Physiologically based pharmacokinetic (PBPK) model for intramuscular injection of aripiprazole

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Introduction

Aripiprazole is an atypical antipsychotics drug that is widely used in the treatment of agitation associated with schizophrenia, schizoaffective disorder, schizophreniform disorder or bipolar I disorder. It has been reported [1] that intramuscular injection of aripiprazole was more effective than placebo in these patient populations. It is also valuable for patients who are unable or unwilling to take oral medication. A mechanistic model was developed to describe the disposition of aripiprazole at the site of intramuscular injection. Local binding, clearance, and blood flow can be specified, with other muscle characteristics similar to those described for muscle tissue by the PBPK model.

Method

An absorption/PBPK model for aripiprazole pharmacokinetics (PK) after intravenous (IV) and intramuscular (IM) administration was developed using GastroPlus™ 9.5-beta (Simulations Plus, Inc.):

- The physicochemical properties of the drug were collected from the experimental published studies or estimated by ADMET Predictor v7.2 (Simulations Plus, Inc.).
- The program’s Advanced Compartmental Absorption and Transit (ACAT™) model described the intestinal absorption of the drug, while PK was simulated with its PBPKPlus™ module.
- Physiologies were generated by the program’s internal Population Estimates for Age-Related (PEAR) Physiology™ module.
- The perfusion-limited tissue model was used to describe drug distribution in all tissues. Tissue/plasma partition coefficients (Kps) were predicted using Lukacova (default) method.
- Aripiprazole clearance was fitted against reported [2] plasma concentration-time profile after a single 2-mg intravenous infusion of aripiprazole in healthy subjects (Figure 2(a))
- The intramuscular model within the GastroPlus Additional Dosage Routes Module™, along with the PBPK model calibrated against intravenous data, was used to predict aripiprazole PK after a single 5-mg intramuscular injection in healthy subjects and 1.0-, 3.0- and 7.5-mg doses once daily for four days in patients with schizophrenia (Figure 2(c)-(e)) [2].

References