In vivo comparison of constitutive cytochrome P450 3A activity assessed by alprazolam, triazolam, and midazolam.

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Background: **Previous studies have not demonstrated good correlations between various presumed phenotypic measures of in vivo cytochrome P450 (CYP) 3A activity. However, in reality, few have used appropriate and validated in vivo probes that consider the complexities of CYP3A. Accordingly, the disposition of 3 closely related benzodiazepines with extensive and similar CYP3A-mediated metabolism characteristics but different pharmacokinetics was investigated, and correlations between the drugs were examined.**

Methods: **The single-dose oral clearances of alprazolam, midazolam, and triazolam and the systemic clearances of the latter 2 drugs were separately determined in 21 healthy subjects (10 men) according to a randomized experimental design with a minimum 1-week period between the individual studies. An erythromycin breath test was also performed.**

Results: **After intravenous administration, systemic clearance varied 3-fold compared with a 6-fold range in clearance after an oral dose for all 3 drugs. However, mean values differed markedly between the drugs, with the systemic clearance of midazolam being almost double that of triazolam (383 ± 73 mL/min versus 222 ± 54 mL/min). Oral clearances were even more dissimilar: alprazolam, 75 ± 36 mL/min; triazolam, 360 ± 195 mL/min; and midazolam, 533 ± 759 mL/min. Estimates of CYP3A-mediated extraction by the intestine and liver indicated approximately equal contributions by both organs but larger values for midazolam than for triazolam, and these differences accounted for the differences in oral bioavailability, 30%±13% versus 55%±20%, respectively. Statistically significant (*P* = .001 to .004) correlations between the 3 drugs' oral clearances ranged from 0.60 to 0.68 (r_s value), whereas the correlation for the systemic clearances of midazolam and triazolam was 0.66 (*P* = .001). No statistically significant relationships were observed between any of the clearance parameters and the erythromycin breath test.**

Conclusion: **Despite alprazolam, midazolam, and triazolam having markedly different pharmacokinetic characteristics, statistically significant correlations were present between the oral and systemic clearances of the 3 drugs, consistent with a major involvement of CYP3A in their metabolism and elimination. However, the magnitude of the coefficients of determination (r_s) was such to suggest that an in vivo probe approach, even with the use of valid phenotypic trait values, will be unable to accurately and reliably predict the pharmacokinetic behavior of another CYP3A substrate, as determined by the enzyme's constitutive activity. (Clin Pharmacol Ther 2004;76:341-9.)**