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Letter to the Editors

The effect of the *CYP2C19*2* heterozygote genotype on the pharmacokinetics of nelfinavir

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Nelfinavir is the only currently licensed HIV-protease inhibitor that has an active metabolite present in potentially therapeutic concentrations. This metabolite, nelfinavir hydroxyl-t-butylamide (also known as M8 or AG1402), is the product of enzymatic conversion of nelfinavir by cytochrome P450 2C19 (*CYP2C19*) [1]. Previous studies have demonstrated that inherited (the homozygote's *CYP2C19*2* allele) and acquired (severe liver disease) deficiency of *CYP2C19* result in diminished formation of M8 [2, 3].

However, the frequency of heterozygote mutants of *CYP2C19*2* (G681A mutation) in the general caucasian population is far greater than that of homozygote mutants (15% *vs.* 2%) [4, 5]. If these heterozygotes differed with respect to nelfinavir pharmacokinetics, the *CYP2C19*2* polymorphism would affect many more patients, and thus may have greater clinical relevance.

Data for this analysis were selected from 24 healthy subjects who participated in a study on the effect of food on the pharmacokinetics of nelfinavir. Prior to enrolment, subjects were screened for the *CYP2C19* polymorphism by polymerase chain reaction. Subjects who were homozygotes for any of the variant alleles of *CYP2C19* (either *2, *3, *4 or *5) were excluded from the trial. Of the 36 subjects screened, one subject was a homozygous carrier of the *CYP2C19*2* mutation and, of the 24 subjects included, eight were heterozygotes. No *CYP2C19* *3, *4 or *5 mutants were found. The pharmacokinetics of nelfinavir and M8 were characterized by noncompartmental methods following a 1250-mg dose taken with a standardized breakfast (containing about 737 kCal, 28 g of fat). At that time of the study, subjects had been taking nelfinavir 1250 mg twice daily for at least 10 days. None of the subjects was taking concurrent medications that are potential inhibitors of *CYP2C19*. Nelfinavir and M8 plasma concentrations were determined by a validated high-performance liquid chromatography assay with a lower limit of quantification for both agents of 0.04 mg l^{-1} [6]. A nelfinavir +M8 concentration at 12 h after dosing ($C_{12\,h}$) that was below 1.0 mg l^{-1} was defined as subtherapeutic based on previous studies in HIV-infected patients [7, 8].

Overall, the median ratio of the AUC of M8 and nelfinavir was 0.34 with an interquartile range of 0.27–0.39. Minimum and maximum values were 0.10 and 0.50, respectively. These figures are consistent with previous reports in HIV-infected patients. No association was observed between the M8/nelfinavir AUC ratio and either gender, age (median age 40 years; range 22–63 years) or smoking habits (six smokers; maximum of 10 cigarettes per day) (*t*-test: all *P*-values were >0.51). In contrast, there was a significant difference in the M8/nelfinavir AUC ratios between *CYP2C19* wt/wt subjects and *CYP2C19* *2/wt subjects {mean difference [95% confidence interval (CI)] 0.14 (0.07, 0.21); $P < 0.001$} (Figure 1). However, the oral clearance of nelfinavir was not significantly different between the two genotypes [mean difference (95% CI) 9.1 l h^{-1} (–5.5, 23.8); $P = 0.21$], nor was there a significant difference in the nelfinavir +M8 $C_{12\,h}$ between groups [mean difference (95% CI) 0.06 mg l^{-1} (–0.68, 0.80); $P = 0.96$]. There was a trend towards fewer subtherapeutic $C_{12\,h}$ concentrations of nelfinavir +M8 (i.e. <1.0 mg l^{-1}) in *CYP2C19* *2/wt genotypes than in wild-type subjects (12.5% *vs.* 37.5%; χ^2 test: $P = 0.20$).

This is the first published report studying the effect of the *CYP2C19* *2/wt genotype on the pharmacokinetics of nelfinavir and M8. Preliminary data from an ACTG (AIDS Clinical Trials Group) study indicate the same nonsignificant trend of higher exposure to nelfinavir in heterozygotes of *CYP2C19*2* [9].

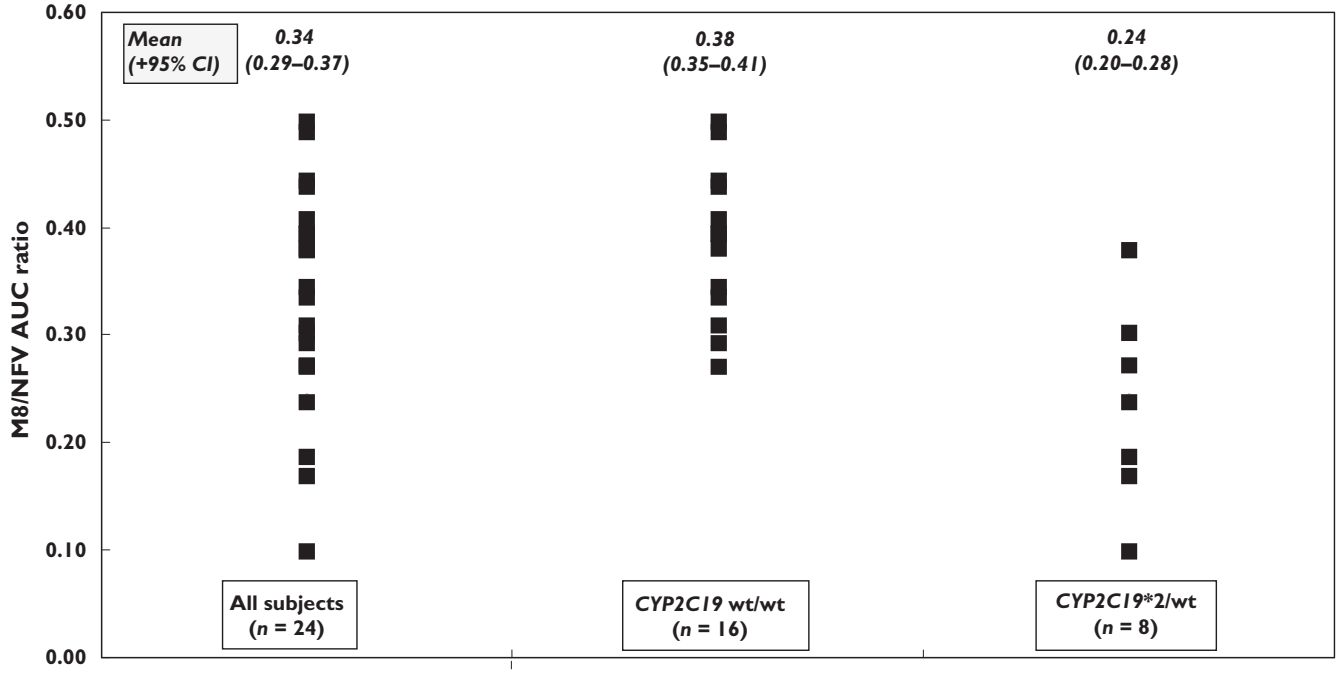

Figure 1
Effect of *CYP2C19* mutations on the M8/nelfinavir AUC ratio

On the assumption that both nelfinavir and M8 are equally active, and differences in their molecular weight are negligible, the sum of the $C_{12\,h}$ concentrations of these agents can be compared with the target threshold of 1.0 mg l^{-1} observed in previous studies [7, 8]. Subjects who are heterozygote for the *CYP2C19*2* allele would be expected to produce less of the active metabolite, but the total sum of nelfinavir +M8 concentrations should be the same. This appears not to be the case, as can be observed from the nonsignificant trend in this study and in the ACTG data [9]. The nonsignificance of the threefold difference in frequency of subtherapeutic nelfinavir +M8 $C_{12\,h}$ concentrations between the two subgroups may indicate that a larger study is needed to clarify these observations.

The total sum of nelfinavir +M8 $C_{2\,h}$ plasma concentrations after intake of nelfinavir 750 mg tid has been shown to be significantly higher when *CYP2C19* activities was impaired (3.9 *vs.* 2.8 mg l^{-1} for *CYP2C19* *2/*2 and *CYP2C19* wt/wt genotypes, respectively, and 3.9 *vs.* 2.9 mg l^{-1} when patients were and were not taking inhibitors of *CYP2C19* [2]). Further clinical, pharmacoepidemiological and pharmacogenetic studies are needed to determine whether these differences in the conversion rates of nelfinavir to M8 result in clinically significant improvements in the antiviral efficacy of nelfinavir-based treatment regimens.

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