Early blood samples of MPH seem to lead to higher DAT occupancy, consistent with an acute tolerance observed in clinical rating scales.

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Introduction

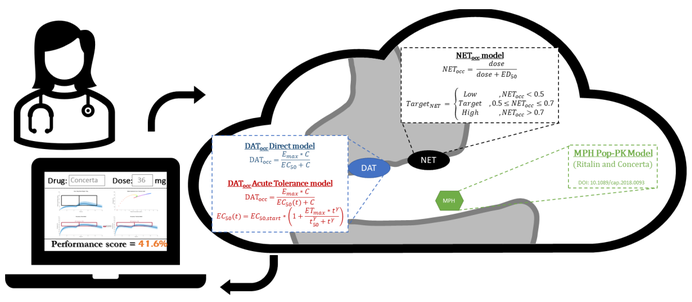
Methylphenidate (MPH) is a psychostimulant which inhibits the uptake of dopamine and norepinephrine transporters, DAT and NET, and is mostly used to treat Attention Deficit/Hyperactivity Disorder. The current dose optimization is done through titration, a cumbersome approach for patients.

An acute tolerance to MPH has been proposed to explain that there is a lower efficacy of MPH in the afternoon compared to the early hours post-dose, despite similar levels of plasma concentration [1].

It is important to work upstream and consider PD endpoints that characterize the time course of MPH effect and quantify its target binding (i.e., to DAT and NET) to allow an exploration of (i) each transporter's involvement in the efficacy of MPH and (ii) an objective and mechanistic rationale for the acute tolerance to MPH upstream of behavioral effects which may be further confounded by environmental factors.

Objectives

1. Propose a quantitative evaluation of the therapeutic performance of MPH regimen based on a PKPD framework
2. Perform and exploratory study of the acute tolerance of DAT_{occ}
3. Assess the availability of current data to base therapeutic performance indices on DAT and NET ocucpancy



Methods

We introduce an in silico framework composed of (i) a population pharmacokinetic model of MPH [2], (ii) a pharmacodynamic (PD) model of DAT and NET occupancy, (iii) a therapeutic box delimited by time and DAT occupancy, and (iv) a performance score computation [3].

PKPD Models of DAT and NET occupancy

DAT occupancy data was digitized (n=152) and described with an indirect Emax model. The acute tolerance model assumes a time-dependent acute tolerance through a change of EC50 in function of time [1].

$$DAT_{occ} = \frac{E_{max} * C_{plasma}}{EC_{50}(t) + C_{plasma}}$$

$$EC_{50}(t) = EC_{50,start} * (1 + \frac{ET_{max} * t^{\gamma}}{t_{50}^{\gamma} + t^{\gamma}})$$

NET occupancy was described with a dose-PD model [4].

$$NET_{Occ} = \frac{dose}{dose + ED_{50}}$$

Performance Score

We used this integrative framework to simulate the performance of extended-release MPH (18-99mg).

$$Performance = \sum_{i \in I} w_i \begin{cases} \text{for minimisation:} \\ \frac{\max(TI_i(.)) - TI_i(\text{ Regimen })}{\max(TI_i(.)) - \min(TI_i(.))} \\ \text{for maximisation:} \\ \frac{\text{TI}_\text{i}(\text{Regimen}) - \min(TI_i(.))}{\max(TI_i(.)) - \min(TI_i(.))} \end{cases}$$

where TI is the therapeutic indicator, i refers to the TI, and w_i is the weight attributed to TI_i based on a practitioner's experience, with $\sum w_i = 1$ [3].

Results

Early blood samples of MPH seem to lead to higher DAT occupancy, consistent with an acute tolerance observed in clinical rating scales.

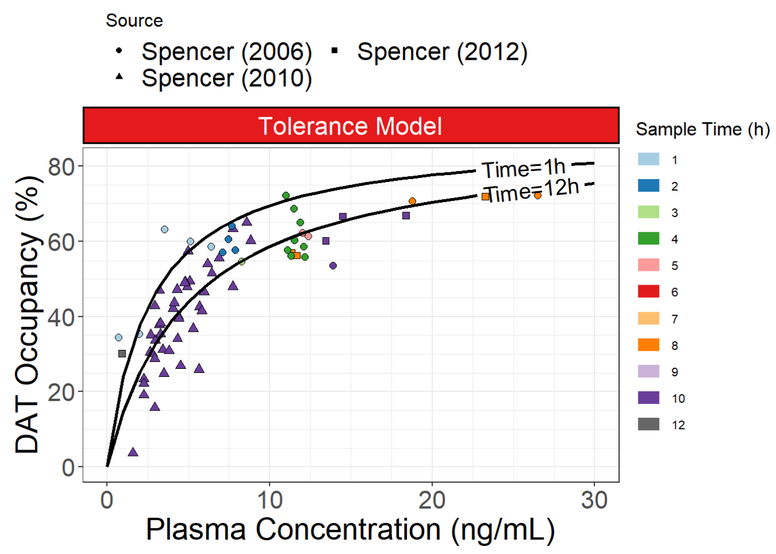


Figure 1: DAT occupancy and d-MPH plasma concentration of digitally extracted data from [5, 6, 7]. The black lines show the model predictions, shown for two examples of sample times (at 1h and 12h post-dose).

Table 1: Parameter estimates of the tolerance DATocc model

	Estimated Parameter Value	RSE (%)
Emax	85.08	2.9
EC50,start	2.68	9.7
ETmax	1	
t50	4.56	8.1
gamma	1	
Additive Residual Error	68.22	12

For more information on this work:

Simulations of MPH Regimen

Peak performance is observed following 63mg of MPH. Higher doses of MPH are associated with PK or DAT occupancy curves which exceed the TB, which leads to a decrease in performance scores.

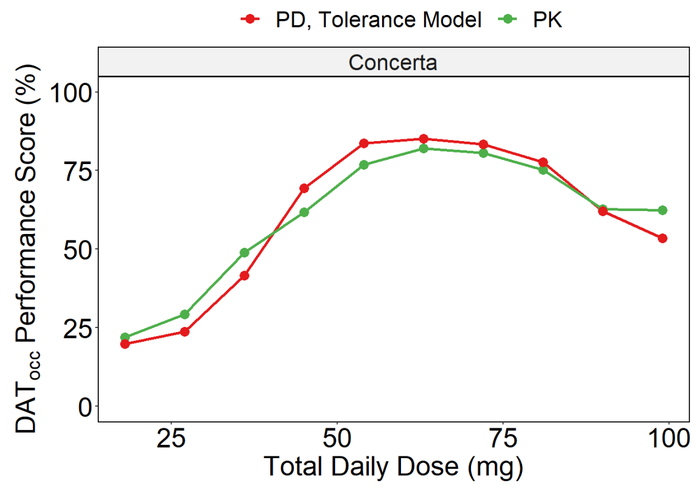


Figure 2: Dopamine transporter occupancy (DAT_{occ}) performance scores for MPH regimen as a function of the total daily dose. The optimized timing refers 7:30am, 9:30am and 12:30pm [3]

Simulations indicate that the smallest commercially available dose of Concerta is the only one which leads to a NET occupancy within the desired range despite very poor performance regarding DAT occupancy (results not shown).

Conclusion

Our analysis is consistent with the notion of clinical overdose and the therapeutic value of low doses for some ADHD patients [8]. As well, it does not deny the existence of an acute tolerance. This work justifies the need for a more systematic collection of DAT and NET occupancy data to further investigate the presence of acute tolerance and assess the impact of low MPH doses on its efficacy [9].

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