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Evaluation of Methamphetamine and Amphetamine Disposition Discrepancy upon Selegiline Transdermal patch Administration in Healthy volunteers versus Special populations using PBPK modelling

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PURPOSE

R (-) Selegiline (SEL) transdermal patch (EMSAM®) has been approved in United States for the treatment of major depressive disorder (MDD) for patients above 12 years. Suicidality is the major risk factor for antidepressant drug therapy[1]. It is primarily metabolized to methamphetamine (MAP) and Desmethyl selegiline (DMS) which is further metabolized to amphetamine (AMP), as shown in Figure 1. The behavioural untoward effects of SEL e is due to the systemic exposure of its metabolites MAP and AMP [2]. The CYP enzymes involved in their biotransformation have variable turnovers in different populations.

OBJECTIVE(S)

The objective of the study was to evaluate disposition discrepancies of SEL and its metabolites between healthy and special populations using physiologically based pharmacokinetic (PBPK) model to minimize therapeutic risk. Absorption and disposition of SEL transdermal patch was evaluated through Multi-Phase Multi-Layer Mechanistic Dermal Absorption ((MPML MechDermA) model) (Figure 2), integrated within a bottom up PBPK model (Simcyp simulator version 18).

METHOD(S)

The transdermal absorption parameters (diffusion and partition coefficients) in different layers of skin were calculated through QSAR models. The drug release from the patch was defined through a first order rate constant (**k = 0.04 h^{-1}**). The intrinsic clearance of selegiline and its primary metabolites of different CYP enzymes involved in their metabolism were calculated using Simcyp Reverse Translation tool. The PBPK model captured parent, primary metabolites (MAP and DMS) and secondary metabolite (AMP) making it the first most detailed PBPK model of SEL disposition. The simulations of SEL and its metabolites were performed in different doses/dosage regimens compared with the corresponding observed literature data [3]. The verified PBPK model was then utilized for the prediction of PK in adolescent (Age 12-20 years) and hepatic and renal impairment populations at the therapeutic dose of 20 mg per 20 cm2.

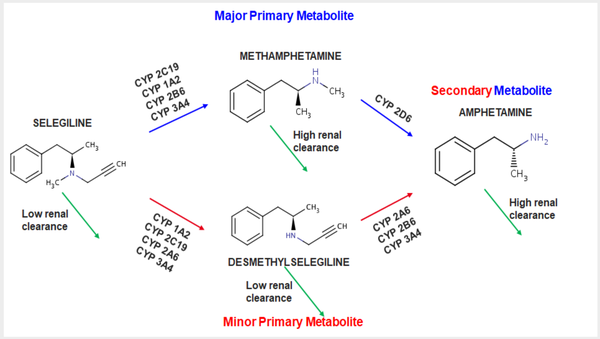


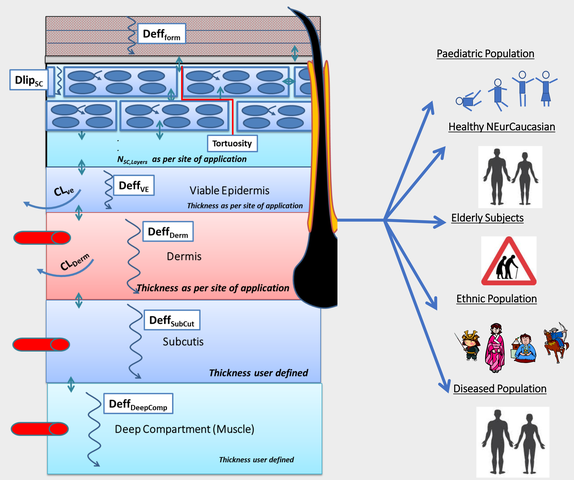
Figure 1 Schematic representation of biotransformation of Selegiline and its metabolites

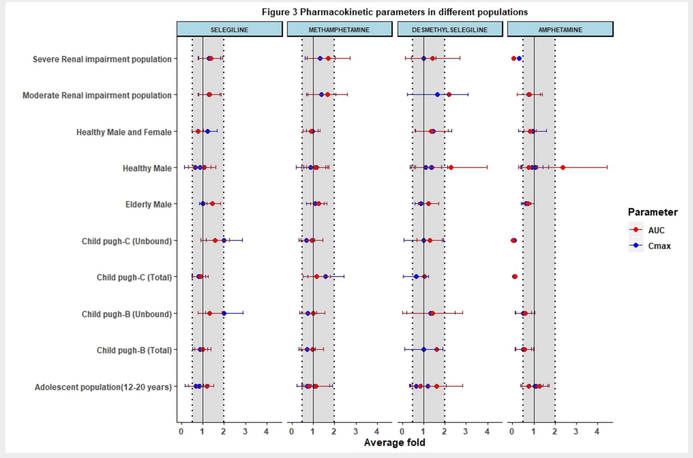
RESULT(S)

The PBPK simulation results of different studies are summarized in Figure 3. The predicted PK parameters of SEL and metabolites were in agreement with observed values within 1.5 fold (Figure 3). Higher mean fold error for AMP and DMS at 18.3 mg dose was due to higher variability in observed values. The PK parameters of parent and metabolites in adolescent population (12-20 years) did not vary significantly from adults (< 2-fold error) indicated that they might be at a minimal risk of untoward effects (Figure 3).

Conversely, Cmax and AUC estimates of SEL in renally impaired (RI, GFR 30-60 in moderate and <30 in severe) were close enough (< 1.5 fold) to the healthy subjects (Figure 3). However, a 2-fold increase in AUC of methamphetamine (primary metabolite) and a significant decrease in amphetamine levels (secondary metabolite) were simulated in those subjects.

The effect of renal impairment (RI) on the PK of these polar metabolites (MAP and AMP) was expected since they are significantly eliminated by renal route (**renal clearances of MAP: 8.74 L/hr** and **AMP: 8.04 L/hr**). Also, the metabolic conversion of MAP to AMP was affected due to decrease in CYP2D6 expression in RI patients (intrinsic hepatic CYP 2D6 clearance of MAP to AMP in healthy: **1.15**, moderate RI: **0.45** and severe RI: **0.35** L/h [4]. CYP2D6 polymorphism in different populations further complicates its disposition (Figure 4A). PK parameters from total systemic concentrations concealed (bound and unbound) the variability of SEL, but it was revealed upon monitoring the PK parameters from unbound plasma concentrations. This was due to increase in free fraction unbound value of SEL (Figure 4B) due to decreased albumin content in hepatic impaired patients [5].





CONCLUSION(S)

- ✓PK of SEL and its metabolites were verified using mechanistic dermal absorption PBPK model at different transdermal doses.
- ✓MAP and AMP disposition differences in RI patients as compared to healthy was observed; it is due to decreased CYP2D6 expression.
- ✓Hepatic and renal impairment patients are at a potential risk of untoward effects of the metabolite, and may require a closer clinical monitoring during the selegiline antidepressant therapy.

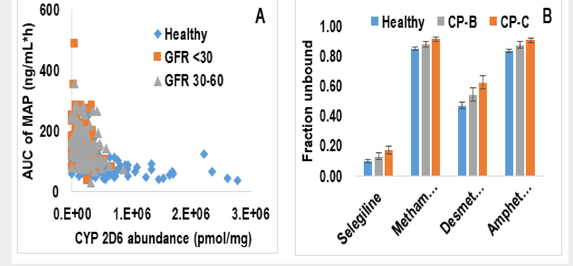


Figure 4 (A) Area under curve versus CYP 2D6 enzyme abundance in renal impaired versus healthy (B) Fraction unbound values of selegiline and metabolites in hepatic impaired versus healthy

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

1. Emsam®(selegiline transdermal system) continuous delivery for once-daily application.
2. Logan, B. K. (2002). "Methamphetamine-effects on human performance and behavior." Forensic science review 14(1): 133-151.

3. New Drug Application number : 21-336/21-708 Clinical Pharmacology and Biopharmaceutics Review. CDER. US-FDA.

4. "Influence of renal failure on the hepatic clearance of bufuralol in man." Journal of pharmacokinetics and biopharmaceutics **8**(5): 421-438.

5. "Oxidative damage of albumin in advanced liver disease". Biochimica et Biophysica Acta, 2008. **1782**(7-8): p. 469-473.

The Simcyp Simulator is freely available, following completion of the relevant workshop, to approved members of academic institutions and other not for -profit organizations for research and teaching purposes.

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