Oral

[O25-5] O25-5: Clinical toxicology (2)

Chairs: Kei Zaitsu, Japan / Manuela Neuman, Canada
Mon. Sep 25, 2017 11:15 AM - 12:00 PM Room C1 (1F)

(Mon. Sep 25, 2017 11:15 AM - 12:00 PM Room C1)

[O25-5-2] New psychoactive substances produce reactive metabolites - a possible mechanism of toxicity?

Moa Andresen Bergstrom[1], Svante Vikingsson[2], Hampus Billing[3], Henrik Green[4], Robert Kronstrand[5], Ariane Wohlfarth[6] (1.Sahlgrenska University Hospital, 2.Linkoping University, 3.National Board of Forensic Medicine, 4.Linkoping University and National Board of Forensic Medicine, 5.Linkoping University and National Board of Forensic Medicine, 6.Linkoping University and National Board of Forensic Medicine)
Keywords: new psychoactive substances, reactive metabolites, high-resolution mass spectrometry

Background

Xenobiotic metabolism is considered to be a detoxification mechanism, however the same transformations may yield highly chemically reactive metabolites (RMs). RMs can covalently bind to endogenous macromolecules (e.g. proteins and DNA) causing severe toxicity reactions such as hepatotoxicity, immune reactions and necrosis. In the pharmaceutical industry, assessment of RM formation is a standard task during preclinical evaluation of candidate drug. In contrast, new psychoactive substances (NPSs) do not undergo any toxicological testing before being marketed. On closer inspection, a worrying number of NPSs contain structural features that are known to form RMs. Apart from the psychoactive effects, many case reports describe severe adverse reactions, which may be related to RMs, e.g. liver damage, abdominal pain, dermatitis, rhabdomyolysis and kidney failure. In this study, we have tested eleven NPSs for their ability to produce RMs.

Methods

To identify RMs, we have performed human liver microsomal incubations with three RM trapping agents; glutathione, potassium cyanide and methoxylamine. The following NPSs were screened: JWH-018, JWH-200, JWH-210, XLR-11, 5F-PB-22, MDPV, MDPPP, 5-MeO-DALT, methiopropamine, glaucine and MT-45. All samples were analyzed using liquid chromatography high-resolution mass spectrometry.

Results

RM adducts were identified from all tested NPSs, showing that NPSs can form RMs. Adducts were formed from all three RM trapping agents suggesting the existence of different RM types, such as aldehydes, iminium ions and epoxides. GSH adducts were detected for 5-MeO-DALT and MT-45; cyanide adducts for JWH-200, MDPV, glaucine and MT-45; MXA adducts for all compounds except glaucine and MT-45. Some NPSs formed RM adducts to a surprisingly high extent.

Conclusions

This study shows that NPSs have the propensity to form RMs which may play a role in the atypical and severe toxicities described for these compounds. However, the formation of adducts in the trapping assay is not a direct link between RM and the observed toxicity and further investigative studies are needed. If this project can establish that RMs significantly contribute to the toxicity of NPS, this would constitute a major breakthrough in our understanding of these drugs, which is key for a correct risk assessment and for effective treatment of intoxicated individuals.