RTI-111 – new research chemical or old acquaintance?

Christina Grumann[1], Maurice Wilde[1], Verena Angerer[1], Sascha Ferlaino[2], Volker Auwärter[1]

[1]*Institute of Forensic Medicine, Medical Center – University of Freiburg, University of Freiburg, Germany,* [2]*Institute of Pharmaceutical Sciences, University of Freiburg, Germany*

UNIVERSITÄTS KLINIKUM FREIBURG
Institute of Forensic Medicine
Forensic Toxicology

Introduction

The phenyltropane RTI-111 (methyl-3-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate), also called dichloropane or O-401, is a stimulant drug showing high resemblance to cocaine regarding chemical structure as well as psychotropic effects. In the early 1990s, this substance and other substituted phenyltropane derivatives were synthesized to investigate the binding affinity of cocaine-like substances at monoamine transporters[1]. Recently, RTI-111 powder emerged as 'research chemical' on the designer drug market being marketed as legal substitute for cocaine. The first seizure of this substance was reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in late 2016 by the Swedish police, while another sample of RTI-111 was collected by the Slovenian National Forensic Laboratory[2].

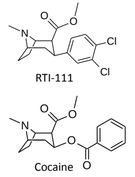


Figure 1: Structures of RTI-111 and cocaine

Objective

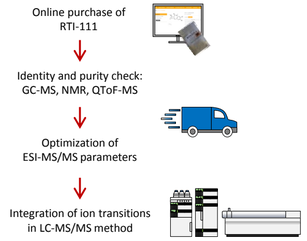
From December 2016 to March 2017 two cases of an assumed RTI-111 uptake were submitted to our laboratory (storage condition: -20°C). In case 1 a serum sample was available for analysis, while case 2 comprised a femoral blood and a urine sample. For investigation of these samples reference material of RTI-111 had to be purchased and characterized. Metabolites of RTI-111 were postulated based on the known cocaine biotransformation (cf. Fig. 2 and 3). Finally, RTI-111 and its metabolites had to be included in our screening method for designer stimulants.

Results

All three samples were tested positive for RTI-111. In case 1 (serum) a concentration of a approx. 0.6 ng/mL RTI-111 was measured. Case 2 showed approx. 1.0 ng/mL RTI-111 in femoral blood and approx. 4.5 ng/mL RTI-111 in urine. While in case 1 (serum) only the ester hydrolysis metabolite was detected, both assumed metabolites were detected in case 2 (femoral blood (cf. Fig. 5) and urine). The signals for the ester hydrolysis metabolite showed the highest abundance in all three samples (RTI-111/RTI-111 ester hydrolysis product: 0.84% for case 1 (serum), 6.2% for case 2 (femoral blood), and 16% for case 2 (urine)), while the *N*-demethylation product was only found in lower (femoral blood) or equal intensities (urine) compared to RTI-111 (cf. Fig. 6). The findings were qualitatively verified by LC-QToF-MS analysis.

Analytical workflow, method development & results

1. Purchase of reference material:



2. Anticipation of metabolites:

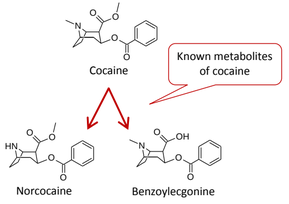


Figure 2: Main metabolites of cocaine

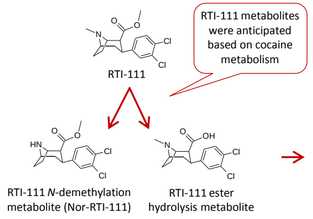
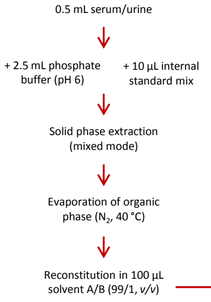
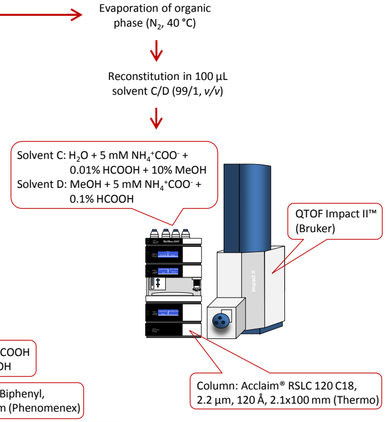


Figure 3: Structures of postulated RTI-111 metabolites

3. Sample preparation:



4. Verification of metabolites:



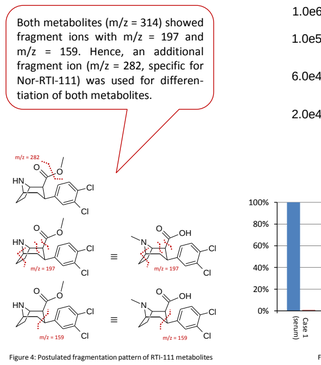


Figure 4: Postulated fragmentation pattern of RTI-111 metabolites

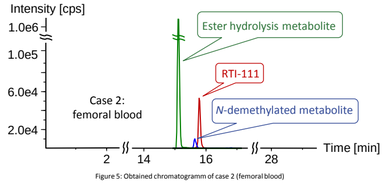


Figure 5: Obtained chromatogramm of case 2 (femoral blood)

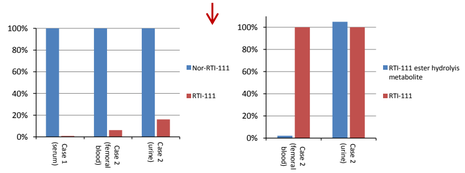


Figure 6: Percentage of peak areas of parent and metabolite peaks in analyzed cases

Conclusion

Unchanged RTI-111 seems to be a suitable consumption marker in human blood/serum and urine samples. However, considering the instability and rapid metabolic breakdown of cocaine and other ester compounds, additional monitoring of metabolites like the *N*-demethylated compound and in particular the ester hydrolysis product should be considered. The latter metabolite showed relatively high signal intensities in urine as well as in serum samples of drug users. Therefore, this metabolite likely offers the largest window of detection. Further studies on pharmacodynamics and pharmacokinetics of RTI-111 are needed for conclusive interpretation of RTI-111 (and metabolite) findings. The two cases show the high dynamics of the market for designer drugs, with elimination of banned substances and replacement by 'new' and still legal alternatives. Therefore, the need for a continuous market-monitoring and up-to-date screening methods is evident.

Literature

[1] Carroll *et al.*, Synthesis, ligand binding, QSAR (CoMFA and Classical) study of 3ß-(3'-substituted phenyl)-, 3ß-(4'-substituted phenyl)-,and 3ß-(3',4'-disubstituted phenyl)tropane-2ß-carboxylic acid methyl esters, *J.Med.Chem* **1994**, *37*, 2865-2873

[2] EMCDDA. Early warning system reports. Accessible via EDND database of the EMCDDA. Accessed: 11 March 2017.

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Contact

Christina Grumann
Medical Center – University of Freiburg
Institute of Forensic Medicine
Forensic Toxicology
Albertstr. 9, 79104 Freiburg, Germany
Christina.grumann@uniklinik-freiburg.de