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Impact of glucocorticoids on the bioavailability and metabolism of abiraterone and calcitriol

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Glucocorticoids, primarily dexamethasone and prednisone, are routinely used in the cancer treatment regimens to minimize chemotherapy-induced nausea and vomiting, and to suppress inflammation. Interestingly, these corticosteroids are the agonists of glucocorticoid receptor and pregnane X receptor that regulate cytochrome P450 3A4 (CYP3A4) expression in humans and rodents. Since numerous anticancer agents (e.g. abiraterone, docetaxel) and chemopreventive agents (e.g. calcitriol, the biologically active vitamin D3) are substrates of CYP3A4 enzyme, glucocorticoids have the potential to alter the metabolism and bioavailability of anticancer agents. The effects of dexamethasone on the bioavailability of abiraterone (a steroidogenesis inhibitor) were evaluated by treating adult CD-1 mice with dexamethasone dissolved in 50% ethanol at a dosage of 80 mg/kg/day for three consecutive days by intraperitoneal injection. On the fourth day morning, a single dose of abiraterone (180 mg/kg) was administered by oral gavage, followed by collection of blood through tail bleeding method in time intervals between 0.5-24 hrs. Serum abiraterone levels in vehicle- or dexamethasone-treated mice were analyzed by an LC-MS/MS assay using deuterated testosterone as the internal standard. Estimation of peak serum concentration, area under the curve and serum half-life suggests that dexamethasone significantly reduced the bioavailability and increased elimination of abiraterone. Similarly, dexamethasone, but not prednisone, stimulated the metabolism of calcitriol in mouse liver. In conclusion, the results from our laboratory suggest that dexamethasone in cancer treatment regimens may alter the serum levels of anticancer agents and this may reflect in the recent preference of prednisone over dexamethasone as an adjuvant therapy.

Biography

Subrata Deb received his PhD from The University of British Columbia (2009) and Postdoctoral fellowship from Vancouver Prostate Centre (2011). His areas of expertise and interests include cytochrome P450-mediated disposition of drugs and chemopreventive agents. Currently, he is an Assistant Professor in the Department of Biopharmaceutical Sciences, Roosevelt University College of Pharmacy (IL, USA). He has published more than 10 papers in reputed journals and currently serves in editorial boards and as reviewer for several journals of repute.

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