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N-acetyltransferase 2 genotype-related sulfapyridine acetylation and its adverse events

Tanigawara Y[1], Kita T[2], Aoyama N[3], Gobara M[2], Komada F[4] (駒田富佐夫) , Sakai T[5], Kasuga M[5], Hatanaka H[6], Sakaeda T[2], Okumura K[2].

Department of Hospital Pharmacy, School of Medicine, Keio University[1]. Department of Hospital Pharmacy[2], & Department of Endoscopy[3], School of Medicine, Kobe University. Department of Drug Informatics, Faculty of Pharmaceutical Sciences, Josai University[4]. Department of Clinical Molecular Medicine, Graduate School of Medicine, Kobe University[5]. Hyogo Prefectural Institute of Public Health[6]

Sulfapyridine (SP), one of the metabolites of sulfasalazine (SASP), is further metabolized into N-acetylsulfapyridine (AcSP) by polymorphic N-acetyltransferase 2 (NAT2). NAT2 activity has been diagnosed by phenotyping, that is, evaluating plasma concentrations or urinary excretions of tentatively administered test drugs for dose individualization and avoidance of serious adverse events. Herein, we investigated the relationship between NAT2 genotypes and the pharmacokinetics of SP in healthy Japanese subjects, as well as the adverse events of SASP in patients with inflammatory bowel disease (IBD). Eight healthy subjects and 13 IBD patients were classified into three groups by NAT2 genotyping; the homozygote for the wild-type allele (Rapid Types), the compound heterozygote for the wild-type and mutant alleles (Intermediate Types), and the homozygote for mutant alleles (Slow Types). A single oral dose of 40 mg/kg SASP was administered to each healthy subject, and plasma and urine samples were taken until 51 and 72 h after administration, respectively. Both the SP and AcSP concentrations in each sample were determined by the HPLC method. The NAT2 genotypes were well-correlated with the plasma concentrations or urinary excretions of SP and AcSP in 8 healthy subjects, except for one Slow Type. In patients with IBD, skin rash was seen in 3 of 6 Rapid Types and 1 of 6 Intermediate Types, consistent with the concept that hypersensitive reactions are independent of serum SP

concentrations. In contrast, SASP dosing-related acute pancreatitis was found in the Slow Type patient. In this case, the NAT2 activity was diagnosed by genotyping in advance, and the medical staff could pay scrupulous attention, resulting in no serious subjective symptoms such as abdominal pain, anorexia or fever. Further investigations on the relationship between the NAT2 genotype and adverse events are required, although genotyping appeared to be a promising method to avoid such serious adverse events.