Effects of MDMA and caffeine on renal cells and drug metabolising enzymes

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We have previously reported that a combination of 20 mg/kg 3-4 methylenedioxymethamphetamine (MDMA) and 20 mg/kg caffeine is lethal to rats (O'Boyle *et al*, 2005). During postmortem analysis of tissue samples, lesions were observed on the liver and kidneys of rats in the co-treatment group. It was hypothesised that acute renal and/or hepatic failure may be contributing factors to this serious drug interaction. The aims of the present study were to determine the toxic effect of MDMA in combination with caffeine on renal cells in culture and to ascertain any possible inhibitory effects this drug combination might have on metabolising enzymes.

The cytotoxic effects of MDMA and caffeine on renal cells (MDCKII and HK2) and a non-renal epithelial cell line (CaCo2) were evaluated using lactate dehydrogenase (LDH) and (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays. Cells were incubated with various concentrations of MDMA, caffeine or a combination of MDMA/caffeine for 24 h and the relative toxicities of treatments were evaluated. CYP2D6 and CYP1A2 inhibition kits were used to investigate possible drug interactions at the level of these cytochrome P450 enzymes.

Results for the LDH assay are summarised in Table 1. MDMA (10 mM) was toxic to renal and non-renal cells and this was not altered by co-treatment with caffeine (1 mM) (1 way ANOVA. $p < 0.05$). The same pattern of results was observed with the MTT assay as in the LDH assay.

Table 1. Toxic effects of MDMA, caffeine and MDMA + caffeine in 3 cell lines

	MDCKII	HK2	CaCo2
MDMA (10 mM)	46.1 ± 16.8	57.4 ± 7.2	49.9 ± 3.8
Caffeine (1 mM)	4.4 ± 0.5	8.3 ± 7.7	0.0 ± 0.0
MDMA (10 mM) + Caffeine (1 mM)	46.3 ± 13.4	59 ± 1.4	35.1 ± 6.1

Data are means ± SEM, n=3

MDMA inhibited the metabolism of 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin by CYP2D6 ($IC_{50} = 6.0x10^{-6}$ M). Caffeine did not inhibit CYP2D6, nor did it alter the IC_{50} for MDMA. MDMA and caffeine were weak inhibitors of CYP1A2 activity (substrate: 3-cyano-7-ethoxycoumarin; $IC_{50} > 3.4\ x10^{-4}$ M for both) and this was not altered when the drugs were combined.

These results provide no evidence for a potentially harmful interaction between MDMA and caffeine on renal cells or on either CYP2D6 or CYP1A2 activity.

O'Boyle KM *et al*, 2005 Proceedings of the British Pharmacological Society at http://www.pa2online.org/abstracts/Vol3Issue4abst 069P.pdf

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