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Relevance of Dosing Time for Everolimus Toxicity on Thyroid Gland and Hormones in Mice

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Abstract : Most physiological processes oscillate in a rhythmic manner in mammals including metabolism and energy homeostasis, locomotor activity, hormone secretion, immune and endocrine system functions. Endocrine body rhythms are tightly regulated by the circadian timing system. The hypothalamic-pituitary-thyroid (HPT) axis is under circadian control at multiple levels from hypothalamus to thyroid gland. Since circadian timing system controls a variety of biological functions in mammals, circadian rhythms of biological functions may modify the drug tolerability/toxicity depending on the dosing time. Selective mTOR (mammalian target of rapamycin) inhibitor everolimus is an immunosuppressant and anticancer agent that is active against many cancers. It was also found to be active in medullary thyroid cancer. The aim of this study was to investigate the dosing time-dependent toxicity of everolimus on the thyroid gland and hormones in mice. Healthy C57BL/6J mice were synchronized with 12h:12h Light-Dark cycle (LD12:12, with Zeitgeber Time 0 – ZT0 – corresponding to Light onset). Everolimus was administered to male (5 mg/kg/day) and female mice (15 mg/kg/day) orally at ZT1-rest period- and ZT13-activity period- for 4 weeks; body weight loss, clinical signs and possible changes in serum thyroid hormone levels (TSH and free T4) were examined. Histological alterations in the thyroid gland were evaluated according to the following criteria: follicular size, colloid density and viscidity, height of the follicular epithelium and the presence of necrotic cells. The statistical significance between differences was analyzed with ANOVA. Study findings included everolimus-related diarrhea, decreased activity, decreased body weight gains, alterations in serum TSH levels, and histopathological changes in thyroid gland. Decreases in mean body weight gains were more evident in mice treated at ZT1 as compared to ZT13 ($p < 0.001$, for both sexes). Control tissue sections of thyroid glands exhibited well-organized histoarchitecture when compared to everolimus-treated groups. Everolimus caused histopathological alterations in thyroid glands in male (5 mg/kg, slightly) and female mice (15 mg/kg; $p < 0.01$ for both ZT as compared to their controls) irrespective of dosing-time. TSH levels were slightly decreased upon everolimus treatment at ZT13 in both males and females. Conversely, increases in TSH levels were observed when everolimus treated at ZT1 in both males (5 mg/kg; $p < 0.05$) and females (15 mg/kg; slightly). No statistically significant alterations in serum free T4 levels were observed. TSH and free T4 is clinically important thyroid hormones since a number of disease states have been linked to alterations in these hormones. Serum free T4 levels within the normal ranges in the presence of abnormal serum TSH levels in everolimus treated mice may suggest subclinical thyroid disease which may have repercussions on the cardiovascular system, as well as on other organs and systems. Our study has revealed the histological damage on thyroid gland induced by subacute everolimus administration, this effect was irrespective of dosing time. However, based on the body weight changes and clinical signs upon everolimus treatment, tolerability for the drug was best following dosing at ZT13 in both male and females. Yet, effects of everolimus on thyroid functions may deserve further studies regarding their clinical importance and chronotoxicity.

Keywords : circadian rhythm, chronotoxicity, everolimus, thyroid gland, thyroid hormones
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