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A quantitative systems pharmacology study on optimal scenarios for switching to paliperidone palmitate once-monthly

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ABSTRACT

Long-acting injectable (LAI) antipsychotic formulations are increasingly used for improving patient compliance and long-term outcomes. Transitioning to LAIs raises questions regarding how optimum efficacy can be rapidly achieved while minimizing potential efficacy and safety concerns related to overlapping plasma levels of prior treatments and the new LAI. Ideally, randomized clinical trials would provide guidance regarding transition algorithms, but the number of studies and sample size required to address relevant questions makes this approach unachievable. We have used quantitative systems pharmacology, a clinically calibrated, mechanism-based computer model for schizophrenia to identify optimal switching scenarios to injectable paliperidone palmitate once-monthly (PP1M) from oral antipsychotics. We show that starting PP1M 1 day after the last oral medication dose or 4 weeks after the last LAI injection provides optimal benefit–risk compared to a delayed PP1M start after 1 week with either a 1- or 2-week overlap with oral paliperidone. Although a similar or better therapeutic effect can be achieved within 2 weeks for oral medications and LAI haloperidol decanoate and 8 weeks for LAI aripiprazole, we identified a potential transient undertreatment liability in all cases except for risperidone. Switching from oral olanzapine may lead to a small reduction of antipsychotic efficacy in some patients. Switching to PP1M decreases extrapyramidal symptom liability in most cases, but increased dopamine D_2 receptor inhibition (except for haloperidol) might potentially increase prolactin synthesis. Overall, these results suggest time-windows for which the treating clinician must be most vigilant for potential efficacy and safety signals when switching to PP1M.

1. Introduction

Increasingly, long-acting injectable (LAI) antipsychotic treatments are recognized as important for enhancing patient compliance as part of good treatment management of schizophrenia (Correll, 2014). Poor adherence, particularly among those early in the course of their illness, leads to worse long-term outcomes than does consistent, well-documented treatment (Subotnik et al., 2011). Despite the clinical benefits of LAIs, numerous challenges remain for their adoption into general psychiatric practice (Kane, 2014; Weiden et al., 2015). It takes months for LAIs to achieve steady-state equilibrium, and knowing how to quickly transition patients from prior treatments to optimal doses of a new LAI regimen can be difficult. A good switching paradigm is important for preventing patients from being exposed to either excessive or inadequate concentrations of antipsychotics during the period of transition.

Performing clinical trials to identify optimal switching paradigms is impractical due to the large number of patients needed to address the multitude of potential switching options and dosing variants. Fortunately, pharmacokinetic (PK) interactions between antipsychotics are not common (see Supplementary information, Section S1). On the other hand, complex nonlinear pharmacodynamic (PD) interactions related to the rich and differential pharmacology of the many antipsychotic treatment options are likely. These differing pharmacologic profiles have important implications at the level of neuronal circuits and are challenging to quantify. For instance, combining other antipsychotics with aripiprazole often results in lower than anticipated clinical efficacies since switching between them involves competition between a full dopamine D_2 receptor (D_2R) antagonist and a partial D_2R agonist (aripiprazole) (Kim et al., 2009; Takeuchi et al., 2009; Wisniewski and Robert, 2012; Takeuchi and Remington, 2013). The level of competition depends on the relative concentration of the two drugs and their binding affinities. The resulting complex PD interactions can affect both efficacy outcome and side-effects, including motor symptoms and prolactin synthesis.

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Statistical analyses of databases that include antipsychotic combinations often fail to identify PD interactions on efficacy and safety measures because of the limited number of representations for each unique drug–dose combination. A novel way to address this issue is to simulate different switching scenarios using quantitative systems pharmacology (QSP) modeling that reflects the neurophysiology, neuropathology, and neuropharmacology of different drugs in "virtual" schizophrenia patients. This requires a mechanism-based computer model that is well calibrated both for motor side-effects (Roberts et al., 2016) and clinical efficacy (Spiros et al., 2012; Spiros et al., 2017) using historical clinical trial data. Blinded prior predictive modeling work that is based on preclinical pharmacology has suggested that this platform can anticipate unexpected clinical outcomes for novel antipsychotic drugs (Geerts et al., 2012; Liu et al., 2014).

In this article, we simulate different scenarios for switching to PP1M from oral risperidone, haloperidol, aripiprazole, and olanzapine, and from long-acting haloperidol decanoate (HALD) and aripiprazole extended-release injectable suspension (AERIS). The objective of this work was to provide guidance for practical and safe scenarios for switching from each of the alternative antipsychotics based on QSP modeling. Treatment of patients with PP1M was based on the recommended dosing regimen (first injection of 234 mg, followed by injections of 156 mg on days 8, 38, and 68, and every 30 days thereafter), thereby fixing the PK profile (Samtani et al., 2011). Although in principle we can simulate many different tapering algorithms of the baseline antipsychotics, we focused here on comparing three simple scenarios (see Section 3.3). The PK parameters for each antipsychotic formulation were derived from publicly available data.

2. Materials and methods

The modeling approach is shown schematically in Fig. 1. Initially, plasma PK profiles of the different drugs were calculated using previously established PK parameters for each of the paired drugs (Methods section 2.1). Plasma levels were then converted to functional intrasynaptic brain concentrations using published studies on positron emission tomography (PET) tracer displacement (Methods section 2.2). Nonlinear PD interactions were simulated in the QSP model for any combination of the two drugs at specific doses to generate look-up tables corresponding to Positive and Negative Syndrome Scale (PANSS) total and extrapyramidal symptom (EPS) liability. Prolactin increase is usually associated with the level of striatal D_2R inhibition (Arakawa et al., 2010). Therefore, we generated look-up tables for the combined level of striatal D_2R inhibition using the functional intrasynaptic concentration of the two drugs. Time-dependent changes in free intrasynaptic drug concentrations for each switching scenario were used to calculate anticipated changes in clinical readouts of PANSS total scores, EPS liability, and D_2R inhibition using linear interpolation from these lookup tables with a time resolution of 24 h over 90 days and 360 days for a switch from oral and LAI antipsychotics, respectively.

2.1. Pharmacokinetics profile simulation

PK parameters for the different drugs are shown in Table 1. Plasma concentrations $C_n(t)$ at t hours after the n-th dose D were determined by (Wakamatsu et al., 2013):

$$C_{n(t)} = \frac{FDk_a}{V_d(k_a - k_e)}\left(\frac{1-e^{-nk_e}}{1-e^{-k_e\tau}} * e^{-k_e t} - \frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}} * e^{-k_a t}\right) \quad (1)$$

where F is the bioavailability, D the dose, k_a and k_e the single-dose absorption and elimination rate constant, respectively, V_d the volume of distribution, and τ the dosing interval.

2.2. The receptor competition model

The receptor competition model as previously described (Spiros et al., 2010; Athan Spiros, 2012), simulates dynamic changes in

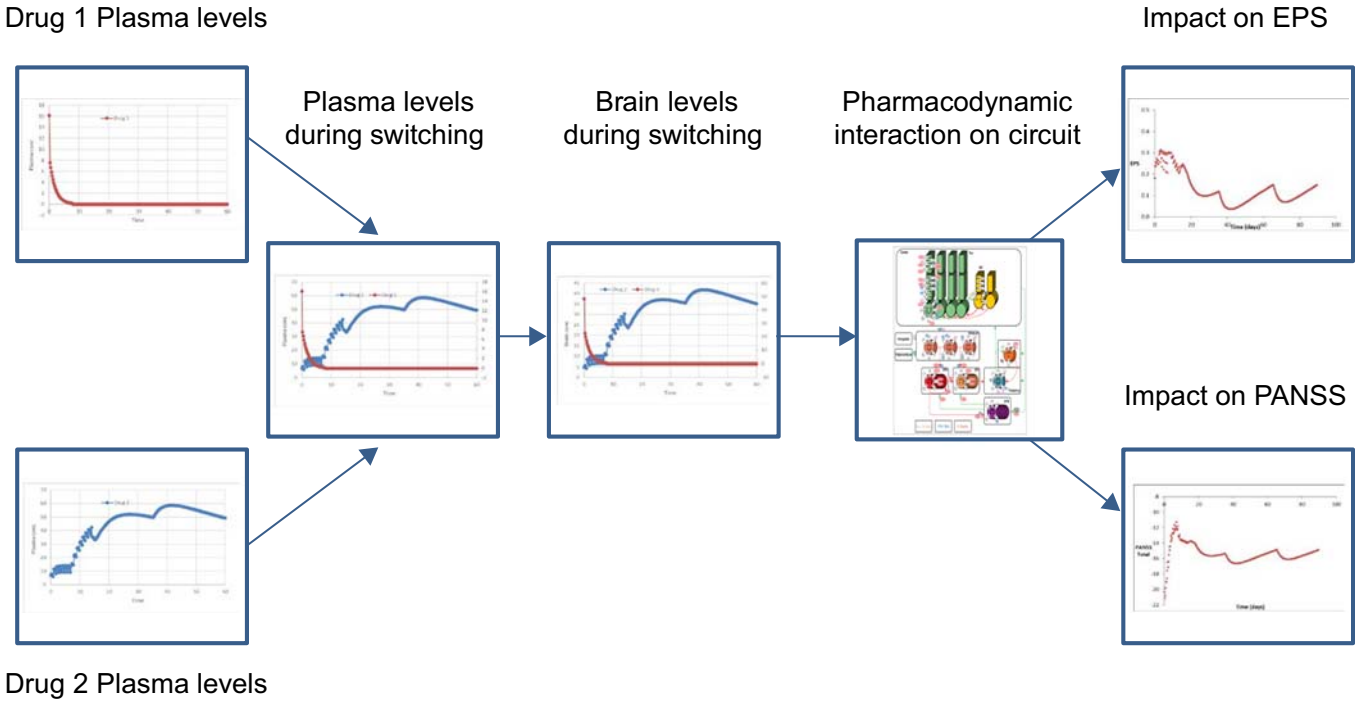

Fig. 1. Modeling pipeline for determining optimal switching paradigm. Plasma profiles for each drug are derived using traditional PK calculations. A particular switching scenario is then implemented and plasma level changes are calculated, assuming no PK–PK interactions. Using historical PET imaging tracer experiments, these plasma levels are then converted into dynamic functional intrasynaptic drug concentrations. For each synapse in the QSP model, the resulting effect on postsynaptic receptor activation by the two drugs using their appropriate multitarget pharmacology profile is then calculated. The pharmacodynamic impact of the combination of the two drugs is then simulated using the mechanism-based QSP platform for PANSS total score, EPS, and D_2R inhibition with the calculated activation changes in all receptors affected by the two drugs based on their appropriate affinity.

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