Since the discovery of polymorphic N-acetylation of drugs nearly 40 years ago, great progress has been made in understanding the molecular genetics of acetylation as well as the clinical consequences of being a rapid or slow acetylator. Inborn errors (several different alleles) at the NAT2 locus are responsible for the traditional acetylator polymorphism. Studies have revealed variant alleles at the NAT1 locus as well. The consequences of pharmacogenetic variation in these enzymes include (i) altered kinetics of specific drug substrates; (ii) drug–drug interactions resulting from altered kinetics; (iii) idiosyncratic adverse drug reactions. The latter have been extensively investigated for the arylamine-containing sulfonamide antimicrobial drugs. Individual differences in multiple metabolic pathways can increase the likelihood of covalent binding of reactive metabolites of the drugs to cell macromolecules with resultant cytotoxicity and immune response to neoantigens. This can result clinically in an idiosyncratic hypersensitivity reaction, manifested by fever, skin rash, and variable toxicity to organs including liver, bone marrow, kidney, lung, heart, and thyroid. Slow acetylation by NAT2 is a risk factor for such reactions to sulfonamides. Given the incidence of these severe adverse drug reactions (much less than 1/1000), slow acetylation cannot be the sole mechanism of predisposition in the population. Differences in rates of production of hydroxylamine metabolites of the drugs by cytochrome P450 (CYP2C9), myeloperoxidase, and thyroid, roxidase, along with an inherited abnormality in detoxification of the hydroxylamines are critically important in determining individual differences in adverse reaction risk. Both NATs, particularly NAT1, also can further metabolize hydroxylamine metabolites to N-acetoxy derivatives. Intensive investigation of patients with these rare adverse reactions using a variety of tools from in vitro cell toxicity assays through molecular genetic analysis will help elucidate mechanisms of predisposition and ultimately lead to diagnostic tools to characterize individual risk and prevent idiosyncratic drug toxicity.

KEY WORDS: N-acetyltransferases; NAT1; NAT2; sulfonamide hypersensitivity reactions; hydroxylamine metabolites.

PHARMACOGENETICS OF ACETYLATION

Recognition of the N-acetylation of drugs dates from the 1950s as does the association of human variability in acetylation capacity with an unexpected outcome of therapy, i.e., isoniazid-induced peripheral neuropathy. The history of the discovery of N-acetylation and clinical consequences of
what is now known to be an inherited difference in acetylation have been reviewed in detail (1,2). Current classification and nomenclature for the human N-acetyltransferases has been published (3). Early experiments demonstrated a bimodal population distribution in the kinetics of isoniazid (INH), that slow excretion of the compound was secondary to diminished acetylation capacity, and that the acetylation phenotype for INH was inherited (4,5). The acetylator polymorphism fits well with most basic principles of human pharmacogenetics: (i) Most genes in the human genome are polymorphic (defined as having a variant allele with a frequency of at least 1% in the population); (ii) several different alleles may be present at the same locus; (iii) allele frequency differs among different human populations. For the acetylator polymorphism, the enzyme involved has been designated “NAT2,” the gene being located on chromosome 8 (6). There are several different alleles which confer the “slow acetylator phenotype”; three alleles, M1, M2, M3 account for 95% of all mutant alleles characterized in Oriental and Caucasian populations (7–12). The prevalence of the allelic variants also varies between Orientals (7,8) and Caucasians (9–11). The slow acetylator phenotype ranges from 10% or less among Oriental populations, to 50–55% among Caucasians, to 83% among Egyptians (2). Such “pharmacoanthropologic” considerations predict that different human populations are likely to vary in the incidence of unexpected outcomes of therapeutic interventions (failure of desired therapeutic effects, “idiosyncratic” adverse drug reactions).

Acetylation phenotype can be characterized using in vivo probe compounds such as sulfamethazine, dapsone, and most often a very safe probe, caffeine (13). Acetylation of a distal metabolite of caffeine to 5-acetylamino-6-formylamino-3-methyluracil (AFMU) is mediated by NAT2. There is an excellent correlation between the amount of immunoreactive NAT2 protein in liver samples of patients undergoing laparotomy and apparent NAT2 activity assessed by measuring urinary excretion of AFMU and other caffeine metabolites (14). Thus, NAT2 can be assessed at the genotypic level using molecular techniques, or phenotypically using caffeine as an in vivo probe. There may be situations where one or the other or both techniques might be employed to gain insight into the role of genotype and phenotype in pharmacologic outcomes (see below).

It has become apparent that not all arylamine compounds exhibit overtly polymorphic kinetics in humans. It is now clear that there is another human N-acetyltransferase, NAT1, which is responsible for major metabolic clearance of “monomorphic” substrates such as p-aminobenzoic acid and p-aminosalicylic acid (15). While clearance of such substrates traditionally has been viewed as unimodally distributed in the population, this does not rule out underlying genetic polymorphisms in NAT1. Indeed, polymorphic