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Quantitative determination of sulfisoxazole and its three N-acetylated metabolites using HPLC–MS/MS, and the saturable pharmacokinetics of sulfisoxazole in mice

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Sulfisoxazole (SFX) is still used in combination with trimethoprim in cattle despite adverse drug reactions (e.g., urolithiasis). Recently, SFX is known to be a promising repositioned drug candidate for pulmonary hypertension and cancer. We developed a simultaneous determination method of SFX and its N-acetylated metabolites (N1-acetyl SFX, N1AS; N4-acetyl SFX, N4AS; di-acetyl SFX, DAS) using HPLC–MS/MS for the first time, and examined the pharmacokinetics of SFX in mice. N1AS and DAS were converted rapidly to SFX and N4AS, respectively, in mouse plasma. The time courses of plasma SFX and N4AS concentrations were well characterized following the oral administration of SFX to mice. The absorption, metabolism, and/or excretion of SFX given at >700 mg/kg may be saturable, and in contrast to humans and rats, the extent of systemic exposure of mice to N4AS was much greater than that of SFX. Interestingly, the acetyl groups at both N1- and N4-positions were degraded during the ionization required to generate precursor ions. In additional experiments, the carboxyl group of N-acetyl-5-aminosalicylic acid (NA5AS) was lost instead of the acetyl group during the ionization, and acetaminophen (AAP) appeared. As the acetyl and carboxyl groups of some substances can be degraded during ionization in the mass spectrometer, caution is appropriate when it is sought to simultaneously quantify similar structures containing these moieties; chromatographic separation is essential.

Biography

Minsoo Kim has completed his Bachelor Degree at Chung-Ang University. He is a Pharmacist and pursuing his Master's Degree focusing on PK/PD modeling and simulation at Chung-Ang University.

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