Assessment of Haematological Toxicity of Inhaled 4-methylethcathinone and 1-pentyl-3-(1-naphthoyl) Indole

MADALINA MOCANU[1], MAGDA BADESCU[1], MARIA-MAGDALENA LEON CONSTANTIN[2]*, IULIAN-COSTIN LUPU[3], OANA-VIOLA BADULESCU[1]*

[1] Grigore T. Popa University of Medicine and Pharmacy, Faculty of Medicine, Department of Pathophysiology, 16 Universitatii Str., 700115, Iaşi, Romania.

[2] Grigore T. Popa University of Medicine and Pharmacy, Faculty of Medicine Iasi, Department of Internal Medicine and Department of Rheumathology, 16, Universitatii Str., 700115, Iasi, Romania

[3] Grigore T. Popa University of Medicine and Pharmacy, Faculty of Dental Medicine, Department of Public Health and Oral-Dental Management, 16 Universitatii Str., 700115, Iaşi, Romania

The consumption of new substances with psychoactive properties, known under the name of Ethnobotanicals, has drawn attention, in the latest years, with their negative effects on the life of children and teenagers who consumed them but also with the rapid and visible development of the phenomenon among the population, in general. Haematological toxicity of some chemical substances contained in these products is more often met in medical practice. Limited information regarding the real content, and also the diversity of the substances incorporated in these chemicals, hinder the strict analysis of the toxicity of each constituent separately. The purpose of this article is to highlight the involvement of 4-methylethcathinone (4-MEC) and 1-pentyl-3-(1-naphthoyl) indole in the occurring of severe thrombocytopenia, at a young person of 21 years old, a chronic consumer of hallucinogenic combinations that contain these two substances preponderantly. The young man says that he has inhaled these substances. Thrombocytopenic purpura may be primary or secondary to other associated pathologies. Also, secondary purpura may be induced by the consumption of some toxic, medicine-related or hallucinogenic substances. It is a haematological disorder, characterized by a low number of platelets in peripheral blood (below 100.000/mm^3, the normal value being =150.000-400.000/mmc). From the clinical point of view, thrombocytopenia manifests by cutaneous-mucous haemorrhage syndrome: petechiae, ecchymoses, gingivorragia, epistaxis, haemorrhages at the level of various organs, some of them having vital risk.

Keywords: thrombocytopenia, 4-methylethcathinone, 1-penthyl-3-(1-naphthoyl) indole, haematological toxicity.

The new psychoactive substances (NPSs) represent a category of compounds recently synthesized, created in order to imitate classic illicit drugs, such as cannabis, ecstasy, cocaine or LSD. From the chemical point of view, these products have different structures than the classic prototypes which effects are desired to be imitated. This strategy proves the manufacturers' intention to keep NPSs in the category of "legal drugs", in order to facilitate the consumers' access and to mask the real risk of exposing to such substances. Considering that they are in a continuous change of name, composition, package, it is difficult to know the adverse effects common to all these substances, the toxic dosage or the lethal effects [1, 2].

The new substances with psychoactive properties traded under the name of "legal drugs" are divided into two large categories:

a) mixes of plants and chemicals, "Spice"- type products, which are smoked;

b) mixes of chemical powders than can be sniffed or injected – psychoactive substances of synthesis, with energizing or hallucinogenic effect, traded under various names and mixed with known energizing substances: caffeine, creatine etc.

We do not have information on the reactions that these substances cause when they are consumed together with other types of substances, such as alcohol, medicines, illegal drugs etc. Despite all these, the specialty literature provides significant proofs of the noxiousness of these substances on the health [3-5].

With this study, we want to highlight the involvement of mephedrone derivatives (4-MEC) and synthetic cannabinoids (1-pentyl-3-(1-naphthoyl) indole) in the etiopathogenesis of idiopathic thrombocytopenia.

Idiopathic thrombocytopenic purpura (ITP) is a disorder characterized by peripheral platelet hyper-destruction, exceeding the capacity of the bone marrow by compensatory thrombopoiesis [6]. Premature hyper-destruction is due to the fixation of antiplatelet antibodies or of some immune complexes on the platelet membrane, process that shall lead to the phagocytosis of the platelets by macrophages [7, 8]. Sometimes, these antibodies have the capacity to stick to megakaryocytes leading to associated megakaryocytic hypoplasia. The mechanism of apparition of antibodies is still unknown [9]. The studies with marked platelets have revealed a major decrease of the lifetime of platelets in the blood circulation of patients with ITP. The average period of survival is between 2 and 3 days, decreasing also at a few minutes. The shortening of the platelets lifetime is the consequence of an autoimmune mechanism [10, 11].

The presence of antiplatelet antibodies is specific to primary immune thrombocytopenic purpura [12]. Secondary immune thrombocytopenia may develop in the context of some disorders, such as autoimmune diseases (erythematic systemic lupus, antiphospholipid syndrome, autoimmune thyroid disease or Evans syndrome), myeloproliferative syndromes (chronic lymphatic

* *email: violabadulescu@yahoo.com; leon_mariamagdalena@yahoo.com*

leukaemia), infections with B or C hepatic virus, HIV infection (humane immunodeficiency virus) or the infection with Helicobacter pylori [13]. Also, secondary purpura may occur during pregnancy or may be induced by the consumption of toxic substances.

In the specialty literature, we find cases of severe thrombocytopenia induced by the consumption of medicines or toxic substances from hallucinogenic preparations.

Drug-induced thrombocytopenic purpura is a severe reaction caused by a lot of substances. This type of thrombocytopenia may be susceptible at all the patients which thrombopenia does not have a known aetiology. Often, thrombocytopenia induced by psychotropic substances is deemed to have autoimmune nature, however the absence of antiplatelet antibodies and the recent intake of a product with thrombocytopenic potential leads to the clear diagnostic of secondary toxic thrombocytopenic purpura. The apparition mechanism consists in medullar inhibition occurred subsequent to the intake of the drug, either by inhalation or by injection. Thrombopoiesis is inefficient, which shall reflect peripherally, by severe thrombocytopenia [14, 15].

Experimental part

Material and method

We present the case of a patient, M.A., of 21 years old, male, living in the city, who came to the Haematological Department of the "Sf. Spiridon" University Hospital from Iaşi, Romania in September 2014, for the investigation of the aetiology of a painless hematoma placed at the left arm, which appeared spontaneously. At the objective clinical examination, the findings were: the presence of the hematoma (about 15 cm) at the left arm, and also hemorrhagic injuries in form of petechiae of moderate intensity, placed at the level of the trunk and lower limbs. Also, the patient's general health status was altered, with psychomotor agitation, facial pallor and cold perspirations. The patient said that he did not consume alcohol and he did not take any medication previously to hospitalization.

In emergency regime, blood sample was collected. The haematological examination revealed severe thrombocytopenia (Platelets = 0/mmc). The peripheral blood smear revealed rare platelets and platelet anisocytosis. The biochemical examination was within normal limits and the immunological tests revealed the absence of antiplatelet antibodies. Also, a liver disorder was excluded – the tests for B and C hepatic virus were negative, and an infection with Helicobacter pylori was infirmed, the anti-HIV antibodies were negative, the same for immunological markers for a collagen disease. The imagistic examination revealed the normal aspect of abdominal ultrasound, with normal dimensions of the spleen. Myelogram was made in order to exclude malign homeopathy. The normal result of the myelogram excluded a central cause of thrombocytopenia. Subsequent to the investigations made, which excluded a secondary pathology suggesting severe thrombocytopenia, the diagnostic of idiopathic thrombocytopenic purpura was put.

The treatment with cortisone derivatives, haemostatics, liver-protective medicines was initiated, the clinical-biological evolution being favourable (upon discharge, the number of platelets being within normal limits – Platelets = 220.000/mmc). Upon discharge, the patient was recommended to avoid toxic environment of any kind and to continue the treatment with cortisone derivatives, oral intake, for two weeks more, being called back for control in four week-time. Four weeks later, and also three months later, the clinical-biological investigations were within normal limits. We do not know the etiological agent that led to the occurring of hematologic pathology. During the hospitalization however, at a detailed anamnesis, the patient declared that previously to the hospitalization and to the occurring of clinical symptomatology, he smoked hallucinogenic substances, known under the name of ethno-botanicals, for 6 months. He mentioned the name of two products which contain, beside other unknown substances, 4-methylcathinone and synthetic cannabinoids, such as 1-pentyl-3-(1-naphthoyl) indole, known with the name of JHW-018.

Results and discussions

The case presented above reveals the capacity of the psychoactive substances, such as 4-MEC and JHW-018, to induce extremely severe toxic adverse reactions, such as severe thrombocytopenia [12, 16]. The platelet pathology is involved in haemostasis abnormalities, which represents a physiological process with role in preventing and stopping haemorrhages. The decrease of the number of platelets (thrombocytopenia) leads to hemorrhagiparous syndromes, tegument and mucous phenomena, such as: petechiae, gingivorragia, ecchymoses, epistaxis and also to severe haemorrhages, at the level of various organs, which may have vital risk. It is compulsory to put a correct diagnostic and to give immediate adequate therapy in order to prevent the occurring of complications, sometimes fatal [17-19].

4-Methylcathinone (4-MEC) is a chemical compound, with a structure similar to mephedrone and is part of the class of synthetic cathinones (Figure 1). Due to the similarity in structure, 4-MEC has similar effects to the compounds of the same class, such as phenethylamine, amphetamine and other chemical cathinones [20].

Substituting the radicals with various chemical groups, there results a diversity of new compounds with a structure

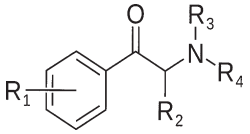

Fig. 1. General Chemical Structure of Substituted Cathinones ¨R_1= hydrogen or any combination of one or more groups: alkyl, alkoxy, alkyl-endoxy, halo-alkyl or halogens.¨R_2 = hydrogen or alkyl group. ¨R_3 = hydrogen, alkyl group or a cyclic structure. ¨R_4 = hydrogen, alkyl group or a cyclic structure.

deriving from the general structure of cathinones. Among these, there is 4-MEC, where the radicals R_1 and R_2 are substituted with a metal, an atom of hydrogen appears in the position R_3 and an ethyl group, in R_4. The chemical structure of 4-MEC is presented in figure 2 [21, 22].

4-MEC is a derivative of mephedrone (4-methyleth-cathinone) with stimulating effects over the central nervous

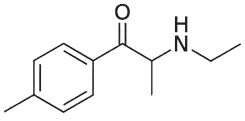

Fig. 2. 4-MEC (4-metyl-N-ethylcathinone)

system, similar to mephedrone [23]. It is found in the composition of new psychoactive products (NPS) consumed by inhalation, in recreational purpose. It has become available online, in 2010, and it has been sold as replacer for 4-methylethcathinone. Since 2011, it has been most often found in form of powder, either represented as 4-methylethcathinone, or included in powders with

unspecified polymorphous composition. The data regarding the toxicity of this substance for human body are limited, because it has been used for a little time [24, 25].

4-MEC causes addiction. The users tend to increase progressively the dosage or to shorten the time between intakes [23]. Many consumers combine oral intake with inhalation of powders containing 4-MEC, thus increasing the concentration of the substance in the body. The official reports present cases where the dosage of 4-MEC was of one gram or more.

JWH-018 or 1-penthyl-3-(1-naphthoyl) indole is one of these analogous substances 9-tetrahydrocannabinol (THC). It is part of the naphthoylindole family [26, 27]. Figure 3 presents the reaction of synthesis for this compound.

The specialty studies show the increased affinity of JHW-018 for the canabinnoid receptor CB five times higher than

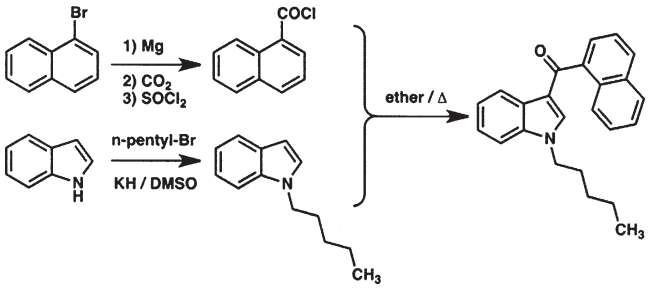

Fig. 3. Reaction of Synthesis of 1-pentyl-3- (1-naphthoyl) indole

at THC. The canabinnoid receptors are found in the brain tissues and spleen, at mammals [28, 29]. JWH-018 may be identified in the urine of rats, which were given this product in form of N-hydroxylated metabolites resulted through dealkylation. Hydroxylation took place on the lateral catena and in both aromatic systems, naphthalene and indole rings, as can be proven by transfer of mass of corresponding fragments. At human, JHW-018 is easily found in urine, using immune-enzymatic tests that identify its omega-hydroxyl and carboxyl metabolites [30].

Conclusions

The consumption of new psychoactive substances has reached in Romania the dimensions of a social phenomenon, due to the rapidity it propagates, to its devastating effects, either direct or indirect, and also to the dramatic decrease of the consumers' age average.

The consumption of these toxic chemical substances has negative consequences at social, psychological, but also medical level. Among the frequently met medical disorders, we mention: depression, exhaustion and mental confusion, neurological, haematological, cardiac disorders, many of them having vital risk [25].

We underline the importance of the physicians knowing the toxicological effects of these drugs, as the number of consumers and pathologies developed has been continuously increasing. The case presented above reveals the involvement of mephedrone derivatives and synthetic cannabinoids in the pathogeny of idiopathic thrombocytopenic purpura.

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