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Proof of a 1-(3-chlorophenyl)piperazine (mCPP) intake – Use as adulterant of cocaine resulting in drug – drug interactions?

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AIMS: In 2004 – 2005 increasing numbers of seizures of 1-(3-chlorophenyl)piperazine (mCPP), a piperazine derived designer drug, have been reported (EMCDDA Joint Report on mCPP). Though, proof of a mCPP intake in human body fluids has not yet been reported. Metabolism, toxicological detection of mCPP and differentiation from intake of precursor drugs have already been studied in male Wistar rats, a model of a CYP2D6 extensive metabolizer phenotype, and it could be shown that mCPP was extensively metabolized and excreted mainly as its major metabolite hydroxy-mCPP (R.F.Staack, H.H.Maurer, J.Anal.Toxicol., 27(2003)560). The formation of hydroxy-mCPP is catalyzed exclusively by the polymorphically expressed cytochrome P450 (CYP) 2D6 (R.F.Staack, H.H.Maurer, Curr.Drug Metab., 6(2005)259). Here we describe the unequivocal proof of a mCPP intake. Pitfalls in toxicological analysis of mCPP will be discussed as well as the possible influence of the CYP2D6 phenotype and possible drug-drug interactions.

METHODS: Blood and urine samples of a 29 year old female, admitting the consumption of cocaine and paracetamol, was submitted to our lab for toxicological analysis.
Toxicological analysis of the urine specimen was performed by immunoassay screening (CEDIA) for common drugs of abuse, analysis by the Remedi™ HS drug profiling system, and GC-MS based systematic toxicological analysis (STA) procedure after acid hydrolysis of half of the urine sample, liquid/liquid extraction at pH 8-9 followed by microwave-assisted acetylation. For details see R.F.Staack, H.H.Maurer, J.Anal.Toxicol., 27(2003)560.
Toxicological analysis of the blood sample was performed by immunoassay screening (CEDIA) followed by GC-MS confirmation of positive results. Furthermore, a general unknown screening of the blood sample after 1-chlorbutane extraction was performed by HPLC-DAD. An aliquot of the blood sample was used for CYP2D6 genotyping (tested for CYP2D6*3,*4,*5,*6 and duplication).

RESULTS AND DISCUSSION: The immunoassay screening in blood and urine indicated the presence of cocaine/metabolites, which could be confirmed by GC-MS. The Remedi™ system indicated cocaine metabolites and mCPP as trazodone metabolite. By means of the STA procedure, paracetamol and diltiazem/metabolites could be detected besides mCPP, hydroxy-mCPP and cocaine/metabolites in urine. The presence of unique metabolites of trazodone and nefazodone, two mCPP precursor drugs, could be excluded by this procedure, allowing unequivocal proof of a mCPP intake. This could further be confirmed by HPLC-DAD analysis of the plasma sample, as only mCPP and none of the precursor drugs were detected.
Diltiazem is a known adulterant of cocaine and one can speculate that mCPP was also used as an adulterant in this case, as this has already been detected in seized material (EMCDDA Joint Report on mCPP).

More mCPP than hydroxy-mCPP was detected in the urine sample, suggesting a CYP2D6 poor metabolizer (PM) phenotype. However, DNA analysis indicated an intermediate metabolizer genotype. A PM phenotype could also be explained by drug – drug interactions. Besides mCPP, cocaine and diltiazem/metabolites could be detected, which are known CYP2D6 inhibitors/substrates, respectively.

CONCLUSION: This is the first report of an unequivocal proof of a mCPP intake. Regarding urinalysis, this proof is unequivocally possible by the described GC-MS based STA procedure. Immunoassay screening is not suitable for mCPP detection at all. The REMEDI™ system does not allow differentiation from the precursor drugs as the unique precursor drug metabolites are not specified. As the major metabolic transformation of mCPP is catalyzed by CYP2D6, different interindividual pharmacokinetic behavior could be expected, however further data is needed in order to assess the influence of CYP2D6 polymorphism. This case suggested drug – drug interactions of mCPP with co-consumed cocaine and diltiazem. Increased mCPP concentrations might lead to a higher toxicological risk, especially as the occurrence of serotonin syndromes have been reported even after common abusers mCPP doses.

KEYWORDS: *mCPP, Drugs of abuse, Interaction, Systematic toxicological analysis*

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