt Lake City, UT; [2] Intermountain Health Care, Salt Lake City, UT; [3] ARUP Laboratories, Institute of Clinical and Experimental Pathology, Salt Lake City, UT.
* Address correspondence to this author at: ARUP Laboratories, 500 Chipeta Way, Salt Lake City, UT 84108. Fax 1-801-584-5207; e-mail mcmillga@aruplab.com.

[4] Nonstandard abbreviations: HSCT, hematopoietic stem cell transplantation; AUC, area under the plasma concentration vs time curve; BMI, body mass index; PK, pharmacokinetics; Css, steady-state concentration; SOS, sinusoidal obstruction syndrome; Vd, volume of distribution.

CASE

A 24-year-old woman with advanced Hodgkin disease received the standard dosing protocol for busulfan/cyclophosphamide before autologous hematopoietic stem cell transplantation (HSCT)[4] from a matched unrelated donor. The target area under the plasma concentration vs time curve (AUC) for busulfan was set at 950 μmol · L^{-1} · min^{-1}, near the low end of the therapeutic interval of 900–1350 μmol · L^{-1} · min^{-1}. The patient's body mass index (BMI) was 45.5 kg/m^2 (height, 170.2 cm; weight, 132.0 kg), so the dose was based on the patient's ideal body weight. The patient received 2-hour intravenous infusions of busulfan every 6 h for 4 days (16 doses total). The patient was concurrently prescribed multiple medications, including an immunosuppressant, an antiviral, an antifungal, an antidepressant, an anxiolytic, a β-blocker, and a muscle relaxant, as well as antibiotics, warfarin, opioids, and antiepileptic drugs.

After the first dose (51 mg Busulfex®; Otsuka Pharmaceutical), timed plasma samples were collected after infusion to determine the AUC. Pharmacokinetics (PK) analysis was performed, and the AUC was determined to be 642 μmol · L^{-1} · min^{-1}. According to these results, the predicted busulfan dosage required to achieve the target AUC was 75 mg per dose for the remaining 14 scheduled doses. Because of the large change in dosage, additional PK monitoring of busulfan was performed after the fifth dose (day 2). The fifth dose was selected to allow time to reach a steady-state concentration (Css) after the dosage adjustment and to avoid challenges in interpretation due to possible circadian variation in busulfan concentrations (*1*). Samples for monitoring were collected at the same time of day as the first monitoring dose. The AUC after the fifth dose was 1342 μmol · L^{-1} · min^{-1}.

On the basis of the PK data from the fifth dose, dose 7 was changed from 75 mg to 53 mg, close to the original calculated dose of 51 mg. Of note is that the patient was started on an oral antifungal agent (fluconazole, 400 mg/day) after dose 6. Additional monitoring of busulfan was performed immediately after the ninth dose because of another change in dose and potential reduced clearance through busulfan interaction with fluconazole. The AUC after dose 9 was 1306 μmol · L^{-1} · min^{-1}. The busulfan dose was decreased to 39 mg for the remaining doses because the AUC was near the high end of the therapeutic range and because clearance was reduced between the fifth and ninth doses. Monitoring was performed after the 14th dose to verify the adjustment; an AUC of 871 μmol · L^{-1} · min^{-1}

DOI: 10.1373/clinchem.2009.134940

was observed. No further dose adjustments were made. The busulfan half-life and elimination constant were relatively stable throughout the dosing regimen (Table 1).

Table 1. Summary of dosing schedule and PK variables.

Variable	Dose 1 (51 mg)	Dose 5 (75 mg)	Dose 9 (53 mg)	Dose 14 (39 mg)
AUC, $\mu mol \cdot L^{-1} \cdot min^{-1}$	642	1342	1306	871
Css, $\mu g/L$	439	918	894	596
Clearance, L/h	19.4	13.6	9.9	10.9
Vd, L	62.3	40.3	37.4	32.3
Ke,[a] h	0.31	0.34	0.26	0.34
Half-life, h	2.5	2.4	2.9	2.4

[a] Ke, elimination constant.

Questions to Consider
• When is the appropriate time to measure plasma busulfan concentrations in a patient? During the distribution phase of the drug or when the patient has reached a Css?
• Should busulfan dose adjustments be based on firstdose PK?
• What factors can affect drug absorption, distribution, metabolism, and excretion in patients?
• Can the coadministration of multiple drugs during busulfan therapy affect the PK of busulfan?

References

1. Vassal G, Challine D, Koscielny S, Hartmann O, Deroussent A, Boland I, et al. Chronopharmacology of high-dose busulfan in children. Cancer Res 1993; 53:1534 –7.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the July 2010 issue of *Clinical Chemistry*. To view the case and comments online, go to http://www.clinchem.org/content/vol56/issue7 and follow the link to the Clinical Case Study and Commentaries.

Educational Centers

If you are associated with an educational center and would like to receive the cases and questions 2-3 weeks in advance of publication, please email clinchem@aacc.org.

DOI: 10.1373/clinchem.2009.134940

All previous Clinical Cases Studies can be accessed and downloaded online at http://www.aacc.org/resourcecenters/casestudies/.

AACC is a leading professional society dedicated to improving healthcare through laboratory medicine. Its nearly 10,000 members are clinical laboratory professionals, physicians, research scientists, and others involved in developing tests and directing laboratory operations. AACC brings this community together with programs that advance knowledge, expertise, and innovation. AACC is best known for the respected scientific journal, *Clinical Chemistry*, the award-winning patient-centered web site *Lab Tests Online*, and the world's largest conference on laboratory medicine and technology. Through these and other programs, AACC advances laboratory medicine and the quality of patient care.

DOI: 10.1373/clinchem.2009.134940