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PRACA POGLĄDOWA
REVIEW

Cardiotoxicity of new psychoactive substances – A review of experimental studies and real clinical and forensic cases

Kardiotoksyczność nowych substancji psychoaktywnych – przegląd badań eksperymentalnych oraz rzeczywistych przypadków klinicznych i sądowych

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ABSTRACT

Designer drugs pose a serious modern health threat, specially the two most popular groups: synthetic cannabinoids and synthetic cathinones. Most of the available literature focuses on the neurological effects and scarcely describes effects on the cardiovascular system, which is responsible for most of the fatal cases. This article reviews the current knowledge about the cardiovascular effects of this new type of drugs. By activating CB1 receptors, cannabinoids cause no effect or may cause myocardial infarction because of vasoconstriction and a chronotropic effect. The arrhythmogenic effect includes tachycardia, atrial fibrillation, and even asystole. Synthetic cathinones contract blood vessels and increase contractility and stroke volume, leading to myocardial infarction through mechanisms unrelated to the autonomic system and independent of indirect sympathomimetic mechanisms. Describing typical symptoms and changes in electrocardiogram after overdosing such substances is crucially important, because unlike other drugs, laboratories cannot keep up with their ever-changing composition. There is a growing need for a proper identification protocol to identify their symptoms.

KEYWORDS

designer drug, intoxication, cathinones, cannabinoids, cardiac arrest, tachycardia, cardiomyopathy, clinical pharmacology

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STRESZCZENIE

„Dopalacze” stanowią poważne zagrożenie dla zdrowia współczesnego świata, zwłaszcza ich dwie najpopularniejsze grupy: syntetyczne kannabinoidy i syntetyczne katynony. Większość dostępnej literatury koncentruje się na skutkach neurologicznych, pobieżnie opisując negatywny wpływ na układ sercowo-naczyniowy. W artykule dokonano przeglądu aktualnej wiedzy na temat wpływu nowego rodzaju narkotyków na układ sercowo-naczyniowy. Kannabinoidy, aktywując receptory CB1, nie wywołują żadnego efektu lub też mogą powodować zawał mięśnia sercowego ze względu na działanie obkurczające naczynia krwionośne i działanie chronotropowe. Działanie arytmogenne obejmuje tachykardię, migotanie przedsionków, a nawet asystolię. Syntetyczne katynony obkurczają naczynia krwionośne i zwiększają kurczliwość oraz objętość wyrzutową, prowadząc do zawału mięśnia sercowego poprzez mechanizmy niezwiązane z układem autonomicznym, niezależne od pośrednich mechanizmów sympatykomimetycznych. Opisanie typowych objawów i zmian w elektrokardiogramie po przedawkowaniu tych substancji ma kluczowe znaczenie, ponieważ – w przeciwieństwie do innych narkotyków – laboratoria nie nadążają za ich stale zmieniającym się składem. Konieczne jest stworzenie odpowiedniego protokołu identyfikacyjnego, który umożliwiłby rozpoznanie tych objawów.

SŁOWA KLUCZOWE

narkotyk projektowany, zatrucie, katynony, kannabinoidy, zatrzymanie akcji serca, tachykardia, kardiomiopatia, farmakologia kliniczna

Introduction

The term “designer drugs” describes various products containing psychoactive substances, which are not listed in the Polish Act Against Drug Use (Ustawa z dnia 29 lipca 2005 r. o przeciwdziałaniu narkomanii). They are becoming a more and more pressing social issue. According to statistics from the USA, in 2001, 11% of high school students had contact with these drugs [1]. The results of the European School Survey Project on Alcohol and Other Drugs (ESPAD) from 2024 in Poland are quite similar: 5.5% of 15–16-year-olds and 4.5% of 17–18-year-olds had used such substances at least once in their lifetime; 4.3% and 3.1%, respectively, had contact with them in the last 12 months [2]. Comparing the dynamics of poisonings in Poland between 2015 and 2024, it should be noted that the highest number of medical interventions occurred in 2015, when 7,357 reports were recorded nationwide. From 2016 to 2018, the number of poisonings remained at a comparable, stable level (4,369, 4,324, and 4,258, respectively), with a clear downward trend starting in 2019, when 2,148 poisonings were recorded. Subsequent years saw a decline in the number of poisonings, from 806 in 2020 to 557 in 2024 [3].

The precise number of fatal cases is difficult to determine for a number of reasons. Proper toxicological samples are not taken in every case, even if the prosecutor commissions an analysis. The results do not always show new kinds of drugs and in many cases, the substances deteriorate before getting to the laboratory. In the Department of Forensic Medicine and Toxicology of the Medical University of Silesia in Katowice, between 2013 and August 2018, 100 cases of fatal intoxication were recorded (about two thirds were cases of poisoning with synthetic cathinones and cannabinoids) [4].

Designer drugs pose a medical problem because the effects of their use are often more severe than those of their well-tested chemical prototypes. Another important problem is that they are also not tested for their impact on the human body. We have to keep in mind that they are most often used with “classic” drugs (marihuana, cocaine, or amphetamine) to increase the desired effect or to soften their side effects [5]. The illegal markets are regularly flooded with new substances, leaving medical professionals unprepared to treat overdoses, or even unable to describe the clinical symptoms of usage.

An online survey conducted by Lank et al. [6] showed the lack of knowledge about this topic among US physicians, 80% of whom did not feel prepared for managing intoxication involving designer drugs. Likewise, 92% of them claimed that they need further education on the topic and 72% did not learn about designer drugs from reliable publications or lectures, but mostly from colleagues. Most of the available literature, which is exiguous, focuses on the neurological effects and only briefly describes the effects on the cardiovascular system, but it is the failure of the cardiovascular system which is responsible for most of the fatal cases. In this article, we systemize the previously assessed knowledge. To do this, we focus on two of the most important chemical groups of these substances, which are found in Poland – synthetic cathinones and synthetic cannabinoids – because a physician is most likely to deal with them. Describing typical symptoms and changes in electrocardiogram (ECG) after overdosing such substances is crucially important, because unlike other drugs, laboratories cannot keep up with their ever-changing composition. There is a growing need for a proper identification protocol to identify their symptoms.

Synthetic cannabinoids

Synthetic cannabinoids emerged in the form of herbal mixtures as a legal alternative to cannabis. The

prototype of these narcotics is delta-9-tetrahydrocannabinol (THC). They are partial agonists of CB1 receptors – which are located throughout the body, especially in the central nervous system – and CB2 receptors, which we can find on cardiomyocytes, for example [7]. Synthetic cannabinoids represent the largest group of substances currently monitored by the European Union Early Warning System, with 169 having been reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) by the end of 2016. According to the Polish State Sanitary Inspection, the most common substance of this kind in Poland is MDMB-CHMICA.

Their mechanism is similar to THC, but it triggers more severe psychosis and sympathycomimetic effects, because they are stronger agonists of CB1 receptors (depending on the substance, from 2 to 800 times stronger [8]). Another factor that increases their damaging effect is the lack of cannabidiol, which can be found in natural THC and has anxiolytic, antipsychotic, and cardioprotective properties [9]. It is also important to differentiate between the effects of activating the cannabinoid receptors CB1 and CB2. Activating CB2 receptors can have a positive effect on the heart; experiments show that it hinders the development of scar tissue after a myocardial infarction [10]. Activating CB1 receptors causes no effect or a negative one: it can cause myocardial infarction through its vasoconstricting and chronotropic effect [11]. Synthetic cannabinoids work selectively stronger on CB1 receptors than natural THC.

A recent study shows how consuming synthetic cannabinoids influences electrocardiographic alterations. An increased QT interval, QTc, and QTd, an increased P wave area in D2, and a higher frequency of abnormal P terminal force in V1 derivation were observed [12]. The arrhythmogenic effect included tachycardia, atrial fibrillation, and even asystole [13]. Delayed ventricular repolarization can lead to potentially lethal dysrhythmias, such as torsade de pointes or polymorphic ventricular tachycardia [14]. In almost every case, clinical symptoms included tachycardia and hypertension, which were affirmed by animal tests [15]. Autopsy findings have suggested that the cause of death was mostly a myocardial ischemia, which was caused by the vasoconstriction and chronotropic effect of these substances [16,17]. Irregularities in coronary angiography made patients more vulnerable to ischemic events [18], but their effect is so strong that ischemic episodes also occur in patients with no signs of arteriosclerosis [19]. Therefore, even adolescent patients have to be considered for this diagnosis [20]. Another good example of how we should consider unusual cardiologic diagnosis when designer drugs are used is the case of a 14-year-old consumer of synthetic cannabinoids, whose post-mortem examination revealed dilated cardiomyopathy, cardiomegaly (520 g), and bilateral pulmonary edema [21]. One of the features of these substances is their ability to cause outbreaks of mass poisonings in a short period of time, after a new chemical type is released on the market. For example, in Russia in 2014, the cannabinoid MDMB-FUBINACA caused more than 600 poisonings in just a 2-week period, 15 of which were fatal. Another example, from Poland, was a mass poisoning with "Mocarz" in 2015, which caused 200 emergencies in just one week [22].

The treatment of intoxication is for the most part supportive. In cases of poisonings where significant atherosclerotic changes in the coronary vessels are present, a percutaneous coronary intervention (PCI) may be needed [23]. ECG monitoring is necessary when antiemetics such as ondansetron, benzodiazepines, or haloperidol are used to relieve the physical or psychiatric signs of intoxication, as these drugs are known to prolong QTc, which can result in potentially lethal arrhythmias, as mentioned above [24]. The use of succinylcholine can cause rhabdomyolysis and hyperkalemia [25], which is why a nondepolarizing neuromuscular blocker (e.g., rocuronium) should be considered for patients who need intubation [26].

Synthetic cathinones

The natural equivalent of synthetic cathinones is khat. The leaves of this bush have traditionally been used in certain regions of East Africa and the Arabian Peninsula. The habit of chewing it was confined to the areas where it grew [27]. In the 1980s, the alkaloid cathinone S(-)alfa-aminopropiophenone was isolated from khat leaves. Today, synthetic cathinones are flooding European markets. Chemically, they differ from amphetamine by possessing a ketone oxygen atom (C=O) on the β (beta) position of the side chain. As recreational drugs, they are in the form of powder or tablets. Like all designer drugs, they are becoming an increasingly serious medical problem. Following the first documented fatal overdose, which happened in Sweden in 2008, the number of toxicological events associated with stimulants doubled, from 6% in 2010 to 12% in 2011 [28]. The most widespread substances in this group are mephedrone, methylone, and MDPV. In Poland, according to State Sanitary Inspection data from 2017, they are 3-CMC, HEX-EN, 4-CEC, and 4-CMC.

Synthetic cathinones constrict blood vessels and increase contractility and stroke volume, leading to myocardial infarction through mechanisms unrelated to the autonomic system and independent of indirect sympathomimetic mechanisms. They affect the release of stored norepinephrine and inhibit the reuptake of serotonin, dopamine, and norepinephrine. The effect is the same in both sexes [29,30,31].

In the largest study about "bath salt" intoxication, involving 1,633 patients, 55.2% of them suffered from tachycardia, 26.1% had hypertension, and just 6.8% felt chest pain [32]. Tachycardia can lead to cardiac arrest, as a case from Poland shows [33]. According to a series of 89 cases of mephedrone intoxication, 79% of the

patients suffered from tachycardia and 74% had a systolic blood pressure above 130 mmHg. Over 20% felt chest pain and palpitations [34]. There has also been a case of hypertrophic cardiomyopathy and associated lowered ejection fraction, but the mechanism of these changes remains unclear; takotsubo was excluded [35]. Cases of myocarditis due to these agents have also been reported [36].

Like all intravenous drugs, the use of synthetic cathinones is a risk factor of endocarditis [37]. Unlike opiates, these substances are dissolved in water without heating, which makes the users prone to such infections [38]. This disease, caused frequently by *Staphylococcus aureus* [39], has an in-hospital mortality between 10% and 25% [40]. The European Society of Cardiology Guidelines recommend transthoracic echocardiography as the first-line imaging [41]. Three findings are considered typical: mobile, echodense masses on the valvular leaflets, mural endocardium, or implanted material; periannular abscesses or new dehiscence of valvular prosthesis; and new valvular regurgitation [42]. Electrocardiography should be performed on admission and during hospitalization. The treatment includes measures, treatment of complications, antimicrobial therapy, and cardiac surgery when necessary.

Synthetic cathinones may, but do not have to, accompany so-called excited delirium syndrome (ExDS) [43]. The characteristic symptoms of ExDS include bizarre and aggressive behavior, shouting, paranoia, panic, violence toward others, unexpected physical strength, and hyperthermia [44]. Taggart et al. [45] suggest that mental stress and emotions may play a role in arrhythmogenesis and sudden death. The psychiatric effect of cathinones alone can cause a fatal cardiovascular response. The insular and infralimbic cortices, which are involved in controlling the cardiovascular system, may play a major role here as well [46].

It is important that in this case, in contrast to synthetic cannabinoids, the diagnostician can determine the presence of these substances in the body with gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–mass spectrometry (LC-MS). However, it should be remembered that they are not routine tests carried out at any facility and that the results are available only after a few hours. After mephedrone intoxication, a urine toxicology screen can be positive for benzodiazepines, but only in heavy users [34]. The treatment is primarily supportive. An ECG is also important. Studies show that benzodiazepines help normalize tachycardia and hypertension. For treatment in the case of recurrent hypertension, we include vasodilators, nitroglycerine, and sodium nitroprusside. Beta blockers are contraindicated because alpha-adrenergic agonists may be uninhibited, resulting in a further increase in blood pressure and reduced oxygen supply to the myocardium, which in turn may lead to myocardial infarction. A combination of alpha and beta blockers such as labetalol or carvedilol was considered, but there are no available reports on the efficacy of such a treatment [47]. Warrick et al. [32] also analyzed the treatment of the 1,633 cases included in their study. Benzodiazepine was used in 58.5% of them and antipsychotics in 15.3%. Antihypertensive and vasopressor drugs were administered in only 1.8% and 1.0% of cases, respectively, which shows once again that clinicians focus on the psychotic aspect and that we know little about the treatment of the cardiovascular component of designer drug intoxication.

Discussion

Considering what a serious problem these legal drugs have become in recent years, the number of well-documented scientific reports on the effects of their use is surprisingly sparse, which most probably results from the fact that clinicians are most often in contact with patients under the influence of these substances in emergency rooms, when they require immediate help and full-spectrum research cannot be conducted. Therefore, it is difficult to create a unified clinical picture. New scientific research is needed if we want to understand and prevent these life-threatening new types of drugs. Despite the similarity to their chemical prototypes, these substances may cause other and much more serious effects as a result of their much stronger effect. Common side effects that affect the cardiovascular system, such as tachycardia or chest pain, are not very specific, which makes diagnosis difficult. However, the available statistics prove that at present cardiologists and other physicians should include designer drug overdose in the differential diagnosis of the above-mentioned symptoms, especially if they occur in the 20–40 age group [48]. The EMCDDA has confirmed the existence of 200 new substances of this type in Europe in 2013 [49], which is not only a legislative problem, but also explains the difficulty of finding one universal set of symptoms. In 2016, the EMCDDA was monitoring 628 new psychoactive substances. The two major groups mentioned in this paper were synthetic cannabinoids and synthetic cathinones [50]. The diversity of these agents and the different types of admixtures and impurities in the products on the market also prevent a simple comparison of their effect. This work shows that there are common symptoms after usage. Therefore, it is necessary to further deepen and most importantly systematize knowledge on this subject, because the presence of designer drugs is a problem for cardiologists which has appeared and shows no signs of disappearing anytime soon.

Authors' contribution
Study design – R. Skowronek, A. Suchodolski
Data collection – R. Skowronek, A. Suchodolski
Manuscript preparation – R. Skowronek, A. Suchodolski
Literature research – R. Skowronek, A. Suchodolski
Final approval of the version to be published – R. Skowronek, A. Suchodolski

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