European Review for Medical and Pharmacological Sciences 2017; 21 (1 Suppl): 1-6

Hepatotoxicity associated to synthetic cannabinoids use

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Abstract. – Synthetic cannabinoids (SCs) are psychotropic compounds, chemically created in laboratory to mimic cannabinergic brain activity of delta-9 tetrahydrocannabinol. The consumption of these compounds for recreational purposes can lead to a variety of adverse effects on health including overdose and deaths. Increasingly popular as substances of abuse since the 2000s, SCs were produced initially to bind and study cannabinoid receptors (they also can be called synthetic cannabimimetics) failing in eliminating the psychoactive effects. Currently, SCs are misused by students and young adults as "natural products" because of their herbal aspect. Actually, these apparently innocuous recreational substances hide toxic effects to health. Reported side effects are cardiovascular, gastrointestinal, neurological, renal, metabolic, ophthalmologic, pulmonary and psychoactive including dependence and withdrawal. A few cases of SCs ingestion have also been associated with liver failure. We herein review the recent literature on the SCs toxicity with particular attention to liver damage aspects.

Key Words:
Synthetic cannabinoids, Hepatotoxicity, Illicit use.

Introduction

Synthetic cannabinoids (SCs) were firstly synthesized in the 1960s with the aim of better understanding the cannabinoid system and receptors inside and outside the central nervous system, in the attempt to maximize analgesic and anti-inflammatory properties of delta-9-tetrahydrocannabinol, the psychoactive cannabis alkaloid, and eliminate the psychotropic effects[1-3].

SCs resulted to be agonists of cannabinoid receptors (CB1 mostly present in the central nervous system and CB2 mostly distributed in peripheral tissues) with affinity bindings higher than that of delta-9-tetrahydrocannabinol, and their metabolites retain varying amounts of biological activity as agonists, neutral antagonists, or inverse agonists[4].

In addiction, it was apparent that SCs share with cannabis products (marijuana, hashish, etc.) psychotropic effects such as the sense of euphoria and mild sedation and adverse effects like anxiety, paranoia, agitation, delusions, tachycardia, diaphoresis, nausea, vomiting, and xerostomia[2].

SCs pertain to at least 13 different types of the following chemical families based on their structures: benzoylindole, naphthoylindole, phenylacetylindole, indazolecarboxamide, cyclohexylphenyl, naphthylmethylindole, napththoylpyrrole, naphthylmethylindene, aminoalkylindole, adamantoylindole, tetramethylcyclopropylketone indole, quinolinyl ester indole, dibenzopyran (Table I)[5]. These structures lack molecular similarity to delta-9-tetrahydrocannabinol, but they are functionally similar in the action on the cannabinoid receptors CB1 and CB2[2].

Not only reported SCs receptor affinities can vary from 2 to 800 times higher than that of delta-9-tetrahydrocannabinol, but also consequent much more and prolonged severe adverse effects, sometimes even fatal[2]. This can also be probably due to the lack of cannabidiol, which acts as anxiolytic and antipsychotic substance[2,6].

At the beginning of 2000s, SCs started to appear on Internet web markets and sold as "spice", a natural herb with cannabimimetic properties. Hundreds of SCs are presently available on e-markets and deep-webs as homologues of SCs synthesized by researchers at Hebrew University

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Table I. Synthetic cannabinoids families.

Synthetic cannabinoids family	Principal compounds
Benzoylindole	AM-694, AM-2233, AM-679, RCS-4, RCS-8
Naphthoylindole	JWH-018, JWH-022, JWH-073, JWH-081, JWH-122, JWH-210, AM-2201, AM-2232, MAM-2201
Phenylacetylindole	JWH-167, JWH-250, JWH-316
Indazolecarboxamide	ADB-PINACA, ADB-FUBINACA, AB-FUBINACA, AB-PINACA, 5F-APINACA, AKB48 (APINACA), MAB-CHMINACA
Cyclohexylphenyl	CP-55, 940, CP-47, 497, CP-47, 497-C8 homologue
Naphthylmethylindole	JWH-175
Naphthylpyrrole	JWH-145, JWH-307, JWH-370
Naphthylmethylindene	JWH-176, JWH-220
Aminoalkylindole	WIN-55,212-2
Adamantoylindoles	AB-001
Tetramethylcyclopropylketone indole	UR-144, XLR-11
Quinolinyl ester indole	5F-PB-22, PB-22
Dibenzopyran	HU-210, JWH-133

in Jerusalem (from which derived the name HU of some SCs) in the 1960s and by Charles Pfizer & Company Inc. (after renamed Pfizer Inc. and from which derived the name CP, a group of SCs) (New York, NY, USA), in the late 1970s, and analogues of those obtained by the researcher John W. Huffman (from which derived the name JWH of another group of SCs), in USA in the 1970s. They were originally marketed in Europe and subsequently started to be banned in 2010[2].

As before stated, these compounds are not derived from herbs or natural plants but they were chemically created in a laboratory as powders, then turned into a liquid mixture that is usually sprayed on dried plants or herbs, used to mask the real content of the product or to create the illusion that a natural product is provided[7]. The herbal components may include dried plants with presumed calming proprieties such as bay bean, beach bean, Indian warrior, blue lotus, dog rose or rosehip, lion's ear or tail, wild dagga, lousewort, dwarf skullcap, maconha brava, blue or sacred lotus, pink lotus, white and blue water lily, marshmallow, red clover, rose, siberian motherwort or honey weed, vanilla, and honey.

SCs are widely known under the name of Spice in Europe, K2 in USA and Kronic in Australia and New Zealand[8]. They are usually sold in metal-foil bags, with the label "not for human consumption" as legal highs or legal alternative to marijuana[9], herbal blends or incense potpourri, through websites and in legal retail outlets, small stores, head shops and gas stations[7,10,11]. The packages do not contain information about health risks.

Users report to prefer SCs because they get a better "high", they can buy these substances anonymously on internet web sites and disclosure of use by drug testing in biological matrices is difficult to be performed for lack of standardized methodologies[1].

SCs way of administration is primarily smoking (through a pipe, a water pipe or rolled in a paper cigarette), but can also be inhaled and drunk as an herbal infusion[10]. New ways of inhalation include vaporization trough electronic cigarette[3,9].

Street names of SCs include: Spice Gold, Spice Silver, Spice Diamond, Yucatan Fire, Sence, Chill X, Smoke, Genie, Blaze, Black Magic, Black Mamba, Algerian Blend, Red Dawn X, Paradise, Demon, Spike, Mr. Nice Guy, Green Buddha, Blonde, Summit, Standard, White rabbit, Banana cream nuke, Happy tiger incense, Citron, Green Giant, Smacked, Wicked-X, AK-47, Special K, Kronic, Barely Legal, Fake Weed, Ninja, Zohai, Dream, Skunk, Serenity, Yucatan, Fire, Crazy Clown, Bombay Blue, Ex-ses, Experience Chill, Ice Bud Extra Cold, Herbal Dream, Mojo, Moon Rocks, Red magic, Space Truckin', Spice Tropical Synergy, SpiceWorld420 and many others are being continuously created[2,3,7,8,11]. The composition of Spice/K2 is not always the same and it depends on the producers, who try to introduce always-new molecules to circumvent the law banning psychotropic substances use[1]. The place of manufacturing is mostly Asia and no quality standard procedures or requirements are followed for production[7].

In the last decade, many SCs have been internationally banned, but when a group of them or an entire family is banned, a new group or a new family or compounds with a different structure are launched on e-markets.

Although the consumption of SCs by youngsters and young adults still constitutes a niche market (0.1-7% in European countries different surveys)[12] on traditional drugs of abuse, several acute intoxications and some fatalities have been reported since secondary effects of these substances are still unknown.

Overdose deaths following SCs ingestion are increasingly reported[7]. As an example, the indolecarboxamide N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (MAB-CHMINACA) was responsible for the hospitalization of 125 individuals in Louisiana area the past October 2014. Most of the side effects reported for the substance included severe toxicity, seizures, excited delirium, cardiotoxicity, multiple overdoses and deaths[9].

In 2015 the American Association of Poison Control Centers notified a huge increase in poison center exposure calls due to SCs: a number of 1.512, more than two times the 657 exposures collected in 2012[9]. The New York City Department of Health and Mental Hygiene (DOHMH) in July 2016 issued an alert about the increasing of Emergency Department (ED) visits regarding SCs adverse effects: 130 individuals accessed EDs for suspected ingestion of synthetic cannabinoids, and more than 8.000 synthetic cannabinoids-related ED visits occurred since January 2015. Males accounted for approximately 90% of the visits; patients had a median age of 37 years. Provisional mortality data show 10 K2-involved fatalities in 2015. Nine of these deaths involved multiple substances, including: cocaine, benzodiazepines, heroin, and/or alcohol[13]. Due to the fact that scientific information available for SCs side effects is still mostly lacking, it is difficult for the physicians at EDs to adequately treat patients with physical and psychological symptoms of hardly attributable drug toxicity[2]. This article reviews the mechanism of action, the potential hepatotoxicity and other side effects of SCs.

Synthetic Cannabinoids Mechanism of Action

SCs are molecules functionally (but not chemically) related to natural occurring psychoactive cannabinoid (also called phytocannabinoid), delta-9-tetraidrocannabinol (THC). THC binds to and acts on two cannabinoid receptors, termed CB1 and CB2, who constitute the endocannabinoid system, naturally activated by endocannabinoids such as the anandamide[8].

THC is considered a partial agonist of the CB1 receptors, present in central nervous system, whereas the synthetic cannabinoids are generally considered as full agonists. Accordingly, the partial or full activation of the CB1 receptors may correlate with the level of the experience with the cannabis or the synthetic cannabinoids[14]. Binding potency of THC and the synthetic cannabinoids is also an important determinant of relative toxicity, especially considering the risk of overdosing[14]. The agonistic activity of the cannabinoids on the CB1 receptor affects the mood, the auditory and visual cognition, the sense of time and the memory. Moreover, CB1 activation can lead to antinociception, hypothermia, and hypomobility[15]. Panic reactions, that occur most often in naïve users or at high doses, and psychotic symptoms have also been described[8]. Human users of synthetic cannabinoids report that these products share some, but not all, the "subjective" effects of cannabis. These effects are generally described as more negative than those experienced with the natural cannabis[8].

CB2 receptors were identified for the first time in immune cells, even if they can also be found in the central nervous system. The major function of this receptors subtype is the control of cytokine release and immune cell migration. Consequently, artificial CB2-receptor agonists are intended to reduce inflammation-induced pain and have been expected to show pharmacological effects such as peripheral antinociception[15].

The metabolism of synthetic cannabinoids involves both phase I (hydroxylation, and to a lower extent, carboxylation) and phase II (conjugation with glucuronic-acid) processes. Oxidative metabolism forms preferably mono-, di- and trihydroxylates, carboxylated and N-dealkylated metabolites. Monohydroxylation is the major metabolic pathway of compounds containing in their structure the indole ring, such as naphthoylindole, phenacetylindoles and benzoylindoles[8]. The main metabolites of synthetic cannabinoids can retain their affinity to bind to the CB receptors: indeed they can act as full, partial or inverse agonists[8,16]. Final metabolites are excreted in urine as glucuronic acid conjugates[17].

Phytocannabinoids are extensively metabolized by cytochromes P450, the drug-metaboliz-

ing enzymes involved in the cellular detoxification of xenobiotics by catalyzing various reactions such as oxidation and reduction. For the most studied THC, cannabinol and cannabidiol, the enzymes CYP2C9, CYP2C19 and CYP3A4 catalyze the majority of the hydroxylations. Conversely, there are only limited data on the metabolism of the great variety of SCs. A recent study suggested that SCs and their basic molecules are capable of inhibiting CYP1A enzymatic activity[18]. CYP2C9 and CYP1A2 were identified as the major responsible for the generation of hydroxylated metabolites of JWH-018 and AM-2201[17]. CYP3A4 were identified as the major responsible for the oxidative metabolism of AKB-48 (also known as APINACA)[16,19].

Although there are only limited data regarding SCs conjugative metabolism, kinetic studies identified UGT1A1, UGT1A9 and UGT2B7 as major UDP-glucuronosyltransferases responsible for conjugation of hydroxylated metabolites of JWH-018 and JWH-073 in the liver[20].

Hepatotoxicity of Synthetic Cannabinoids

SCs use has been associated with liver damage[21]. In this concern, a single animal study showed that JWH-133, a CB2 agonist from dibenzopyran family, potentiated adipose tissue inflammation in high-fat diet-fed wild-type mice as well as moderately contributed to liver inflammation. Hepatic steatosis (fatty liver disease) induced by the high-fat diet was increased in the mice treated with JWH-133 and mitigated in mice knockout for CB2 receptors[22].

Regarding studies on the human model, no systematic clinical studies exist concerning SCs toxicity on different target organs including liver. The studies available on humans are only case reports of liver injury caused by Spice/K2 consumption.

The first case of Spice/k2 induced hepatotoxicity concerned a 45 years old male, with a past abuse of heroin and withdrawal treatment with methadone, who underwent toxic hepatitis following the use of Spice. Other comorbidities included bipolar and seizure disorder (treated with sertraline, trazodone and gabapentin). Toxicological tests were negative for all the classical drugs of abuse and positive to methadone[1]. The individual was hospitalized with liver enzymes (such as aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin) increasingly worsening. The cause of liver failure was unknown until the patient reported the continuative use of 2 grams of Spice for 7 days. At that point he started to be treated with N-acetylcysteine (hepatoprotective agent)[1].

In this, as in other intoxication by SCs, the problem is that information about Spice hepatotoxicity in the literature is scarce, and there is no availability of suitable assays to detect these substances and/or their metabolites in urine. Therefore, in this case, the association between liver injury and Spice ingestion was made upon patient's admission. Anyhow, the cumulative oxidative hepatocellular necrosis was hypothesized to be dose-related[1].

Four fatalities in young males were recently reported and attributed to ingestion of the synthetic quinolinyl-ester-indole cannabinoid 5F-PB-22[23]. Two of those reported a liver damage, which was cause or concourse of death.

One of these deaths, concerning a 27 years old male, was attributed to a fulminant liver failure due to simultaneous exposure to cannabis (positivity to delta-9-THC acid metabolite, 11-nor-9-carboxy-THC in serum at 246 ng/mL) and 5F-PB-22 (concentration in serum specimen 1.3 ng/mL). He was admitted to medical intensive care unit with severe liver and kidney injury, coagulopathy, acute respiratory failure, hypoxemia, anion gap metabolic and lactic acidosis. The clinical condition continued to deteriorate till death[23]. In another case, a male 18 years old was found dead after a night party and the autopsy revealed bilateral pulmonary vasocongestion and congestion in liver, spleen and kidneys. The concentration of 5F-PB-22 detected in iliac blood was 1.5 ng/mL[23].

Generally speaking on hepatotoxicity due to SCs, in Japan a multicenter retrospective survey was conducted on 518 patients from 60 emergency facilities, mostly males between 20-30 years of age, intoxicated by synthetic cannabinoids, synthetic cathinone and methoxetamine during the period 2006-2012[24]. Overall, the physical complications concerning liver dysfunction were detected in 25 patients. The most observed physical side effects in 20 hospitalized (for at least 7 days) patients were rhabdomyolysis in 12 individuals, liver dysfunction in 5, renal dysfunction in 11, and physical injuries in 3[24]. It has not been specifically reported to which substances liver damage was attributed. In 12 samples, in the form of herb or powder, the following synthetic cannabinoids were detected: UR-144 and XLR-11 (tetramethylcyclo-

propylketone indole); MAM-2201, JWH122N-(4-pentenyl) analog, JWH-081, JWH-122, JWH-210, AM-2232 (naphthylindole); AKB-48, AB-PINACA (indazolecarboxamide); 5-fluoro PB-22, PB-22 (quinolinyl ester indole); AM-694 (benzoylindole)[24].

The SCs action on cannabinoid receptors CB2 has been associated with liver disease, inflammation linked with obesity and insulin resistance, although the clear mechanism of such metabolic derangements has not well yet understood[4].

Although the studies about SCs health consequences on the liver are sparse, considering the case reports herein indicated we can draw the conclusion that a nonnegligible hepatotoxicity appears to be related to SCs use. It also has to be taken into account that these substances are abused with cannabis itself or other drugs in polyabuse, which is typical of the consumers of this kind of drugs.

Other Side Effects of Synthetic Cannabinoids

Spice/K2 causes adverse effects similar to those of THC, but different in variety and intensity. The most reported side effects involve: central nervous system (agitation or restlessness, confusion, vertigo, hallucinations, aphasia, aggressive behavior, changes in mood, perception, thinking and attention, short-term memory deficits, initial unconsciousness followed by somnolence, seizures, amnesia, psychosis, paranoia, panic attack, delusions, dizziness, suicidal behavior, tolerance and withdrawal); neuromuscular system (muscle pain or cramps, myoclonia, shaking, rhabdomyolysis); cardiovascular system (hypertension, hypotension, heart palpitations, tachycardia, bradycardia, syncope, dyspnea, chest pain); gastrointestinal system (nausea, vomiting, excessive thirst, diarrhoea); eyes (mydriasis, blurry vision, light sensitivity, conjunctival hyperaemia); metabolic system (hyperthermia, hypokalemia, hyperglycemia, acidosis, diaphoresis); respiratory symptoms (hyperventilation, apnea, alveolar infiltrates, pneumonia); renal damage and in several cases deaths[1-3,5,22,24,25]. Several psychopathological effects associated with SCs have been stressed in acute and chronic users[6]. Young adults or adolescents frequently present to the emergency room with acute intoxication following SCs ingestion. Pediatricians are urged to know these drugs and how they affect the human body, so that when a patient present with typical symptoms, such as myocardial infarction, seizures or acute kidney injury, they should not exclude a SCs-related adverse reaction. Laboratory analysis should evaluate hepatic, kidney and cardiac function as well as electrolytes balance[3].

Conclusions

SCs consumption is dangerously widespread worldwide and cases of severe health effects, including overdoses and deaths, are alarmingly growing. Young people use SCs as an apparently legal alternative to cannabis also being tricked by the external aspect of the product made of herbs, marketed as harmless, but actually added with potent synthetic compounds. Unexplained liver injuries can be suspected to be Spice/K2-related, particularly in substance abusers[1]. An increasing use of SCs in adolescents and young adults is a matter of great concern, especially for physicians and paediatricians who have to deal with toxic health effects (cardiovascular, psychoactive, neurological, metabolic, gastrointestinal, renal, pulmonary, ophthalmologic) more severe than those caused by cannabis a and difficult to be clinically identified[3,26,27].

Authors' Contributions

R.S., M.C.R., L.M., C.M., A.M. F.P., M.P. and I.P. made substantial contributions to conception and design of the manuscript; R.S. and I.P. performed the literature search. All the authors have been involved in drafting the manuscript and revising it critically for important intellectual content and all of them have given final approval to the version to be published.

Acknowledgements

The authors thank Michele Sciotti, Stefano Gentili, Simonetta di Carlo and Antonella Bacosi for technical assistance.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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