

Analytica Conference 2012 “Emerging Drugs of Abuse: From Chemistry to Medicine” – Lecture Abstracts

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Emerging Drugs of Abuse: What's on Today?

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Since the first seizure of synthetic cannabinoids (“Spice” in 2007) on the illegal drug market in Switzerland, there has been an enormous increase of substances of different chemical classes. A new area of drugs - from its manufacturing, distribution on the drug market and way of consuming has been borne. With these so called ‘Research Chemicals’, ‘Legal Highs’ or Designerdrugs the ‘world of drugs’ has been ‘upgraded’ significantly. The diversity of different cannabinoids (JWH-, WIN-, CP-, HU-, AM-, URB-substances) increased greatly and different amphetamines (e.g. fluoroamphetamine), cathinone derivatives (e.g. mephedrone, methylon, fluormethcathinone) piperazines (e.g. m-CPP, o-CPP) tryptamines and more recently alkyl amines (e.g. geranamine), benzofuranes (e.g. 6-APB) and indanes (e.g. 5-IAI) appeared both on the market and as seizures.

Little is known about the toxicological and pharmacological effects of those single substances let alone of interactions between mixtures of such substances. Frequently seized products consist of mixtures e.g. stimulants combined with local anaesthetics and hypnotics. Many products with very professional appearance (fancy wrappings with faked ingredient lists and even holographic quality labels) mislead consumers and pretend quality controlled production. Examples of such seizures are presented.

The legal status of such substances or products in many european countries is still poorly defined as according to the misuse act the single substances have to be listed individually and the process of listing new substances is very slow. Substances, even though they are pharmacologically active are not considered medicals unless they were used therapeutically at any time or place. Rapid scheduling of critical substances and the introduction of substance classes in the drug legislation becomes necessary and needs to be reconcilable with the interests of the pharmaceutical industry. Such a change in the swiss drug legislation has been successfully implemented end of 2011.

From the Seized Sample to the Chemical Structure

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In recent years a new phenomenon on the illicit drug market increasingly gained in importance all over the world – the substitution of classic drugs by allegedly legal alternative products containing new designer drug substances with comparable psychotropic properties. Most important in this context are herbal mixtures, sold and marketed a.o. as herbal incense but used as a substitute for Marijuana with synthetic cannabimimetic designer drugs, typically aminoalkylindoles (e.g. from the JWH- and the AM-series) as the psychoactive ingredients. Other examples are “bath salts”, powdered products containing synthetic derivatives of cathinone with amphetamine-like effects or “herbal Ecstasy” capsules containing piperazine designer drugs with effects comparable to MDMA.

Typically, the biggest share of the products that are sold in a certain period of time do not contain substances that are listed in the annexes of the Narcotics acts in many countries at that

time and are immediately replaced by new designer drugs of the same class in case of submission. This situation has not only caused enormous problems for legislation and criminal prosecution, but also for the forensic laboratories with new synthetic substances surfacing every few weeks, some of them only marginally treated in the scientific literature and most of them not commercially available as reference compounds and their analytical characteristics (especially MS-, IR- and NMR-spectra) not listed in commercially available databases or published in any way.

This development imposes tremendous instrumental-analytical challenges to forensic laboratories that are concerned with seizures of new designer drugs and the meanwhile almost innumerable amount of different products on the market. In this contribution some of the analytical methods and techniques are presented alongside of examples from forensic case work, that have proven to be helpful or even necessary for the elucidation of the chemical structures of completely new designer drugs, namely NMR and High-Resolution-MS. A further focus will be rapid analysis techniques that are appropriate for the examination of a significant number of items of evidence like ion mobility spectrometry (IMS) and the combination of thin layer chromatography (TLC) and Desorption-Electrospray-Ionization-Mass Spectrometry (DESI-MS). As a significant number of the named designer drugs can be present in the form of different positional isomers (e.g. RCS-4 and ortho-RCS-4 or the three chlorophenylpiperazines), different diastereomers (e.g. CP47,497-C8) or even different enantiomers (e.g. amphetamine and cathinone derivatives) also some attention will be given to techniques for the separation and identification of stereoisomers like capillary electrophoresis (CE) and CE-MS with chiral selectors

Metabolism and detectability of emerging drugs of abuse

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In recent years, besides the classic designer drugs of the amphetamine-type, a series of new drug classes appeared on the illicit drugs market intended to be abused as stimulants, narcotics, and/or hallucinogens [1-3]. Prevalence of consumption, abuse, and finally risk assessment of such compounds can only be realized if suitable toxicological screening procedure exists to detect them or their metabolites in human biosamples. Metabolism studies are, therefore, a prerequisite for developing such procedures, especially if the compound is excreted into urine only in form of metabolites. However, further risk assessment such as drug-drug interaction or inter-individual variations in pharmacokinetic profiles and an increased appearance of side effects and serious poisonings is only possible if the metabolizing enzymes and their kinetics are known. Therefore, the metabolism and detectability of emerging drugs of abuse such as 2,5-dimethoxy amphetamines [1, 2], 2,5-dimethoxy phenethylamines [1, 2], phencyclidine derivatives [1, 2], beta-keto drugs (cathinones or pyrrolidinophenones) [4, 5], fentanyl derivatives [6] as well as alkaloids of the herbal drug Kratom [7, 8] will be discussed.

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Clinical signs and treatment of emerging drugs of abuse toxicity

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There is increasing interest in the use and potential acute toxicity (harm) of novel psychoactive substances (also known as “legal highs”). There have been increasing numbers of these substances across a range of different classes of compounds. They include the cathinones (e.g. mephedrone), the piperazines (e.g. 1-benzylpiperazine), the synthetic cannabinoid receptor agonists, the pipradrol-related drugs (e.g. D2PM and 2-DPMP) and ketamine analogues (e.g. methoxetamine). These compounds are not only available from street-level drug dealers, but also from Internet suppliers, where they are often sold with minimal information to the user about the potential toxicity (harm) associated with their use.

The majority of these substances have not undergone pre-clinical, animal studies or human clinical trials to determine the pattern of acute toxicity before they are marketed to users. It is possible to use a process known as data triangulation, to bring together information from a range of different sources, to minimise the limitations of each data source and to overall build a better pattern of the acute toxicity associated with the use of the substance(s) of interest. These different data sources include: Internet discussion fora, where individuals post information on their own personal experiences; case reports/series; poisons centre data series; animal models and human studies. Overall the majority of the initial information comes from user discussion fora and then subsequently case reports/series. The main limitation of these sources is that they are often there is not analytical confirmation of the substance(s) used.

Classical recreational drugs can clinically be divided into three broad categories based on the clinical effects seen with acute toxicity; these are hallucinogenic (e.g. LSD, ketamine), depressant (e.g. opioids, gamma-hydroxybutyrate (GHB)), and stimulants (e.g. cocaine, amphetamine, MDMA). Using the information available from the different data sources discussed above, it is possible to demonstrate that through data triangulation that these categories are also applicable to novel psychoactive substances. The cathinones, piperazines and pipradrol-related drugs have a stimulant-like pattern of acute toxicity and the synthetic cannabinoid receptor agonists and methoxetamine have hallucinogenic-like toxicity. There appears to be additional toxicity seen with novel psychoactive substances; for example methoxetamine has been reported to be associated with both stimulant-like toxicity and cerebellar toxicity, whereas the pipradrol-related drugs have been associated with prolonged neuro-psychiatric toxicity.

The management of the acute toxicity of novel psychoactive substances, like classical recreational drugs, is largely based on the pattern of acute toxicity seen rather than there being specific treatments required for each individual novel psychoactive substance. In addition, there may be the need for early involvement of psychiatric services in individuals presenting with prolonged neuro-psychiatric toxicity. It is possible as the range of novel psychoactive substances increases that future substances may require specific interventions / treatments.

Current Knowledge of 3,4-methylenedioxymethamphetamine (MDMA) Neurotoxicity

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(±)-3,4-methylenedioxymethamphetamine (MDMA, *Ecstasy*) is a psychoactive drug with abuse potential. Furthermore, experimental and therapeutic trials with MDMA in humans are underway. A large number of studies have demonstrated that MDMA has the ability to induce neurotoxicity in both, human and laboratory animals. Depending on the species investigated,

either serotonergic (human, non-human primate, rat) or dopaminergic (mouse) neuronal pathways are attacked. MDMA-related brain nerve injury is indicated by long-term decreases in markers of monoamine neurotransmission (e.g. long-lasting depletion of neurotransmitter and reduction of vesicular monoamine transporters) mainly affecting the nerve terminals. Additionally, damages of cell bodies of monoamine-containing neurons and cell death as result of necrosis have been reported. Despite two decades of research, the precise mechanisms by which MDMA produces its neurotoxic effects are not fully understood. Several mechanisms have been proposed including, but not limited to, a) formation of neurotoxic metabolites of either the endogenous neurotransmitter or of MDMA itself; b) involvement of brain dopamine; c) glycogen depletion; and d) excitotoxicity. Additionally, numerous studies have demonstrated that MDMA-induced hyperthermia markedly influences the magnitude of neurotoxicity. Studies in recreational MDMA users showed decreased levels of 5-hydroxyindoleacetic acid, the main metabolite of serotonin (5-HT), in the cerebrospinal fluid and a reduced density of 5-HT transporters (SERT) in the brain as determined by positron emission computed tomography. The brain 5-HT neurotoxicity evokes a number of neuropsychiatric sequelae such as cognitive deficits (e.g. impaired visual and verbal memory) correlating with the loss of SERT, alteration in circadian activity, changed sleep patterns, endocrine dysfunctions, impulsivity, and mood disorders, such as anxiety and depression.

Spice, JWH & Co.: What's the current knowledge?

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Although in the last years an increasing number of synthetic cannabinoids, mainly of the aminoalkylindoles type, entered the drug market as a substitute for cannabis and many people consume these drugs, comprehensive methods for the detection in biomatrices are still lacking in most forensic laboratories. The main reason for this is the significant lag-time between occurrence of a compound in 'legal high' products and commercial availability of reference standards. Another difficulty consists in the high potency of the target compounds resulting in very low concentrations and the need for highly sensitive analytical methods. In urine testing, knowledge on the drug metabolism is necessary as usually the unchanged compounds are not excreted biliarly.

Relatively little is known about the toxicity of aminoalkylindoles and most other synthetic cannabimimetics. Apart from affinities to the cannabinoid receptors type 1 (CB1) and 2 (CB2), only for a few compounds data on intrinsic activity is available. None of the compounds has been evaluated in clinical trials. From clinical reports on intoxication cases it is known that these drugs show effects similar to cannabis in some aspects, but markedly different in others. Some of the symptoms frequently seen after analytically confirmed consume of Spice products (without concomitant use of other drugs) like generalised seizures, hypokalemia and nausea/vomiting in combination with somnolence give cause for serious concern. Furthermore, recent results of toxicological tests using e.g. single cell gel electrophoresis (SCGE) assays, suggest a carcinogenic potential of some of the CB1 receptor agonists. Even though these data are preliminary, it can be concluded that synthetic cannabinoid receptor agonists present in Spice products show a significantly higher toxicity compared to cannabis and pose a serious threat to public health.