

An API LC-MS-MS Quantitation Method for Decitabine (5-aza-2'-deoxycytidine) in Rat and Human Plasma and Its Pharmacokinetics in Rats

Z. Liu¹, G. Marcucci², J. Byrd², M. Grever², J. Xiao¹, K. Chan³

¹ Division of Pharmaceutics, College of Pharmacy, The Ohio State University, ² Division of Hematology and Oncology, College of Medicine and Public Health, The Ohio State University, ³ Division of Pharmaceutics, Colleges of Pharmacy and Medicine and Public Health, The Ohio State University

Purpose: Aberrant DNA methylation patterns resulting in gene transcriptional repression are observed in numerous cancers. Decitabine, a DNA methyltransferase inhibitor, is being clinically evaluated in patients with hematologic malignancies and solid tumors. We developed a novel LC-MS/MS method for quantification of decitabine in human and rat plasma and performed preclinical pharmacokinetics. **Methods:** Decitabine and the internal standard (I.S.) 5, 6-dihydro-5-azacytidine were extracted from plasma by MCX Oasis SPE cartridge. The precursor/product ion pairs at m/z 229/113 and 247/115 for decitabine and the I.S., respectively, were used. Separation of analytes was carried out with a C₁₈ Aquasil column using a mobile phase of 5% methanol in 10 mM ammonium formate, plus post-column addition of acetonitrile. Plasma pharmacokinetics of decitabine in the rat was studied using this LC-MS/MS method. **Results:** The LC-MS/MS analytical method was validated in human and rat plasma giving a linear range from 2 to 500 ng/mL for human plasma (0.2 mL) and 10 to 500 ng/mL for rat plasma (0.1 mL). The within-day % coefficient of variation (CV) ranged from 1.7% to 13.4% for human plasma and 1.3% to 8.9 % for rat plasma. The between-day %CV ranged from 2.5% to 13.1% for human plasma, and 1.8% to 17.2% for rat plasma. The accuracy varied from 98.1% to 110.4% for human plasma and 91.7% to 99.6 % for rat plasma. Plasma concentration-time profiles in the rat were found to follow a bi-exponential decline with mean terminal t_{1/2s} of 180 and 153 min following i.v. bolus doses of 1 and 5 mg/kg, respectively. The mean respective total clearance values were 8.1 and 7.6 mL/min/kg. **Conclusion:** Using this LC-MS/MS method, we have characterized the plasma pharmacokinetics of decitabine in the rat and found to be dose-independent. Studies on human plasma samples from treated patients are underway. Supported by NIH-NCI-RO1-CA 102031.