K37 Brain Concentrations of 3,4-Methylenedioxypyrovalerone (MDPV) and Its Metabolites in Male Rats: The Relationship to Pharmacodynamic Effects

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Learning Overview: After attending this presentation, attendees will have gained knowledge in how the synthetic cathinone MDPV and its metabolites distribute in the brain and the pharmacological effect of these substances on the rat locomotor behavior, temperature, and postmortem neurochemistry.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by improving the competence and performance of attendees in toxicological tools for the analysis of synthetic cathinones and metabolites in plasma and brain samples and the pharmacological interpretation of the analytical results.

Background: MDPV is a novel stimulant belonging to the synthetic cathinone class, which has caused severe intoxications and deaths. MDPV mimics the effects of other stimulants such as cocaine and methamphetamine, and possesses a high potential for abuse. Acquisition of preclinical data about MDPV pharmacokinetics is lacking, especially with regard to brain concentration of the drug and its metabolites.

Objectives: The goal of the present study was two-fold: (1) to determine the brain concentrations of MDPV and its two major metabolites, 3,4-hydroxypyrovalerone (3,4-catechol-PV) and 4-hydroxy-3-methoxy-pyrovalerone (4-OH-3-MeO-PV), after systemic administration of MDPV to rats; and (2) to relate brain kinetic parameters to MDPV-induced locomotor activation, body temperature, and postmortem neurochemistry.

Methods: Male Sprague-Dawley rats (300–400g) received subcutaneous (s.c.) injections of MDPV (1, 2, or 4mg/kg) or its saline vehicle (n=6/dose group). Groups of rats were decapitated at 40min and 240min post-injection, and trunk blood and brains were collected. Blood was centrifuged to obtain plasma, whereas brains were dissected to obtain prefrontal cortex, frontal cortex, and dorsal striatum. Plasma and brain tissue were stored at -80°C until analysis. Just prior to decapitation, rats were observed and rated for locomotor behavior using a numerical score, and core temperature was taken using a rectal probe. Plasma and prefrontal cortex were analyzed by liquid chromatography/mass spectrometry to determine concentrations of parent drug and its metabolites. Frontal cortex and striatum were analyzed by high-pressure liquid chromatography/electrochemical detection to determine concentrations of Norepinephrine (NE), Dopamine (DA), and Serotonin (5-HT). All statistical analyses were performed with GraphPad Prism.

Results: Brain and plasma concentrations of MDPV increased with increasing the dose administered. This rise was dose-proportional up to 2mg/kg dose but showed non-linear accumulation at 4mg/kg. The ratio of brain-to-plasma analyte concentration was determined at both time points and at the three different doses. In all cases, MDPV showed brain-to-plasma ratios much greater than 1 (8.8–12.1), whereas 3,4-catechol-PV and 4-OH-3-MeO-PV showed brain-to-plasma ratios much less than <1 (0–0.3). MDPV induced dose-related increases in locomotor activation at 40 and 240min, and a delayed increase in body temperature. MDPV produced a dose-related increase in cortical NE, but only at the 40min time point ($p<0.05$). Brain MDPV concentrations were significantly correlated with locomotor activity but not changes in body temperature or postmortem neurochemical measures.

Conclusion/Discussion: MDPV displays linear pharmacokinetics in plasma and brain at 1 and 2mg/kg doses, but non-linear accumulation at 4mg/kg. MDPV freely crosses the blood-brain barrier, but its hydroxylated metabolites do not. MDPV metabolites are more polar and conjugated, which may impede brain penetration. Targeting the glucuronide metabolites in plasma could be more useful than targeting MDPV to extend the window of detection in drug testing. Despite its well-known inhibition of DA uptake, MDPV had no effect on brain tissue DA. MDPV caused a small increase in cortical NE, but this effect was transient. In summary, these findings show that MDPV-induced behavioral effects are related to brain concentrations of the parent compound and not its metabolites. However, the lack of effect of MDPV on monoamine systems suggests other mechanisms may contribute to effects of the drug *in vivo*.

MDPV, Pharmacokinetics, Pharmacodynamics

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