Rapid Quantification of the Cytotoxic Drug, Busulfan, in Plasma for Rapid Dose Adjustment by Laser Diode Thermal Desorption (LDTD)-MS/MS

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Background: Busulfan, a potent cytotoxic drug, is used to treat cancer such as leukemia[1,2]. In patients undergoing hematopoietic stem cell transplantation (HSCT), it is important to carry out rapid monitoring of the concentration of busulfan in blood plasma to target the optimal dose for preparation for surgical intervention, and to reduce the toxicity of this drug[1,2]. Laser Diode Thermal Desorption (LDTD) technology with mass spectrometer enables the rapid quantification of busulfan in plasma using a simple crash extraction and an analysis performed in less than 11 seconds.
Methods: Samples are extracted using an automated sample preparation. 50 uL of plasma is mixed with 100 uL of internal standard. Acetonitrile (400 uL) is added to extract busulfan. After mixing and centrifugation, 5 uL of upper layer was spotted onto a LazWell-96 plate. Samples are evaporated to dryness at 40°C then analyzed by LDTD-MS/MS. Triple quadrupole operates in positive ionization mode. The peak area against the internal standard (IS) ratio was used to normalize the signal.
Results: Calibration curve of 8 points, and five QCs, ranging from 25 to 2000 ng/mL, were prepared in negative EDTA-K2 plasmas. Luxon ion source produced the molecular ion at $(M+H)^+$ with 247→55 and 247→155 MRM transition compared to the adduct formation in ESI. Preliminary data shows that using an eight-point calibration curve, the regression correlation coefficient (r) is higher than 0.999. For inter-run precision and accuracy (n=6), the obtained %CV was below 4.4% and the accuracy was within 2.4% of the nominal value. When LDTD-MS/MS is used, the stability in solution (wet stability, kept at 4°C for 24 hours) and dry sample on LazWell-96 plate (dry stability, kept at room temperature for 1 hour) is evaluated instead of studying the autosampler's stability in LC-MS. After a given stability time, calibration curves and QCs are analyzed. The precision obtained for quality control samples was between 1.2 and 2.4%CV. The accuracy obtained was between 98.5% and 103.6%. The matrix effect is evaluated using eight different plasmas.
Conclusion: LDTD-MS/MS analysis applied at clinical levels to evaluate the concentration of Busulfan in 11 seconds per sample for dosage adjustment.

Keywords: Plasma, Therapeutic Drug Monitoring, Busulfan, LDTD-MS/MS

Conflict of Interest Disclosure *

I have a financial relationship with Phytronix Technologies as a salaried employee.

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