K52 MDMA, HMMA, MDA, and HMA Plasma Pharmacokinetics in Humans Following Controlled MDMA Administration

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Attendees of this presentation will be informed about the plasma pharmacokinetics of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy), 4-hydroxy-3-methoxymethamphetamine (HMMA), 3,4-methyl- enedioxyamphetamine (MDA), and 4-hydroxy-3-methoxyamphetamine (HMA).

This presentation will impact the forensic science community by presenting data to improve the interpretation of MDMA and metabolite plasma concentrations.

The pharmacokinetics of MDMA after controlled oral dosing will be presented. These results are part of a larger investigation of the effect of MDMA on human brain activity and cognitive performance and the relationship of effects to plasma MDMA and metabolite concentrations.

Seventeen young adults, ages 18-27, volunteered for this Institutional Review Board-approved study. Eight African-American males, six African- American females, two Caucasian males, and one Caucasian female provided written informed consent. Volunteers received three doses of MDMA, 0 (placebo), 1.0 (low) and 1.6 (high) mg/kg MDMA, in a double-blind, within- subject, randomized and balanced design. 150 mg was the upper limit of dosing for safety purposes. Dosing was separated by a minimum of one week. Participants resided on a closed research unit and plasma was collected for 47-167 h after MDMA administration. A fully validated 2D GC/MS method simultaneously quantified MDMA, HMMA, MDA, and HMA in human plasma. Calibration curves were MDA, 1-100 ng/mL; HMA, 2.5-100 ng/mL; and MDMA and HMMA, 2.5-400 ng/mL. The lowest calibrator concentration was equal to the limit of quantification. WinNonlin was used to determine pharmacokinetic parameters. Paired t- and Wilcoxon Signed Rank tests were performed using SPSS v 14.0. $p < 0.05$ (two-tailed) was considered significant. Data are presented as mean ± standard deviation (SD).

In general, participants were positive for MDMA and HMMA by 30 min post-dose; MDA was quantifiable in all subjects by 1.25 h. HMA had a variable first detection time, ranging from 1.25-9 h. Mean maximum plasma concentrations (C_{max}) of 162.9±39.8 and 171.9±79.5 ng/mL wereobserved for MDMA and HMMA, respectively, after the low dose. After the high dose, mean MDMA C_{max} increased to 291.8±76.5 ng/mL, while mean HMMA C_{max} was relatively unchanged at 173.5±66.3 ng/mL. High inter-subject variability in C_{max} was observed. The highest individual C_{max} were 465.3 (MDMA) and 318.1 (HMMA) ng/mL. Mean MDA C_{max} were 8.4±2.1 (low) and 13.8±3.8 (high) ng/mL. HMA C_{max} were lower at 3.5±0.4 and 3.9±0.9 ng/mL after the low and high dose, respectively. C_{max} of all analytes except HMMA were significantly higher after the high dose. A comparison of MDMA and HMMA C_{max} revealed a significant difference after the high dose only (n=17, p=0.001), indicating non-linear HMMA pharmacokinetics. Mean time to maximum concentrations (T_{max}) after the low dose were MDMA, 2.4±0.6 h; HMMA, 1.8±0.7 h; MDA, 7.5±1.7 h; and HMA, 10.6±2.6 h. T_{max} did not significantly differ between dose for any analyte. 100% of participants were positive for MDMA, HMMA and MDA at 23 h after both doses. Similar patterns of detection were noted for MDMA and MDA; 48 h after the low dose, <25% of subjects were positive, while after the high dose, positivity increased to >80%. >90% were HMMA posi- tive 48 h after the low and high doses; HMMA had the longest window of detection of up to 95 h, while HMA was not measurable beyond 47 h. Mean half lives ($t_{1/2}$) of MDMA were 6.9±3.4 h (range: 4.1-18.3) and 8.1±2.1 h (range: 4.7-13.3) after the low and high dose, respectively. HMMA mean $t_{1/2}$ was 11.5±5.5 h after the low and 13.5±2.7 h after the high dose. MDA $t_{1/2}$ were shorter than previous reports, at 10.6±4.3 (low) and 12.3±3.7 (high) h. HMA $t_{1/2}$ showed high variability due to low concentrations. Half- lives of all analytes except HMA were significantly longer after the high dose. Mean MDMA volume of distribution was 5.5 L/kg after both doses; clearance was significantly higher after the low (0.62±0.19 L/h/kg), as compared to the high (0.48±0.11 L/h/kg) dose (n=17, p=0.004).

Extended plasma collection, large sample size, and multiple doses permitted a comprehensive evaluation of MDMA, HMMA, MDA, and HMA pharmacokinetics. These data will impact the forensic science com- munity by improving the interpretation of MDMA and metabolite plasma concentrations.

MDMA, Ecstasy, Pharmacokinetics

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