Göteborg, 2023

Pharmacokinetics and pharmacodynamics of the psychedelic compound DMT

Akademisk avhandling

Som för avläggande av farmacie doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, den 13 december, klockan 09:00

av Emma Eckernäs

Fakultetsopponent:
Professor Iñaki Troconiz
Universidad de Navarra, Spanien

Avhandlingen baseras på följande delarbeten

I. **Eckernäs E**, Bendrioua A, Cancellerini C, Timmermann C, Carhart-Harris R, Hoffmann K-J, Ashton M. Development and application of a highly sensitive LC-MS/MS method for simultaneous quantification of N,N-dimethyltryptamine and two of its metabolites in human plasma. *Journal of Pharmaceutical and Biomedical Analysis,* 2022;212:114642.

II. **Eckernäs E**, Timmermann C, Carhart-Harris R, Röshammar D, Ashton M. Population pharmacokinetic/pharmacodynamic modeling of the subjective psychedelic experience induced by N,N-dimethyltryptamine – implications for dose considerations. *Clinical and Translational Science,* 2022;15(12):2928-2937

III. **Eckernäs E**, Timmermann C, Carhart-Harris R, Röshammar D, Ashton M. N,N-dimethyltryptamine affects electroencephalography response in a concentration dependent manner – a pharmacokinetic/pharmacodynamic analysis. *CPT:Pharmacometrics and Systems Pharmacology,* 2023;12(4):474-486.

IV. **Eckernäs E,** Macan-Schönleben A, Andresen-Bergström M, Birgersson S, Hoffmann K-J, Ashton M. N,N-dimethyltryptamine forms oxygenated metabolites via CYP2D6 - an in vitro investigation. *Submitted*

V. **Eckernäs E**, Koomen J, Timmermann C, Carhart-Harris R, Röshammar D, Ashton M. Optimized infusion rates for N,N-dimethyltryptamine to achieve a target psychedelic intensity based on a modeling and simulation framework. *CPT:Pharmacometrics and Systems Pharmacology,* 2023;12(10):1398-1410

VI. **Eckernäs E**, Luan L, Timmermann C, Carhart-Harris R, Röshammar D, Ashton M. Using pharmacokinetic/pharmacodynamic modeling and simulation to design individually tailored infusion rates for an extended DMT experience. *In manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Pharmacokinetics and pharmacodynamics of the psychedelic compound DMT

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Abstract

N,N-dimethyltryptamine (DMT) is a psychedelic compound that is being investigated as a treatment option in depression. It is also being used as a research tool in research aiming to investigate the neurobiology of the human consciousness using brain imaging techniques. However, despite the increasing research on DMT, much remains to be known about its pharmacokinetic and pharmacodynamic properties. Increasing this understanding is essential in assuring safe and efficacious use of DMT in the future.

The aim of this thesis was to investigate the pharmacokinetics and pharmacodynamics of DMT as well as to use the newly gained knowledge to design new dose regimens. A liquid chromatography tandem mass spectrometry method was developed and validated to enable quantification of DMT and two of its metabolites in biological samples. Nonlinear mixed effects modeling was used to describe the pharmacokinetics and pharmacodynamics of DMT using data obtained from two clinical studies. The models were used to provide dose recommendations for administering DMT as a continuous intravenous infusion. A more individualized dose regimen, based on observed psychedelic intensity ratings, was also developed. The metabolism of DMT *in vitro* was assessed using human liver microsomes as well as recombinant cytochrome P450 enzymes. These experiments showed that DMT is a substrate for CYP2D6 and that this likely leads to formation of hydroxylated metabolites.

Overall, this thesis provides new knowledge on the pharmacokinetics and pharmacodynamics of DMT. It also presents novel dosing strategies and demonstrates how pharmacokinetic and pharmacodynamic modeling and simulation can be used to further optimize DMT dosing in future clinical studies.

Keywords: N,N-dimethyltryptamine, psychedelic, nonlinear mixed effects modeling, pharmacokinetics, pharmacodynamics

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