K34 Pharmacokinetic and Pharmacodynamic Differences Between Paramethoxymethamphetamine (PMMA), Paramethoxyamphetamine (PMA), 3,4-Methylenedioxymethamphetamine (MDMA), and Amphetamine in a Mouse Model

Robert Kronstrand, PhD, National Board of Forensic Medicine, Dept of Forensic Toxicology, Artillerigatan 12, Linkoping SE 58758, SWEDEN; Mikael Andersson, PhLic, National Board of Forensic Medicine, Artillerigatan 12, Linkoping 58758, SWEDEN; and Hanna Göthe, MSc, National Board of Forensic Medicine, Artillerigatan 12, Linkoping 58758, SWEDEN*

After attending this presentation, attendees will be able to describe the pharmacokinetics of PMMA and related drugs. Attendees will also recognize the differences in behavior the drugs induce in a mouse model.

This presentation will impact the forensic science community by adding pharmacokinetic and pharmacodynamics data for PMMA and related drugs in a mouse model.

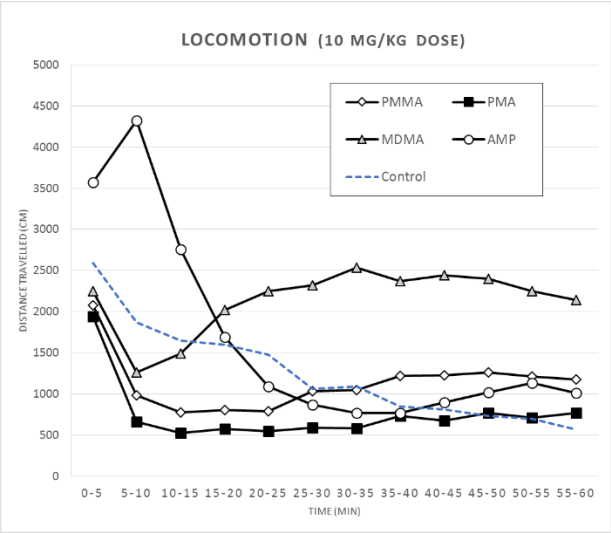
Background: Controlled study data regarding the pharmacology of PMMA and PMA in humans are lacking, but some data is available for the rat, pointing toward MDMA-like effects. Also, studies have suggested there is a delay in brain uptake that may trigger the user to take another dose because of absence of effect.

Goals: The goals of this study were to investigate the pharmacokinetics of PMMA and PMA in a mouse model and to compare their pharmacodynamics with MDMA and amphetamine.

Methods: The experiments were approved by the Animal Ethics Committee in Linköping, Sweden. Male C57/BL6 mice, 8-12 weeks old, weighing 25±1g were used for the experiments. The behavioral experiments were performed in an open field model. A video camera recorded the movements of the mouse during 60min and the movements were analyzed using EthoVision XT 9. Total distance travelled and time spent in the central zone were measured. In the behavior experiments, the animals (*N*=10) were dosed via intraperitoneal injection (i.p.) with either 0, 1, 5, or 10mg/kg of each substance immediately prior to the open field session.

Two pharmacokinetic experiments were conducted. First, dose concentration relationships were investigated using the same doses as in the behavior experiments with animals (*N*=5) sacrificed at 60 minutes. In addition, blood and brain kinetics were investigated for PMA and PMMA at 5mg/kg and 10mg/kg, respectively. The higher PMMA dose was chosen to increase the possibility of also measuring PMA formed from PMMA. Samples were obtained at 5, 10, 20, 40, 60, 80, and 120 minutes after injection.

Blood and brain concentrations of the substances were determined by Ultra High-Performance Liquid Chromatography-Tandem Mass Spectrometry (UHPLC-MS/MS) using an AB Sciex™ 4500 coupled to a Shimadzu® LC-30AD liquid chromatograph. The column used was an Acquity® UPLC® BEH Phenyl (2.1mm x 50mm, 1.7µm). In brief, 100µL whole blood was fortified with internal standard, precipitated, then further diluted 10 times before analysis. The whole brain was weighed and homogenized in 0,075% HFo in acetonitril/ethanol (90:10), an aliquot fortified with internal standard and then diluted 20 times.



Results: There was a good positive correlation between dose and both blood and brain concentrations for all four substances with Pearson's *r* between 0.90 and 0.99.

The kinetics of PMA and PMMA were slightly different. PMMA distributed equally fast to blood and brain whereas PMA demonstrated a delay in maximum brain concentrations. Also, the disappearance of PMA from the brain was slower than for PMMA. The brain concentrations correlated well with the effects from the behavior experiments, with a longer duration of locomotor suppression for PMA. As can be seen in the figure, both PMA and PMMA resembled MDMA in their temporal pattern but with less pronounced effect, whereas amphetamine exhibited quite the opposite. The time spent in the center zone is a measure of anxiety. The only significant result was PMA at the 10mg/kg dose, which acted anxiolytic with more time spent in the center zone.

Conclusion: The findings suggest that the behavior effects are correlated to brain concentrations of PMMA and PMA and that the effects resembled those of MDMA, rather than amphetamine.

PMMA, Open Field, Pharmacology

*Presenting Author