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## Abiraterone inhibits CYP3A4-mediated inactivation of 1α, 25-dihydroxyvitamin D3 in human liver and intestine

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The chemopreventive and therapeutic effects of vitamin  $D_3$  are exerted through its dihydroxylated metabolite,  $1\alpha$ , 25dihydroxyvitamin D, [1a,25(OH),D,]. Inactivation of 1a,25(OH),D, by cytochrome P450 3A4 (CYP3A4) may be an important determinant of its serum and tissue levels. Abiraterone, a steroidogenesis inhibitor used in late stage prostate cancer treatment, is a CYP17A1 inhibitor. The purpose of this study was to assess the potential of abiraterone to block hepatic and intestinal inactivation of biologically active vitamin D, in vitro and to evaluate if abiraterone can alter CYP3A4 marker substrate activities. Biotransformation reactions were initiated with NADPH regenerating solutions following initial pre-incubation of pooled human hepatic or intestinal microsomal protein or human recombinant CYP3A4 supersomes with 1a,25(OH),D,, midazolam or triazolam for 10 min at 37°C. Formation of hydroxylated metabolites of 1a,25(OH)2D3, midazolam or triazolam was analyzed by liquid chromatography-mass spectrometry method. Co-incubation of 1a,25(OH),D, with abiraterone at varying concentrations (0.2-100  $\mu$ M) led to up to ~85% inhibition of formation of hydroxylated metabolites of 1 $\alpha$ ,25(OH)2D3 thus preventing inactivation of active vitamin D3. The IC50 values for individual metabolites of  $1\alpha_2 25(OH)_2 D_2$  ranged from 0.4 to 2.2 µM in human liver microsomes or human intestinal microsomes. The mechanism of CYP3A4-mediated inhibition of  $1\alpha$ ,25(OH), D, by abiraterone was competitive (apparent Ki 2.8-4.3  $\mu$ M). Similar inhibitory effects were also observed upon inclusion of abiraterone into midazolam or triazolam hydroxylation assays. In summary, our results suggest that abiraterone inhibits the CYP3A4-mediated inactivation of active vitamin D<sub>2</sub> in human liver and intestine, potentially providing additional anti-cancer benefits to prostate cancer patients.

## Biography

Subrata Deb has completed his PhD from The University of British Columbia (2009) and postdoctoral fellowship from Vancouver Prostate Centre (2011). His areas of expertise include metabolism of endobiotics (e.g. vitamins, androgens) and xenobiotics (e.g. drugs, toxicants). He has published more than 10 papers in reputed journals and currently serves as an ad-hoc peer reviewer for several journals of repute.

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