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Relevance of Dosing Time for Everolimus Toxicity in Respect to the Circadian P-Glycoprotein Expression in Mdr1a::Luc Mice

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Abstract : P-glycoprotein (P-gp, MDR1, ABCB1) is a transmembrane protein acting as an ATP-dependent efflux pump and functions as a biological barrier by extruding drugs and xenobiotics out of cells in healthy tissues especially in intestines, liver and brain as well as in tumor cells. The circadian timing system controls a variety of biological functions in mammals including xenobiotic metabolism and detoxification, proliferation and cell cycle events, and may affect pharmacokinetics, toxicity and efficacy of drugs. Selective mTOR (mammalian target of rapamycin) inhibitor everolimus is an immunosuppressant and anticancer drug that is active against many cancers, and its pharmacokinetics depend on P-gp. The aim of this study was to investigate the dosing time-dependent toxicity of everolimus with respect to the intestinal P-gp expression rhythms in mdr1a::Luc mice using Real Time-Biolumicorder (RT-BIO) System. Mdr1a::Luc male mice were synchronized with 12 h of Light and 12 h of Dark (LD12:12, with Zeitgeber Time 0 – ZT0 – corresponding Light onset). After 1-week baseline recordings, everolimus (5 mg/kg/day x 14 days) was administered orally at ZT1-resting period- and ZT13-activity period- to mdr1a::Luc mice singly housed in an innovative monitoring device, Real Time-Biolumicorder units which let us monitor real-time and long-term gene expression in freely moving mice. D-luciferin (1.5 mg/mL) was dissolved in drinking water. Mouse intestinal mdr1a::Luc oscillation profile reflecting P-gp gene expression and locomotor activity pattern were recorded every minute with the photomultiplier tube and infrared sensor respectively. General behavior and clinical signs were monitored, and body weight was measured every day as an index of toxicity. Drug-induced body weight change was expressed relative to body weight on the initial treatment day. Statistical significance of differences between groups was validated with ANOVA. Circadian rhythms were validated with Cosinor Analysis. Everolimus toxicity changed as a function of drug timing, which was least following dosing at ZT13, near the onset of the activity span in male mice. Mean body weight loss was nearly twice as large in mice treated with 5 mg/kg everolimus at ZT1 as compared to ZT13 (8.9% vs. 5.4%; ANOVA, $p < 0.001$). Based on the body weight loss and clinical signs upon everolimus treatment, tolerability for the drug was best following dosing at ZT13. Both rest-activity and mdr1a::Luc expression displayed stable 24-h periodic rhythms before everolimus and in both vehicle-treated controls. Real-time bioluminescence pattern of mdr1a revealed a circadian rhythm with a 24-h period with an acrophase at ZT16 (Cosinor, $p < 0.001$). Mdr1a expression remained rhythmic in everolimus-treated mice, whereas down-regulation was observed in P-gp expression in 2 of 4 mice. The study identified the circadian pattern of intestinal P-gp expression with an unprecedented precision. The circadian timing depending on the P-gp expression rhythms may play a crucial role in the tolerability/toxicity of everolimus. The circadian changes in mdr1a genes deserve further studies regarding their relevance for in vitro and in vivo chronotolerance of mdr1a-transported anticancer drugs. Chronotherapy with P-gp-effluxed anticancer drugs could then be applied according to their rhythmic patterns in host and tumor to jointly maximize treatment efficacy and minimize toxicity.

Keywords : circadian rhythm, chronotoxicity, everolimus, mdr1a::Luc mice, p-glycoprotein
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