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Acetylator phenotype prevalence in HIV-infected patients without previous trimethoprim-sulfamethoxazole hypersensitivity

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Summary – This trial was conducted to study the frequency of the slow acetylator phenotype in asymptomatic HIV patients having no previous reaction to sulfa-drugs, and to compare this frequency with the frequency found in healthy controls. Results show that HIV alone is not capable of modifying the acetylator phenotype; the prevalence of slow acetylator phenotype is the same in immune competent subjects and HIV-positive patients. It is more common in HIV-positive patients with a $CD4^+$ lymphocyte count of less than 200 mm^{-3}.

acetylator phenotype / drug hypersensitivity / HIV / sulfa-drugs

The increased frequency of hypersensitivity reactions to sulfa-drugs among HIV-infected patients is a well known problem, but its pathogenesis is still obscure. Some studies have suggested a toxic hypothesis related to the metabolism of sulfa-drugs [1-4]. In fact sulfamethoxazole is metabolized predominantly by hepatic acetylation to a stable N4-acetylsulfametoxazole, and by cythochrome P450 to 5-hydroxysulfametoxazole or to a highly reactive hydroxylamine metabolite. This pattern of metabolism is typical of subjects with 'fast acetylator phenotype'. The pattern of the 'slow acetylator phenotype' is a shortage of transacetylase, in this case the sulfa-drugs are metabolized by cythochrome P450 with the overproduction of hydroxylamine [5, 6]. Several hydroxylamine metabolites may have cytotoxic effects or may activate the immune system. In a study on HIV-infected patients, Carr et al. found a 42% prevalence of the slow acetylator phenotype in those patients who had never shown hypersensitivity reactions to sulfa-drugs vs. 94% in those who had such reactions [7]. The aim of our study was to evaluate whether HIV infection alone or related to the degree of immune deficiency influences the prevalence of the slow acetylator phenotype in HIV-positive patients without ongoing acute infections, who had never had hypersensitivity reactions to sulfa-drugs.

Two groups of patients were evaluated for acetylator phenotype: a group of HIV-infected patients without previous hypersensitivity to sulfa-drugs, and a group of healthy subjects as a control. Patients with acute infections were excluded since these patients show a prevalence of slow acetylator phenotype similar to that observed in patients with hypersensitivity reactions [8]. A wash-out period of at least a week was mandatory for all HIV patients who were receiving trimethoprim/sulfamethoxazole for *Pneumocystis carinii* pneumonia prophylaxis before entering the study (i.e., those with a $CD4^+$ count of less than 200 mm^{-3}); a pentamidine aerosol was administrated to those patients. The concomitant use of drugs that might interfere with the P450 cythochrome pathway (i.e., cimetidine, rifampicin, azoles) was the main exclusion condition.

The data investigated in our study had never before been tested, therefore it was difficult to define in statistical terms the sample size required. Patients were not stratified by sex or age since no relationship between these factors and the acetylator phenotype has been demonstrated. The chi-square test was performed for comparison of the groups.

Since the patients in our study had never experienced hypersensitivity reactions to sulfa-drugs, we could employ a method using sulfametazine (SMZ) for the characterization of the acetylator phenotype. The acetylation phenotype was established using the modified Bratton-Marshall procedure [9] for the evaluation of unacetylated and total (acetylated and unacetylated)

Table I. Prevalence of slow and fast acetylators in health and HIV-infected patients.

	Slow acetylator	*Fast acetylator*
Healthy subjects	24 (60%)	16 (40%)
HIV-infected patients	50 (61%)	32 (39%)
Patients with $CD4^+ > 200\ mm^{-3}$	21 (50%)	21 (50%)
Patients with $CD4^+ < 200\ mm^{-3}$	29 (72.5%)	11 (27.5%)

sulfamethazine excretions in urine. Briefly, a single dose of 10 mg/kg of SMZ was administered orally to the fasting patient. Urine volumes were measured four hours later and two quantities each of 10 mL were stored at –20°. Later on, 7 mL of urine was added to 2.1 mL of 20% trichloroacetic acid (TCA) and mixed; this procedure was followed by centrifugation at 1,500 rpm for 10 min. Then a quantity of 1 mL was used for the determination of unacetylated sulfamethazine by adding 8.5 mL of water and 500 g/L of HCL (4N); a second quantity of 200 mL was used for the determination of total SMZ by adding 0.2 mL of 4 N HCL. Each tube was then immersed in a boiling water for 1 h. After this step the procedure was identical for both determinations. Freshly prepared 0.1% sodium nitrite was added to each tube and mixed; then 0.5% ammonium sulphamate was added and mixed. Finally, 1 mL of 0.05% N-1 naphthylethylendiamine dihydrochloride was added and the mixture was allowed to stand for 10 min for color development. Absorbance reading was determined at 540 nm in a Gilford 300 N recording spectrophotometer against water as a blank with the use of an automatic sampling cuvette. Fast acetylators were those with free sulphametazine concentrations greater than 75%.

Eighty-two HIV positive patients, 56 males and 26 females with a mean age of 34 years, were enrolled: 50 IVDU, 23 heterosexuals, eight homosexuals and one transfused. Forty patients (20 males and 20 females with a mean age 32 years) were selected for the control group. The slow acetylator phenotype was observed in 50 out of 82 patients with HIV infection (61%) and in 24 out of 40 healthy subjects (60%) as reported in *table I*; this was without statistical significance.

We then stratified the HIV-infected group by immune depression between those with a $CD4^+$ count higher or lower than 200 mm^{-3}. Out of 40 patients with $CD4^+$ counts less than 200 mm^{-3} (72.5%), and 21 out of the 42 subjects with $CD4^+$ cell counts greater than 200 (50%) were slow acetylators *(table I)*. This difference did not reach statistical significance ($P = 0.06$), but showed a certain relationship between the two parameters.

Our results allowed us to conclude that the acetylator phenotype, though playing an important role, is probably not the only cause of hypersensitivity reactions in HIV subjects. Indeed, among asymptomatic patients, the frequency of slow and fast acetylators was the same as in healthy volunteers. We cannot also draw any conclusion regarding a possible concomitant role of the level of immune depression, although it seems that in the most immune deficient subjects the percentage of slow acetylators was higher, though this was not statistically significant.

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