SIDE EFFECTS OF OFF LABEL DRUGS

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Introduction. In most countries in the world where drug turnover (LS) is regulated at the legislative level, medications should be licensed by the regulatory authorities (FDA, HEC) for their use so that doctors and patients can use them. Before a drug must appear in the pharmaceutical market, a favorable balance between its use and harmful effects must be proven. The purpose of drug licensing is to ensure their use after the registration of high-quality, safe and effective drugs, and also after it has been proven that the benefits of their use prevail over the risk.

Aim. In most cases, the use of medication on indications not included in the instruction is prohibited. However, in real medical practice, the appointment of off label drugs is very common in all areas of medicine, and for some drugs it is a common practice, especially in pediatrics, psychiatry and oncology.

Materials and methods. Analysis of the normative basis for the use of off-label in Ukraine and in the world.

Results and discussion. According to the World Health Organization (WHO), half of all medicines have been prescribed according to indications that were not in the instructions and such use of the drug was called off label. As long as off label medications are effective, safe, well tolerated and relatively inexpensive, their use is not anxiety. However, despite of the benefits of using off label drugs, but the lack of regulation by health authorities, they can create certain risks in this area. Therefore, one of the potential concerns for physicians is that off label medicines do not always have convincing scientific support, which may not always be a known risk from the use of the drug for the patient and the doctor. Sometimes off label use of the medication carries more heightened risks for the patient and the doctor than his counterpart, a registered remedy that has an approved instruction. According to the results of the analytical analysis, the serious consequences of the use of off label medicines develop in 68.2% of the cases, including fatal outcomes - 9.8% of cases (10.4% of them are fatal outcomes in children from 0 to 9 years) The most frequent errors leading to fatal outcomes is the off label of the drug in inadequate doses (40.9%), irrational drug selection (16%) and incorrect route of administration (9.5%). In pharmacology, axioms are adhered to, if the drug is used in different directions of pharmacotherapy, then a higher risk of its toxicity should be expected. The safety of off label drugs is largely due to the risk of their adverse reactions and the particularly high risk of side effects of drugs is associated with the use of off label in children. Many problems in pediatrics arise because of the absence or limitation of evidence of side effects and contraindications to off label drugs, especially for rare diseases in children.

Conclusions. Consequently, in the health system, misuse of off label drugs is a serious concern about their safety, especially when the drug is widely used, regardless of the fact that regulators did not determine the risk-benefit ratio for it. Decisions on the prescription of any medications should always be weighed against the potential benefit and the possibility of harm. It must be remembered that prescribing a medicine is one of the most risky actions that a physician performs with a patient.

PATHOLOGICAL EFFECTS OF SUSTANON ON THE LIVER

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Introduction. The phenomenon of abusing Anabolic androgenic steroids (AAS) by many youth and athletes is aserious health phenomenon which increase rapidly in recent years. Sustanon (Androgenicum prolongatum) is one of these AAS and has many useful pharmacological effects. It is used to treat cases of osteoporosis, male hypogonadism and infertility. Sustanon is characterized by a unique

pharmacological structure and properties compared to other AAS drugs, it consists of four testosterone esters, which ensure the continuous release of testosterone into the serum for 3 to 4 weeks. It has the ability to significantly increase muscle mass and strength, so many bodybuilders prefer to include sustanone in the cycle, because it can give immediate results as a high-speed steroid. A number of studies have also reported many serious side effects caused by the abuse of these anabolic drugs that cause cardiovascular disorders (in particular, an increase in the left ventricle) that can lead to sudden death, acute hepatitis and jaundice, testicular dysfunction that lead to infertility, hypertension, behavioral disorders. The instructions state that Sustanon-250 is generally well tolerated and does not adversely affect liver function. However, there is sufficient evidence of adverse effects of steroids on the liver, especially when taken orally.

Aim. A study of the hepatotoxic effect of sustanone in long-term injectable administration.

Materials and methods. Experiments were performed with 40 male rats weighing 200-250 g, which were divided into 4 groups. The first group - intact control, animals of the remaining groups intramuscularly once a week received the drug Sustanon-250 («Organon», Holland) at a dose of 5, 10 and 20 mg/kg body weight, respectively, for 60 days. Blood was taken at 15, 30 and 60 days after treatment, and then 30 days after the termination of administration of sustanone. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) - marker cytolysis enzymes that catalyze the transamination processes, were determined by the method of Raitman and Frenkel. Also, at the indicated time, a histological examination of the liver was performed. For histological studies, biopsy specimens were fixed in a 10% solution of neutral formalin, dehydrated in alcohols of ascending concentration, and poured into paraffin. Histological sections 3-5 μm thick were stained with hematoxylin and eosin. The microscopic examination was performed under a Granum light microscope. Statistical processing of data was carried out using parametric methods of statistics on Student's t-criterion. All animal manipulations were performed under hexenal anesthesia (60 mg/kg) in accordance with the International Principles of the European Convention for the Protection of Vertebrates used for experiments and other scientific purposes (Strasbourg, 18.03.1986) and the First National Congress on Bioethics (Kiev, 2001).

Results and discussion. The results of the study showed that injections of sustanone at doses of 5, 10, 20 mg/kg for 15, 30 and 60 days induce hepatotoxicity in male rats of groups III, IV and V, as confirmed by biochemical and histological studies, as well as a marked increase in ALT and AST in the blood serum of males in the experimental groups compared to the control, and this increase continued after the cessation of hormone administration for 30 days, which indicates liver damage. Increase in ALT and AST in the blood serum with increasing dose means death of hepatocytes due to mitochondrial damage, which leads to leakage of this enzyme outside the hepatocytes and into the blood. ALT is more specific for liver damage than AST.

Histopathological lesions also observed in this study started in 5 mg/kg, and reach to 20 mg/kg in 15, 30, 60 days which continues after stopping treatment for 30 days, this means that sustanon have ability to induce progress liver cell injury because its considered as a first organ responsible for metabolism of sustanon compound. So, this injury induced by accumulation of toxic metabolite from sustanon metabolism that includes 17-α-testosterone. On the other hand, figures showed cell swelling, sinusoid dilation and congestion in addition to centrolobular necrosis, these lesions occurs due to that sustanon like other anabolic androgenic steroid have ability to cause injury of hepatocytes through the effect on mitochondria particularly mitochondrial membrane and inhibit mitochondrial respiration which lead to swelling of mitochondria and cause leakage of ALT and AST.

We noted the presence of programmed death of hepatocytes, as with other anabolic androgenic steroids. Perhaps the drug is capable of causing a programmed cell death by increasing the P53 protein, which is responsible for apoptosis. In addition, this study showed the presence of fibrosis, which progressed in animals for 30 days after cessation of administration of sustanone. This means that replacement of damaged hepatocytes occurs due to connective tissue, and not due to the regeneration of other hepatocytes. Progressing fibrosis indicates the continuing effect of sustanon on hepatocytes, which remains in the tissue for 4 weeks after discontinuation of its administration.

Conclusions. The study showed that sustanon in doses of 5, 10, 20 mg/kg of body weight of the animal for 15, 30 and 60 days is able to induce a hepatotoxic effect on the liver of male rats, and this effect is irreversible and progresses within 30 days after discontinuation of the drug administration.