Life Sciences 219 (2019) 31–39

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

PK-PD based optimal dose and time for orally administered supra-pharmacological dose of melatonin to prevent radiation induced mortality in mice

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ARTICLE INFO

Keywords:
Melatonin
Pharmacokinetics
Pharmacodynamics
Optimal dose
Drug radiation gap period
Gamma radiation

ABSTRACT

Aims: The study reports preclinical pharmacokinetics (PK) and correlation with pharmacological effect at supra-pharmacological dose of orally administered melatonin along with time and dose optimization, which have been lacking in earlier reports of radioprotection using melatonin.

Methods: PK of melatonin in C57BL/6 mice was evaluated after dose of 250 mg/kg using HPLC. Tissue distribution study was conducted in vital organs following oral administration. Plasma total antioxidant capacity (TAC) was determined by $ABTS^{\cdot+}$ radical assay and was correlated to plasma concentrations of melatonin. Using the outcomes of PK and Pharmacodynamics (PD), survival study was conducted for optimization of 'drug radiation gap period' (DRGP). Optimal oral dose for radioprotection was determined using survival as an end point.

Key findings: PK analysis of melatonin revealed T_{max} at 5 min with closely spaced another distinct concentration peak at 20 min. Plasma TAC of melatonin showed similar peaks at 5 min and 45 min, with the highest TAC at 45 min. Survival following a lethal (9 Gy) radiation dose was 20% and 40% after 5 and 45 min of melatonin administration, respectively. DRGP for melatonin was thus 45 min, while optimal oral dose ranged from 125 to 250 mg/kg. PK parameters at 250 mg/kg dose were qualitatively similar to low dose of melatonin, thus preventing chances of unexpected toxicity.

Significance: Survival enhancement at 45 min suggested as probable interval required as 'DRGP'. The optimum oral therapeutic window appears large with no substantial toxicity. The outcomes will be useful in development of radioprotectors as well as other therapeutic applications.

1. Background

Melatonin (*N*-acetyl-5-methoxytryptamine) is secreted from the pineal gland, and also synthesized in the gastrointestinal and other tissues in trace amount. Melatonin has multiple properties including free radical scavenger [1]. Several reports suggest that melatonin pre-treatment protects biomolecules in cells from oxidative damages [2]. It enhances activity of antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) and inhibits action of pro-oxidant enzyme (nitric oxide synthase) [3,4]. Melatonin receptors are present in cells and have multiple roles, including protection of normal cells from oxidative damage for example by ionizing radiation [5,6].

Protection against radiation injuries during accidental exposure is an unmet medical need. Melatonin was first demonstrated for radioprotection by Blickenstaff et al. [7] and further by Vijayalaxmi et al. [8]. The beneficial effect of melatonin against radiation induced injury was confirmed in Swiss ND4 and CD2-F1 mice at 30 min intraperitoneal (i.p) preadministration [7,8]. Its radio-protective efficacy has been reported at varying doses in mice administered intraperitoneally 30 min prior to radiation [7–10].

A series of reports by Vijayalaxmi et al. [8,11,12], using cytogenetic assays in animal and human peripheral blood cells (in vitro) exposed to irradiation demonstrated protective effects of melatonin. Furthermore, in human study, after a 300 mg oral dose, the blood samples were

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https://doi.org/10.1016/j.lfs.2019.01.007
Received 27 October 2018; Received in revised form 31 December 2018; Accepted 6 January 2019
Available online 06 January 2019
0024-3205/

Self Attested