N-acetylation genotype and risk of severe reactions to sulphonamides in AIDS patients

The hepatic arylamine *N*-acetyltransferase enzyme encoded by the *NAT2* gene locus is responsible for the genetically-based polymorphic acetylation of a variety of arylamine and hydrazine-containing drugs or xenobiotics [1]. The 'slow acetylator' phenotype has been implicated in predisposition to both dose-related and idiosyncratic toxicity to a wide spectrum of compounds including sulphonamides and dapsone [2]. Although trimethoprim-sulphamethoxazole is effective in the treatment of pneumonia caused by *Pneumocystis carinii* in AIDS patients, its use is often limited by severe side effects occurring in about 50% of treated patients [3]. It has been reported that the prevalence of apparently slow acetylators was higher in acutely ill AIDS patients than in stable patients or control subjects [4]. More recently, it has also been observed that the prevalence of the slow acetylator phenotype was greater in AIDS patients with sulphonamide hypersensitivity than in sulphonamide-tolerant patients, leading to the suggestion that acetylator phenotype is a risk factor for the observed toxicity [5]. However, since the latter study was also conducted only in patients with acute illness, it remains to be determined whether apparently slow acetylation is causal or whether it results from the illness itself. In an attempt to clarify the role of the acetylation polymorphism in these adverse reactions, we compared the *NAT2* gene allele distribution and resultant acetylator genotypes of 39 acutely ill, unrelated Caucasian AIDS patients with those of 46 healthy controls. Eleven of the AIDS patients were classified as intolerant to sulphonamide treatment, presenting with fever, and/or skin rash after primary therapy and faster reactivity in cases where drug rechallenge was attempted. On the other hand, 28 patients showed no signs of hypersensitivity and were thus classified as tolerant. All patients were considered to be too ill to justify undertaking *in vivo* probe drug phenotyping tests. The genetic basis of the human acetylation polymorphism has already been studied extensively in various healthy populations [1, 6]. Each of the known allelic variants (the 'S' alleles) at the *NAT2* gene locus possesses a combination of nucleotide substitutions at characteristic positions within the protein coding region that change one or more amino acids, and ultimately result in a reduction in the amount of the *NAT2* enzyme in the liver cytosol of genetically slow acetylators. We detected these polymorphic nucleotides at positions 282, 481 590, 803 and 857 in the *NAT2* gene coding region by PCR amplification of 835 bp gene fragment

Table 1 *NAT2* haplotypes in patients and controls

Haplotypes	Healthy subjects	Number of alleles	
		Sulphonamide tolerant	Sulphonamide intolerant
R	18	9	6
S1A	41	23	11
S1B	2	0	1
S1C	0	2	0
S2	24	19	3
S3	0	3	1
S4	7	0	0

followed by diagnostic restriction endonuclease digestion using the enzymes *FokI*, *KpnI*, *TaqI*, *DdeI* and *BamHI*, respectively, and that at position 341 using allele-specific amplification. From this information *NAT2* haplotypes could be determined, the 'rapid acetylator' allele being designated 'R'.

As shown in Table 1, no significant differences were observed among the three groups with respect to the occurrence of *NAT2* allelic variants ($\chi^2 = 1.25$, $df = 2$, $P > 0.05$). The small number of subjects analyzed warrants caution regarding the statistical data as the possibility of a type II error cannot be excluded. All individuals were also assigned a genotype and an expected acetylator phenotype. Assuming a recessive transmission of the slow acetylator phenotype, its frequency was 69% in control subjects and 67% in AIDS patients. In addition, genetically slow acetylators comprised 71% of drug-tolerant and 55% of drug-intolerant AIDS patients. Thus we found no excess of the genetically-determined slow acetylator phenotype either in AIDS patients in general or in those with sulphonamide-induced hypersensitivity. These data suggest strongly that previously observed variations in acetylation capacity in AIDS patients, and the association with sulphonamide hypersensitivity, are likely caused by metabolic dysfunction related to the illness rather than by the genetically determined acetylator phenotype. Our work also emphasizes the value of using direct genetic approaches to investigate underlying mechanisms associated with the occurrence of toxic phenomena, especially in instances where functional tests may be compromised by acute pathology or concurrent drug therapies.

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Received 12 May 1994,
accepted 4 August 1994

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