IV[TH] MEDITERRANEAN ACADEMY
OF FORENSIC SCIENCES MEETING
14 - 18 OCTOBER 2009

Toxicovigilance of cannabinomimetic drugs: pertinence and contribution of predictive toxicology

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Toxicovigilance conducted by world-wide health survey institutes, is currently based on epidemiological methods, consisting of collection, medical assessment and statistical analyses of individual cases of intoxications. However, to identify and assess emerging risks, the classical toxicolovigilance approach is low-efficient and, particularly, requires more targeted and reliable detection methods, which could be provided by predictive toxicology tools [1]. In this context, some european countries have recently prohibited sales of products containing cannabinomimetic drugs, such as HU 210, JWH-018 and other analogues. A typical example is a product commonly referred to as “Spice”, an herbal smoking blend sold by online store and used for its hallucinogenic effects. Some of these cannabinomimetic drugs are known to be much more potent than the main active compound of cannabis (THC), so appear to be more addictive.These products could also be used as chemical submission agents for criminal or delictual purposes, mainly drug-facilitated sexual assault. Given the increased availability of these drugs via the Internet, the importance of having access to reliable analytical methods to detect and report intoxications has become more and more crucial. However, little data on predictive toxicology of these compounds is currently available, particularly concerning their in vivo biological behaviour. With this in mind, the toxicology workgroup of AFPReMed has recently initiated predictive toxicology studies on these drugs. In this abstract we report the preliminary results of a study in mice on HU210 and JWH015.

Material and methods

Two groups of six C57/Black 6 J mice received a 20 mg/kg dose of HU 210 [N°CAS: 112830-95-2] or JWH 015 [N° CAS: 155471-08-2] either po (b y gavage) or iv (tail injection).
These rodents were placed in metabolism cage in order to regularly collect stools and urine samples.

- Sample preparation

Urinary samples are typicaly prepared by the following procedure: each sample was centrifuged for 10 min at 3.5 rpm, and conjugated compounds were hydrolyzed by incubating with HCl for 2 hours, then neutralized and diluted with methanol (1/5). The mixture was shaken using Heidolph, then centrifuged during 10 min at 3.5 rpm. 150 µL of this mixture were transferred to sampler vials for LC-MS analyses. The LCMS system consisted of separation on Xterra C18 column 150 cm lenght and 3 µm pore size in 96LC apparatus from Waters, and detection with MRM mode in QuatroMicro quadripole MSMS from Waters.

Results and discussion

Neither native nor conjugated form of the parent compound was detected in the urinary or stools samples collected during the first 24 hours. It is worth mentionning that urine is a biological fluid which can be fairly easily collected in common practice. However, intense peaks were observed at m/z=360 for JWH-015 and at m/z=325 for HU-210 corresponding to

the main metabolites of these canabinomimetic drugs. Concerning HU210 metabolite spectrum , m/z at 325 is consistent with loss of C_3H_80 by pyran dimethyl bond cleavage

Conclusion

No trace of the parent compounds was found in urinary samples, but the main metabolites were detected by LC-MS (m/z=360 for JWH-015 and m/z=325 for HU-210). Moreover, these results highlight the need for further investigations on the biological behaviour of these drugs to determine the most relevant detection methods. Finally, predictive toxicology must play a critical role in detection of cannabinomimetics drugs in biological fluids and subsequently in the early identification and assessment of emerging risks.

Reference

[1] Belhadj-Tahar and coll. Toxicovigilance: new biochemical tool used in sulfonylurea herbicides toxicology studies. Acta Pharm. 2003; 53:111-8