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Enantiomeric analysis of MDMA (Ecstasy) in plasma and urine by capillary gc: a preliminary investigation of the stereoselective disposition in man

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3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") is a commonly used recreational drug. MDMA use is a cause of concern due to potential neurotoxicity and hyponatraemia (Henry et al 1998); fatalities have been reported (Henry et al 1992). MDMA undergoes demethylation in man to 3,4-methylenedioxyamphetamine (MDA), which is also a compound of abuse. Little is known concerning the disposition of MDMA in man. In order to address this problem we have developed an indirect enantiospecific method for the determination of both MDMA and MDA in plasma and urine.

Plasma (2 mL), to which internal standards (50 μL of *(R,S)*-methoxyphenamine, 4 mg L^{-1} and *(R,S)*-amphetamine, 1 mg L^{-1}) were added, was adjusted to pH ~13. The mixture was extracted with n-hexane:ethyl acetate (1:1 v/v; 2 mL), centrifuged, the organic phase transferred to a clean vial and *(R)*-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (*(R)*-MTP) added (20 μL of a 3.3 % v/v solution in hexane). The mixture was heated at 80 °C for 20 min. Following derivatisation, the organic phase was evaporated under nitrogen and the residue reconstituted in n-hexane:ethyl acetate (1:1 v/v) and 1 μL injected onto the GC-MS. Analysis was carried out using a HP Ultra 1 column (25 m x 0.2 mm, film thickness 0.11 μm); temperature programme: 15 °C min^{-1} from 100°C to 285 °C, then held for 5 min; detection by selected ion monitoring. Under these conditions the diastereomeric *(R)*-MTP derivatives eluted as follows: amphetamine, *(R)* 11.63 and *(S)* 11.76 min; methoxyphenamine 13.18 and 13.24 min; MDA, *(R)* 13.61 and *(S)* 13.78 min; MDMA, *(R)* 14.22 and *(S)* 14.30 min.

Urine (5 mL), to which internal standards (50 μL of *(R,S)*-methoxyphenamine, 400 mg L^{-1} and *(R,S)*-amphetamine, 200 mg L^{-1}) were added, was adjusted to pH ~13 and extracted and derivatised as described above. After cooling to room temperature, 1 μL of the derivatised extract was injected onto the GC. Analysis was carried out using a DB17 column (30 m x 0.25 mm; film thickness 0.25 μm), temperature programme, initial temperature 50 °C; 25 °C min^{-1} to 250 °C, then 2 °C min^{-1} to 290 °C; detection, NPD. Under these conditions the diastereomeric *(R)*-MTP derivatives eluted as follows: amphetamine, *(R)* 15.60 and *(S)* 15.87 min; methoxyphenamine, 19.92 and 20.08 min; MDA, *(R)* 22.01 and *(S)* 22.72 min; MDMA, *(R)* 24.55 and *(S)* 24.86 min.

Single enantiomer calibration curves of MDMA and MDA in plasma were constructed over the ranges 0.1 to 80 μg L^{-1} and 0.025 to 8 μg L^{-1}. The calibration ranges in urine were 0.05 to 6 mg L^{-1} and 0.02 to 0.6 mg L^{-1} for MDMA and MDA respectively.

These methods were used to examine the enantiomeric disposition of MDMA following the oral administration of the racemic drug (20 mg) to a healthy male volunteer (Figure). Home Office approval and written informed consent were obtained.

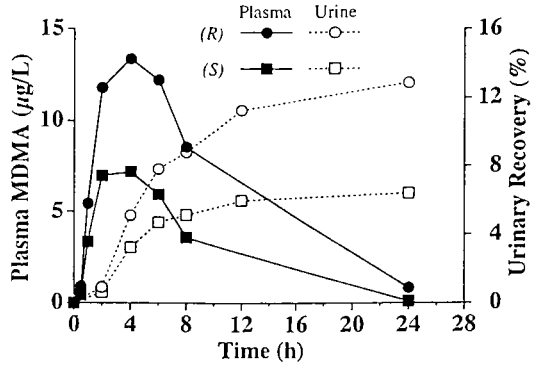

Figure: Plasma concentrations and urinary recovery of MDMA enantiomers following administration of the racemate.

The calculated half-lives of *(R)*- and *(S)*-MDMA were 4.8 h and 3.2 h respectively, and the drug could not be detected in urine after 24 h. The plasma MDA enantiomer concentrations reached their maxima (C_{max}, *(R)* 0.49 μg L^{-1}, *(S)* 1.45 μg L^{-1}) at 6 h *(R)* and 4 h *(S)* post drug administration. The plasma concentrations of *(S)*-MDA exceeded those of the *R*-enantiomer at all times up to 8 h. The urinary recoveries of the MDA enantiomers were *(R)* 0.60 % and *(S)* 0.68 %.

This is the first report, to our knowledge, indicating that the plasma disposition of MDMA is stereoselective in man, the more pharmacologically active *S*-enantiomer having a reduced AUC and shorter half-life than the less active *(R)*-MDMA.

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