PBPK model for prediction and simulation of melatonin pharmacokinetics
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Introduction

- Melatonin is a biogenic amine that is found in animals, plants and microbes. Aaron B. Lerner of Yale University is credited for naming the hormone and for defining its chemical structure in 1958.
- In humans, melatonin is produced mainly by the pineal gland starting from tryptophan which is converted to serotonin. Serotonin conversion to melatonin involves two different enzymes (SNAT and HIOMT) whose activity rise soon after the onset of darkness following the release of the neurotransmitter norepinephrine from sympathetic neurons terminating on the pineal parenchymal cells. In fact, melatonin production follows a circadian rhythm (day-night cycle).
- Endogenous concentrations of melatonin decrease with age.

Mathematical formulation

- The model consists of ordinary differential equations representing the material balances of melatonin in the compartments. The general formulation of these material balances is the following:

\[
\frac{da}{dt} = IN - OUt + PRDB
\]

Where in IN represents the fluxes entering the compartments or the input drug rate, OUt represents the fluxes exiting the compartments and PRDB indicates the production rate, which is only present in the pineal gland compartment.

The model accounts for the intravenous and oral (immediate and controlled release formulations) routes of administration.

Results

- After identification of the non-individualized parameters, the model is validated with experimental data extracted from literature.
- The model results to be reliable in the prediction of the pharmacokinetics of endogenous melatonin, and exogenous melatonin administered via either enteral and parenteral route.

Conclusions

- The model can find multiple applications:
  - Support in the selection of the optimal route of administration/dosing regime with the aim of producing either pharmacological or endogenous levels.
  - Optimization of the dosing regime through correlation with pharmacodynamic indexes
  - Individualization of the PK prediction through introduction of correction factors (e.g., renal disease; liver disease)

Future work will focus on the study of the effects of melatonin on tumoral cells and the development of models of the target organs of melatonin.

References


ADME processes and exogenous melatonin

- The physiologically-based pharmacokinetic (PBPK) model allows determining melatonin concentration in the different body organs and tissues, accounting for the processes of absorption, distribution, metabolism and elimination (ADME).
- In the figure, the rectangles indicate the compartments which are assimilated to the body parts, the black arrows indicate the convective or diffusive fluxes between the compartments; the dashed light blue arrows indicate the routes of administration and the red dashed arrows indicate the metabolism/elminination pathways.

Endogenous production

- Production of melatonin is described by a periodic function multiplied for a correction factor that accounts for the age of the patient.

\[
PC = \cos(t_{\text{age}}) + \cos(t_{\text{age}} + 2\pi n) + \sin(t_{\text{age}} + 2\pi n) + \phi) + 220 \text{ min} + \phi) + 30 \text{ hr} + \phi) + 7 \text{ days} \]

Where \( t_{\text{age}} = \frac{\text{age}}{365} \text{ years} \)

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