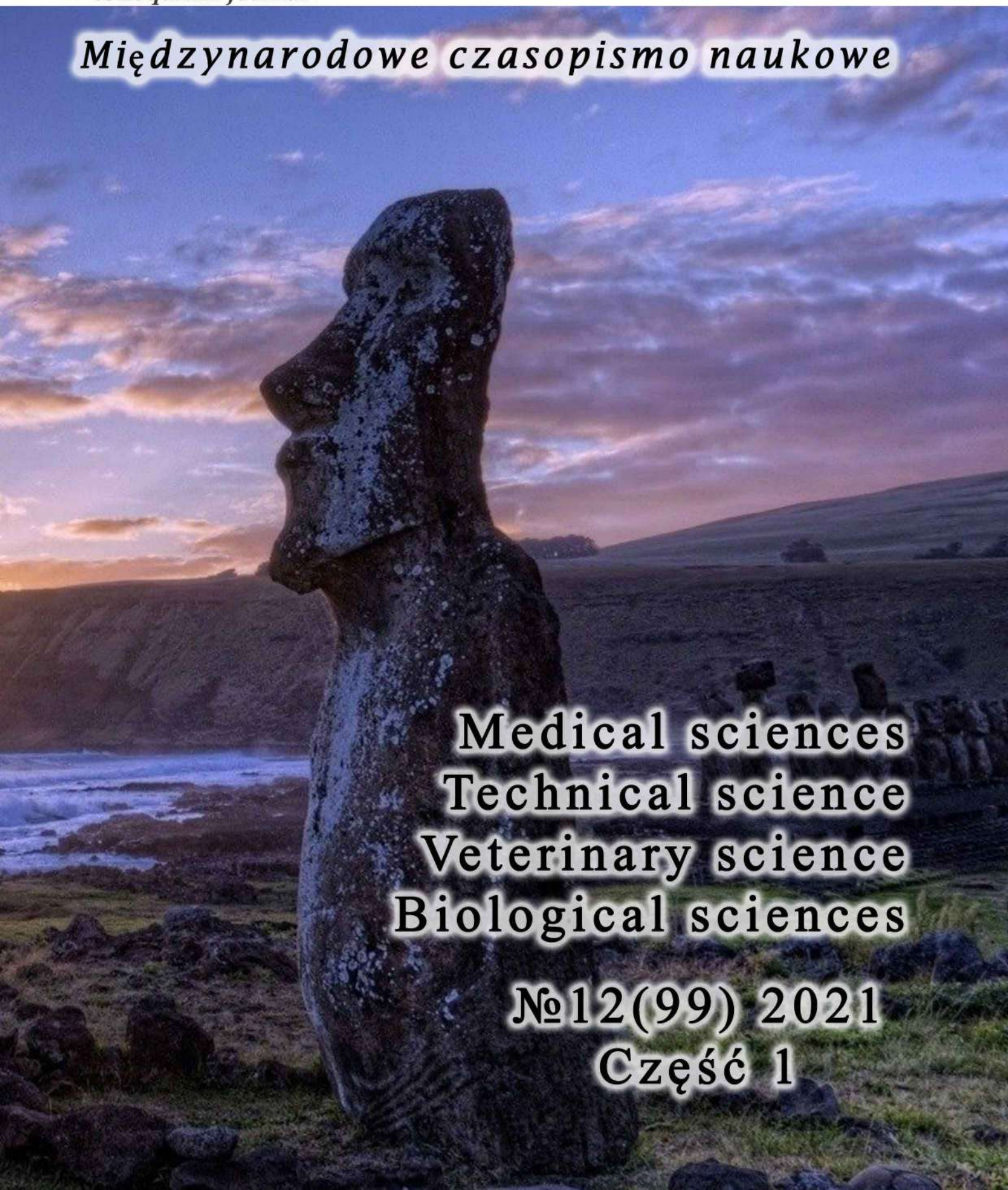
colloquium-journal

ISSN 2520-6990

Międzynarodowe czasopismo naukowe



Medical sciences
Technical science
Veterinary science
Biological sciences

№12(99) 2021
Część 1

colloquium-journal

ISSN 2520-6990

ISSN 2520-2480

Colloquium-journal №12 (99), 2021

Część 1

(Warszawa, Polska)

«Colloquium-journal»
Wydawca «Interdruk» Poland, Warszawa
Annopol 4, 03-236
E-mail: info@colloquium-journal.org
http://www.colloquium-journal.org/

MEDICAL SCIENCES

Каньовська Л.В.,
Антонів А.А.,
Гайдичук В.С.,
Гав'юк С.С,
Пьонтик М.В.
«Буковинський державний медичний університет»

МЕДИКАМЕНТ-ІНДУКОВАНІ ВРАЖЕННЯ ПЕЧІНКИ: ОКРЕМІ АСПЕКТИ ПАТОГЕНЕЗУ, КЛІНІКИ ТА ДІАГНОСТИКИ

Kanyovska L.V.,
Antoniv A.A.,
Gaidychuk V.S.,
Gavyuk S.S.,
Piontyk M.V.
Bukovynian State Medical University

DRUG-INDUCED LIVER IMPRESSIONS: SOME ASPECTS OF PATHOGENESIS, CLINICS AND FORTH AND AGNOSTICS

Анотація.
Медикамент-індуковані враження печінки можуть виникати при дії ліків, в середньому від 5 до 90 днів від початку прийому. Діапазон клінічних проявів різноманітний і може нагадувати майже всі існуючі захворювання печінки: гострий гепатит, стеатогепатит, гостру печінкову недостатність, холестатичне враження. Для правильної діагностики даної патології необхідні знання щодо можливої гепатотоксичності при призначенні певних препаратів.

Аннотация.
Медикамент-индуцированные поражения печени могут возникать при действии лекарств, в среднем от 5 до 90 дней от начала приема. Диапазон клинических проявлений разнообразен и может напоминать почти все существующие заболевания печени: острый гепатит, стеатогепатит, острый печеночную недостаточность, холестатическое впечатление. Для правильной диагностики данной патологии необходимы знания о возможной гепатотоксичности при назначении определенных препаратов.

Abstract.
Drug-induced liver effects can occur with the action of drugs, on average, from 5 to 90 days from the start of administration. A range of varied clinical manifestations and WMS is reminded almost every existing liver disease, acute hepatitis, steatohepatitis, acute liver failure, cholestatic impression. For the correct diagnosis of this pathology requires knowledge about the possible hepatotoxicity in the appointment of certain drugs.

Ключові слова*: медикамент-індуковані враження, печінка, ідіосинкразія, гепатотоксичність, медикаменти*

Ключевые слова: *медикамент-индуцированные впечатление, печень, идиосинкразия, гепатотоксичность, медикаменты*

Keywords*: drug-induced impressions, liver, idiosyncrasy, hepatotoxicity, drugs.*

Introduction. In today's world, a serious problem is drug-induced liver disease, this problem became especially acute during the pandemic, when in many cases completely unreasonably used a variety of drugs, without taking into account their toxic effects on the human body. Dangerous is the fact that for self-medication patients take drugs , the daily and course dose of which may be exceeded, in addition, the uncontrolled intake of antibiotics, and sometimes even in combination, does not improve the situation .

Medicinal impressions of the liver have been known for more than 60 years. According to world statistics in the structure of general liver pathology, toxic effects due to the use of drugs range from 0.7 to 20%. Every year, about 1 million people in the world report side effects from pharmacotherapy. The widespread use of invasive treatments increases the life expectancy of older people who have comorbid conditions and take several medications over a long period of time. It can cause liver dysfunction, which can clinically manifest acute or chronic course of varying severity (from asymptomatic increase in transaminases to severe decompensated hepatitis. The said issue is relevant not only in Ukraine but also in the world. On this suggests the creation of centers of study and management problems of drug-induced liver disease [MIZP] (« drug - induced liver injury» - DILI) , located in North Carolina, Indiana, San - Francisco, Michigan and Connecticut. It should be emphasized that liver damage due to the influence of medications does not always is poisoning due to drug overdose.

According to the WHO, 50 out of 1000 hospitalized patients are referred for treatment due to drug complications [1]. Among outpatients, their frequency is 2-3%, and among critically ill patients treated in the hospital - from 6 to 35%. At the same time, adverse effects

due to medication are not only a serious medical, social, but also economic problem. MI C P should be diagnosed at an earlier date, because long-term use of drugs can repeatedly increase the severity of clinical manifestations and significantly affect the prognosis of the disease as a whole

In clinical practice, more than 80 drugs with certain hepatotoxicity are used, among which the most well-known are paracetamol, anti-TB drugs, tetracyclines, augmentin, erythromycin, diclofenac and others [8]. The severity of the lesion and its nature is determined by the chemical structure of drugs, duration of treatment and dosage, as well as genetically determined predisposition or deficiency of enzymes of the cytochrome P-450 system. Drug-induced liver damage is one of the most common manifestations of adverse drug reactions, due to the active participation of this organ in the biotransformation of xenobiotics [1, 9, 12].

By definition L ikarsk and liver damage (BOB) is liver damage caused by is all types of drugs prescription or not, including small chemical molecules and biological agents, herbs (AF), dietary supplements and biological food supplements (dietary supplements) , arising in the period average of 5 to 90 days after the initiation of [1, 2]

The range of clinical manifestations BOB varied and WMS is reminded almost every existing liver disease: acute hepatitis, steatohepatitis, acute liver failure, cholestatic experience and so on.

Among the drugs there are many drugs that have toxic effects on the liver. These include acetaminophen/paracetamol; nonsteroidal anti-inflammatory drugs naproxen, ibuprofen; anabolic steroids, antibiotics: methyltestosterone drugs, erythromycin, amoxicillin/clavulanate, tetracyclines (doxycycline, minocycline, tetracycline); antipsychotic drugs: risperidone, chlorpromazine; statins, antifungals: terbinafil, ketoconazole; antihypertensive: methyldopa; contraceptives, antidepressants: sertraline, fluoxetine, bupropion; anticonvulsants: phenobarbital, carbamazepine, phenytoin; several drug along with slimming and psychotropic drugs (cocaine, amphetamine, methamphetamine, heroin, inhalants, etc.). The danger is that even in therapeutic doses, these drugs can cause hepatopathy of varying severity. [5,7]

The mechanism of adverse effects of drugs is complex and not fully understood.

The liver metabolizes almost every drug that enters the body. Most drugs have a lipophilic structure, which allows them to easily penetrate cell membranes. As a result of a number of biochemical processes in hepatocytes, they become hydrophilic, which contributes to their inactivation and easier excretion [4, 9, 15]. Drug metabolism occurs in two phases. In the first they are subjected to oxidation, hydroxylation, which enhances their polarization. Cytochrome P450 enzymes catalyze the first phase of metabolic reactions. Most of these intermediates are unstable and highly reactive. Reactions can produce metabolites that are more toxic than the parent substance, which may actually cause liver damage. In humans, drug metabolism is mainly provided by cytochromes, which belong to three families: P450 - I, P450 - II, P450 - III. Some drugs can induce and inhibit P450 enzymes. (Table 1) [1,8]. Reactions of the second phase occur directly in the liver or outside it. It consists in conjugation with endogenous compounds (acetic, sulfuric, glucuronic acids, amino acids, glutathione), resulting in increased solubility. Later, high molecular weight drugs can be excreted in the bile, while the kidneys excrete smaller molecules.

Table 1

List of drugs and substances that affect on the activity of enzymes P450

Induction	Inhibition
Phenobarbital	Amiodarone
Phenytoin	Cimetidine
Carbamazepine	Erythromycin
Primidone	Grapefruit juice
Ethanol	Isoniazid
Glucocorticoids	Ketoconazole
Rifampin	Metronidazole
Griseofulvin	Sulfanilamides
Quinine	Quinidine

Council of International Organizations of Medical Sciences (Council for International Organizations of Medical Sciences - CIOMS) identified 3 types of idiosyncratic M FROM Q. hepatocellular, cholestatic and mixed.

Table 2

Types of acute MI with P

Type of lesion	ALT	LF	The ratio of ALT / LF
Hepatocellular	> 2	name	high > 5
cholestatic	norm	> 2	Low < 2
Mixed	> 2	> 2	2 5

In the case of hepatocellular lesions, drug withdrawal leads to an improvement in biochemical parameters for an average of 2 weeks. With cholestatic or mixed types of lesions, the positive dynamics may be absent for 4 weeks. Biochemical shifts, which are observed for a longer time, suggest the presence of concomitant liver pathology or other etiology of existing disorders [6,8,10]

In addition to idiosyncratic, with clinically isolated specific phenotypes M FROM Q. reaction to medications with eosinophilia and systemic symptoms (DRESS -syndrom); drug-induced autoimmune hepatitis; cholestatic liver lesions (secondary sclerosing cholangitis, ductopenic syndrome); acute fatty degeneration; nodular regenerative hyperplasia; liver tumors. The cause of neoplastic liver tumors is the use of anabolic androgenic steroids and oral contraceptives [4.12].

Early diagnosis of MI Since P is extremely important as well because of the high risk of progression of the disease without discontinuation. Due to the large number oligosymptomatic MI Since P in patients receiving hepatotoxic drugs, and with polypharmacy advisable to regularly (at least once in two weeks and, while long-term therapy - once a month) Determine spare active at art and aminotransferase, ALP and ditch tion of bilirubin in the blood serum. If the activity of transaminases is increased more than 3 times, the drug is canceled. An alternative to drug withdrawal, as well as the need to continue treatment with hepatotoxic drugs, is to reduce the dose of hepatotox and edging with hepatoprotector [3].

At the heart of the diagnosis of MI C P - carefully collected complaints and medical history of drugs used, duration of use and their dosage. With the help of biochemical and immunological studies, ultrasonography (and in some cases other methods of radiological diagnosis) liver disease of other etiologies is established. The diagnosis is confirmed if clinical symptoms, changes in biochemical parameters and histological signs of liver damage disappear or decrease after discontinuation of the drug. Liver biopsy may be indicated if previous liver pathology is suspected or in the absence of normalization of biochemical parameters after drug withdrawal [14,15]. There are no specific histological changes for MIUP.

In the treatment of MIUP, first of all, it is necessary to cancel the drug, the reception of which may be associated with liver damage. This helps to stabilize the process in most cases and possibly recovery. Reverse development of clinical symptoms, normalization of transaminases and markers of cholestasis can occur at different times - from several weeks to 2-3 months or more [2,7,8,16]. Detoxification, hepatoprotective, antidote therapy, and in some cases even glucocorticoids are used for treatment.

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