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Review on AMB-FUBINACA one of synthetic cannabinoids present in Egypt

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Abstract

Background: Synthetic cannabinoids are currently the largest group of new psychoactive substances. Those that have been subjected to legal control are replaced by newer uncontrolled substances, which cause constant and dynamic changes to the drug market. AMB-FUBINACA is one of the recent synthetic cannabinoids appeared globally. In 2018, the official spokesman for the Ministry of Health in Egypt announced that the Strox consists of five types of synthetic cannabinoids which have been added to the Egyptian list of highly addictive and dangerous narcotics. These SCs are; AB-FUBINACA, AMB-FUBINACA, 5F-ADB, AB-CHMINACA, and XLR-11. **Aim of the work:** To spotlight the toxic effect of AMB-FUBINACA as a new synthetic cannabinoid. **Conclusion:** AMB-FUBINACA has been the focus of interest by health care professionals, as their use put the health of many humans at risk especially young adults.

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Key words synthetic cannabinoids –AMB-FUBINACA-Toxicity

Introduction

AMB-FUBINACA (methyl(2S)-2- ({1-[(4-fluorophenyl) methyl]-1H- indazole-3-carbonyl} amino) -3-methylbutanoate) is a synthetic cannabinoid that is also referred to as MMB-FUBINACA and FUB-AMB (WHO, 2019).

Historical background:-

AB-FUBINACA was developed by Pfizer and described to patients in 2009 as analgesic which first identified as synthetic cannabinoid product in Japan in 2012 and was designated as a Schedule I controlled substance in the United States in January 2014 (Adams et al., 2017).

On July 3, 2014, an ester analog of AB-FUBINACA, AMB- FUBINACA was discovered in a product under name of "Train Wreck 2" in Louisiana and was prohibited immediately by the state. On the morning of July 12, 2016, AMB-FUBINACA caused hospitalization of many persons in New York City, and turned a block in Brooklyn called Bedford–Stuyvesant area to what was described by the press as a "Zombieland" (Adams et al., 2017).

Magnitude of the problem

AMB-FUBINACA use was confirmed in case reports of mass intoxication in the United States in 2016 (WHO, 2019).

The predominant symptom was severe central nervous system depression, resulting in markedly slowed behavior and speech. It was reported that in New Zealand, there were at least 20 deaths related to the use of AMB-FUBINACA as well as numerous hospitalizations. The amounts of AMB-FUBINACA in confiscated products in New Zealand were found to be 2 to 25 times greater than those reported in the incident in the United States ***(WHO, 2019).***

In 2018, the official spokesman for the Egyptian Ministry of Health announced that the five common types of Synthetic Cannabinoids (SCs) present in "Strox" have been added to the Egyptian list of highly addictive and dangerous narcotics (Law 182/1960, act No. 440 of 2018, that prohibits the possession or trafficking of narcotics). These SCs are; AB-FUBINACA, AMB-FUBINACA, 5F-ADB, AB-CHMINACA, and XLR-11 **(Zahraa and Hasnaa, 2020).**

Pharmacology

Pharmacokinetics

AMB-FUBINACA is consumed by smoking like other synthetic cannabinoids. Products containing SCs include ready-to-smoke herbal mixtures ('incense blends') and liquids for e-cigarettes ('cannabinoid liquids') in addition to highly pure substances in powder form ('research chemicals') (Franz et al., 2020).

Hydrolysis of most esterified drugs such as AMB-FUBINACA occurs rapidly after intake and the corresponding acid metabolites are detectable in biologic samples (Andersson et al., 2016).

In the case of FUB-AMB, the process of hydrolysis occurred rapidly, and the de-esterified acid metabolite of FUB-AMB, 2-(1-(4-fluorobenzyl)-1H-

indazole-3-carboxamido)-3-methylbutanoic acid was detected in every patient (Adams et al., 2017).

Ester hydrolysis, methylation, hydroxylation, ester hydrolysis combined with indazole ring hydroxylation are the phase I metabolic pathways of AMB-FUBINACA while glucuronidation serves as phase II metabolic pathway (Xu et al., 2019).

Pharmacodynamics

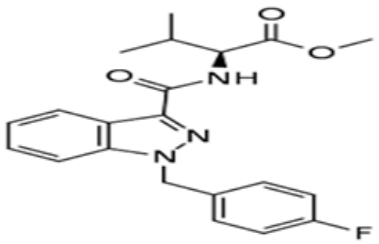
In vitro pharmacologic studies on actions of AMB-FUBINACA at the cannabinoid receptor type1 indicated that its potency is 85 times more than delta-9-tetrahydrocannabinol (Δ9-THC) and 50 times more than JWH-018 "K2" which was found in the early outbreaks of synthetic cannabinoid product. This potency is consistent with the strong CNS depressant effects of AMB-FUBINACA that would account for the reported "zombie-like" behavior of the users (Banister et al., 2016).

Cannabinoid receptors are part of the complex endocannabinoid system that is not fully understood. They are G-protein coupled receptors (GPCRs). Their activation results in presynaptic hyperpolarization through changes in potassium efflux and calcium influx leading to neuronal hyperpolarization and a decrease in neurotransmitter release. Pathways of signal transduction include inhibition of cyclic adenosine monophosphate (cAMP) production, modulation of ion channels and promotion of mitogen-activated protein kinase (MAPK) activation (Gurney et al., 2014 and Seely et al., 2012).

Cannabinoid receptors type 1 (CB1) are primarily located in the brain, and they are responsible for the psychoactive effects of cannabinoids. They are found in the central and peripheral nervous system, bone, heart, liver, lungs, vascular endothelium, and reproductive system. Cannabinoid receptors type 2 (CB2) are primarily found in the immune system. They are present also in the central nervous system however in smaller numbers relative to CB1 receptors (Bilici, 2014 and Wiley et al., 2014).

AMB-FUBINACA binds with high affinity at both cannabinoid receptors. Full activation was also observed at both receptors as measured by [35S] GTPS binding by inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP) and by the opening of G protein-gated inwardly rectifying potassium channels (GIRKs). At CB1 receptors, efficacy was substantially greater than that of Δ9-THC. At CB2 receptors, AMB-FUBINACA was a full agonist with high potency. Published data are confined to results from a drug discrimination study in which AMB-FUBINACA was found to fully substitute for Δ9-THC in male C57/Bl6 mice, with an ED50 of 0.04 mg/kg (Gamage et al., 2018).

Chemical structure



(Islam et al., 2018)

Synthesis of AMB_FUBINACA

The synthesis of indazole analogs started from methyl 1H-indazole-3-carboxylate, which was regioselectively alkylated with the suitable bromoalkane to give the 1-alkyl-1H-indazole-3-carboxylate methyl esters. Saponification of esters afforded the corresponding acids, which were coupled to methyl L-valinate or methyl tert-L-leucinate using the HOBt/EDC method, to furnish 1-alkyl-1H-indazole-3-carboxamides (Bainster et al., 2016).

Toxicity of AMB-FUBINACA

Toxicity of AMB-FUBINACA occurs at lower doses as suggested by increased reports of deaths and serious adverse reactions with this class of cannabinoids as compared to cannabis (European Monitoring Centre for Drugs and Drug Addiction, 2015).

The most common effects elicited by AMB-FUBINACA can be classified into two major groups, psychological and physical effects. The acute psychological effects of AMB-FUBINACA include euphoria, relaxation, feelings of anguish, confusion, anxiety, fear, drowsiness, dizziness, delusions, agitation, headache, verbiage, psychedelic effects, an altered perception of sounds, distorted perception of time, hallucinations and paranoia. Less common but more severe psychological effects include severe psychosis, catatonia, or coma. Physical effects include eye flushing (ocular vascularization), tachycardia, chest pain, nausea, vomiting, seizures, myoclonus, and impaired motor performance. In addition, pathologically effects include encephalopathies, hypertension, stroke, acute kidney injury, and renal failure (Lobato-Freitas et al., 2021).

Also adverse health effects reported in these incidents involving AMB-FUBINACA have included: Nausea, persistent vomiting, cardiotoxicity (myocardial infarction and arrhythmia), altered mental status, agitation, convulsions loss of consciousness and rhabdomyolysis (Rule and Authority, 2018).

Dependence

There are no reports of controlled experimental studies examining the dependence potential of AMB-FUBINACA in humans or animals were available. However, based on its central nervous system action as a full CBRs1 agonist and its efficacy is greater than THC on CBRs1, FUB-AMB would be expected to produce dependence in a manner similar to or more pronounced than cannabis (Gamage et al., 2018).

Detection of AMB-FUBINACA:

Urine is typically the preferred sample for abstinence control testing as sampling is non-invasive and urine usually provides a wider detection window

for most drugs of abuse when compared to other body fluids (e.g. blood or oral fluid). In contrast to hair or oral fluid testing where contamination can be a problem a positive urine test result unambiguously proves drug uptake (Franz et al., 2020).

AB-FUBINACA and AMB- FUBINACA have an extraordinarily long renal elimination time of a common main metabolite of both SCs (N-{[1-(4-fluorobenzyl)-1H-indazol-3-yl]carbonyl} valine). This acidic hydrolysis metabolite is an important analytical target for urine screening as the parent compounds themselves are not excreted in urine to a relevant extent (Franz et al., 2020).

Given a period of extensive consumption, an elimination phase of several months and even over one year after the last uptake seems plausible and their metabolite were detected in urine samples (Franz et al., 2020).

Colorimetric detection

The Duquenois–Levine color test which is used to identify classical cannabinoids such as delta 9-tetrahydrocannabinol is negative for the synthetic cannabinoids. The van Urk color test, the Marquis reagent and Dragendorff reagent can be used for detection of synthetic cannabinoids groups such as the naphthoylindole, phenylacetylindole, benzoylindole, and cyclopropylindole groups. Unfortunately, there is no colorimetric test to detect indazole based synthetic cannabinoids like AMB-FUBINACA (Isaacs, 2014, Jpn et al., 2012 and Zaitsu et al., 2011).

Immunochemical detection

Some commercially available immunoassay kits, such as Drug Check K2/Spice Test, Drug Smart Cassette and RapiCard InstaTest have been developed for the detection of JWH-018 and JWH-250 in urine. These devices are more useful than the colorimetric methods, because they do not require special reagents or tools, and the results are obtained easily and quickly. Unfortunately, there is no immunochemical kits for detection of AMB-FUBINACA (Namera et al., 2015).

Confirmatory methods

Various methods have been used to confirm identification and/or analyze AMB-FUBINACA. These methods have included liquid chromatography-quadrupole time-of-flight mass spectrometry (LC–QTOF/MS), gas chromatography-mass spectrometry and infrared analysis (GC-MS-IR), ion chromatography (IC), gas chromatography-mass spectrometer (GC-MS), high-performance liquid chromatography with time of flight mass spectrometry (HPLC-TOF), nuclear magnetic resonance spectroscopy (NMR), and surface-enhanced Raman scattering (SERS) (Kevin et al.,2019, Islam et al., 2018, Adams et al.,2017 and Hamilton et al., 2017)

Treatment

There is no specific treatment described for the cases of acute toxicity by AMB-FUBINACA. However the general treatment of acute poisoning by synthetic cannabinoids is often performed through supportive measures, namely by controlling signs and symptoms and fluid therapy to obviate electrolyte disturbances. Patients experiencing irritability, agitation, anxiety and seizures, both associated with synthetic cannabinoids intoxication and withdrawal syndrome are usually treated with benzodiazepines as the first-line approach. Neuroleptics such as haloperidol are also administered to manage psychotic symptoms (Lobato-Freitas et al., 2021).

Conclusion

There has been an increase in the consumption of various synthetic cannabinoids worldwide in the last few years. AMB-FUBINACA has been the focus of interest by health care professionals, as their use put the health of many humans at risk especially young adults.

Recommendation

1. Scientists and health care providers should perform more researches to find out more information about AMB-FUBINACA toxic effects.
2. Increase public awareness about the harmful effects of synthetic cannabinoids among the general population.
3. Training programs and treatment protocols should be established to help physicians to deal efficiently with cases of acute intoxication of synthetic cannabinoids.
4. Continuous updates of the law are essential to include all substances that have cannabis-like actions in the schedules of prohibited substances.

Schedules of prohibited substances should be updated to include all substances that have cannabis-like actions.

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مراجعة عن مادة AMB-FUBINACA كواحدة من القنبيات المصنعة الجديدة فى مصر

مصعب محمود رشوان[١] و مها عبد الحميد هلال[١] و هدى محمد السيد[٢] و خالد مسعود محمد[٣] و ولاء أحمد السيد[١]

الملخص العربى

المقدمة: تعد القنبيات المصنعة حاليًا أكبر مجموعة من مواد المؤثرات العقلية الجديدة. تم استبدال المواد التي خضعت للمراقبة القانونية بمواد أحدث غير خاضعة للرقابة مما يؤدي إلى تغييرات مستمرة وديناميكية في سوق الأدوية. مادة AMB-FUBINACA هى أحد القنبيات المصنعة الحديثة التي ظهرت على مستوى العالم. في عام ٢٠١٨، أعلن المتحدث الرسمي باسم وزارة الصحة المصرية أن مخدر الاستروكس يتكون من خمسة أنواع من القنبيات المصنعة التي تمت إضافتها ضمن القائمة المصرية للمخدرات الخطرة والمسببة للإدمان وهذه القنبيات المصنعة هى AB-FUBINACA و AMB-FUBINACA و F-ADB5 و AB-CHMINACA و XLR-11. **الهدف من الدراسة** : تسليط الضوء على التأثير السام لمادة AMB-FUBINACA باعتبارها واحدة من القنبيات المصنعة. **الخلاصة:** لقد كانت مادة AMB-FUBINACA محط اهتمام متخصصي الرعاية الصحية حيث أن استخدامها يعرض صحة العديد من البشر للخطر وخاصة الشباب.

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