Poster

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[P25-9-9] UPLC-MS/MS analysis of plasma busulfan for clinical research

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Background

Busulfan is a bifunctional alkylating agent whose bioavailability varies greatly between individuals due to factors such as age, underlying diseases and drug-drug interactions. An accurate, sensitive and specific analytical method may play a role in assessing the pharmacokinetic and pharmacodynamic effects of busulfan administration in clinical research.

Methods

Samples (50L) were deproteinised with busulfan-$^{2}H_{8}$ internal standard in methanol. Elution was achieved within 3 minutes using a HSS-T3 C18 UPLC column (2.1x50mm, 1.8m) on the Waters ACQUITY UPLC® I-Class with a water/methanol/ammonium acetate/formic acid gradient. Ammonium adducts of busulfan were analyzed using electrospray ionization in positive mode with multiple reaction monitoring using the Waters XEVO® TQD mass spectrometer.

Matrix-matched calibrators (0.025-5 g/mL) and quality control samples (0.05, 0.75, 1.5 and 3.5 g/mL) were prepared. Due to known instability of busulfan in plasma, aliquots of in-house calibrators and quality control samples were stored frozen and thawed prior to use each time the method was used.

Results

Analytical sensitivity was calculated to be 0.020 g/mL (n=10 extractions, five occasions, 16.0% CV). Linearity was demonstrated over the concentration range 0.0175-6.51 g/mL and system carryover was negligible in samples 10 g/mL.

Precision studies (n=5, five occasions) demonstrated repeatability and total precision 7.3%. A comparison was made by analysing anonymized plasma samples (n=40, range 0.20-2.28 g/mL) against an independent UPLC-MS/MS method. An ordinary linear fit comparison of r=0.998, a mean bias of 5.3% from Altman-Bland analysis and a Deming equation of y = 1.01x+0.04 were obtained.

The mean recovery for busulfan pooled plasma samples (n=3, 0.05 and 3.5 g/mL) was between 85.1-106.1% in the presence of high concentrations of endogenous compounds albumin, bilirubin, cholesterol, triglycerides and uric acid and exogenous Intralipid®. The mean recovery was between 93.2-103.0% in the presence of acetaminophen, fluconazole, ketoconazole, itraconazole, phenytoin, posaconazole and voriconazole.
Negligible matrix effects were observed at low (0.05 g/mL) and high (3.5 g/mL) concentrations as indicated by respective mean internal standard adjusted matrix factors of 0.99 (range 0.97-1.02) and 0.98 (range 0.95-1.00).

Conclusions

The clinical research method developed for the quantification of plasma busulfan demonstrated good linearity, analytical sensitivity and precision with negligible matrix effects.

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