

**ANALYSIS OF THE STUDY OF 2% LIDOCAINE HYDROCHLORIDE SOLUTION
HEPATOTOXICITY AT VARIOUS NUMBER OF INJECTIONS IN THE EXPERIMENT**¹Belarusian State Medical University (Minsk, Republic of Belarus)²5th city clinical Polyclinic (Minsk, Republic of Belarus)³Association of Oral and Maxillofacial Surgeons of the Republic of Belarus (Minsk, Republic of Belarus)
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The connection of the publication with planned research works. The topic of scientific research work of the Department of Oral Surgery of the educational institution "Belarusian State Medical University" in 2018-2022 is "Prediction, diagnostics, treatment, prevention of complications and rehabilitation of patients with surgical pathology of the maxillofacial region" (State register No. 20180755 of 25.05.2018).

Introduction. According to A. F. Bizyaev et al. (2002), from 30% to 76% of patients visiting a dentist have concomitant somatic diseases. According to V.A. Alekseev et al. (2017) it was presented that in patients in emergency dental medical care, concomitant somatic pathology was detected in 50% of individuals, 40% of respondents reported the presence of two or more diseases, among which in comorbidities there were diseases of liver [1].

And in recent years, doctors have recorded the increasing in the number of drug-induced liver injury (DILI) [2]. Drugs with hepatotoxic side effects also include local anesthetics of the amide group, which are widely used in dental practice, particularly, 2% solution of lidocaine hydrochloride [3, 4]. The patients with multiple foci of chronic odontogenic infection received the local anesthetic injections multiple times, usually every 3 to 4 days.

It should be noted that DILI can be caused not only by amide local anesthetics but also by different others medications, herbal and dietary supplements (HDS), or any other xenobiotics because all of them are metabolized in liver. And these can result in abnormalities in liver tests or in hepatic dysfunction. So, there are two types of DILI: intrinsic and idiosyncratic [5, 6].

Intrinsic DILI are written when liver toxicity is induced by a drug in a predictable and interactions dose-alcoholic related manner. Idiosyncratic DILI occurs less frequently, but it's bound associated with a less consistent dose-toxicity relationship and a more varied presentation [6, 7]. According the scientists there are different mechanisms of DILI. Among them there are direct lesions of the structural (e.g., mitochondrial dysfunction) and functional integrity of the liver, production of a metabolite that alters hepatocellular structure and its function (like in a case of lidocaine hydrochloride) and production of a reactive drug metabolite that binds to hepatic proteins to produce new antigenic drug-protein adducts, which are targeted by hosts' defenses and initiation of a systemic hypersensitivity response (i.e., drug allergy) that damages the liver [6, 8].

There are several risk factors for patients for developing more of DILI they are: genetics, race, age (older or younger), gender (female), pregnancy, malnutrition, obesity, gut microbiome, diabetes mellitus, hormonal status, comorbidities including preexisting liver disease

or HIV, and indications for therapy. Environmental factors also can increase the risk of DILI, they are smoking, alcohol consumption, and infections or inflammatory episodes [6, 9, 10].

Drug-related factors that can contribute to the development of DILI are: daily dose, metabolic profile, class effect and cross-sensitization, and drug interactions or polypharmacy (that is an often situation in dental practice in patients with comorbidities). Higher doses of drugs can lead to increasing intrahepatic levels of the drug or its metabolite; and then greater lipophilicity can dystrophy lead infiltrate to odontogenic more lead extensive state metabolism, liver that after can lead to covalently bound haptens and produce an adverse immune response in genetically susceptible individuals. And it should be mentioned that drugs that undergo extensive hepatic metabolism may lead to drug-induced autoimmune hepatitis [11].

According the articles of scientists, the idiosyncratic (unpredictable) drug-induced liver injury is noted to be the one of the most challenging liver disorders disease that faced by hepatologists. The fact is that nowadays there is absence of specific biomarkers instead of the ability of toxicity the condition to present with a variety of clinical and pathological phenotypes because of a lot of drugs used in clinical practice, herbs and dietary supplements with hepatotoxic potential.

All these facts make the diagnosis of DILI difficult, requires a high degree of the condition awareness and the exclusion of alternative etiologies of liver disease. In clinical practice idiosyncratic hepatotoxicity can be severe, leads to a serious variety of acute liver failure and can lead to the death of patient.

According the Clinical Practice Guidelines (2019) that summarized the available evidence on risk factors, diagnosis, management and risk minimization strategies for drug-induced liver injury, DILI is classified as intrinsic (or direct) vs idiosyncratic [6]. So, intrinsic DILI is usually dose-related and is diagnosed in a large part of patients exposed to the drug (predictable) and onset is within a short time (hours to days). Idiosyncratic DILI is usually not dose-related, is diagnosed in only a small number of individuals (unpredictable) and manifests a variable latency to onset of days to weeks.

According pathogenesis of these 2 types of DILI the common features are - in both types the chemical structure of the drug are important, especially lipophilicity and pharmacological biotransformation. This exposes the liver to reactive metabolites which can covalently bind to proteins and result in organelle stress (e.g. mitochondrial or endoplasmic reticulum stress), because of inducing of oxidative stress, activating signal transduction pathways interfere with bile acid transport and fi-

nally lead to necrosis or apoptosis of liver cells. And, this stress can provoke innate immune responses that provide a co-stimulation for an adaptive immune response in persons with a genetic predisposition to adaptive immunity.

It should be noted that the chief position in idiosyncratic DILI with most drugs is the critical role of the adaptive immune acute. So, many drugs that cause immunemediated idiosyncratic DILI exhibit no systemic allergic features such as rash and eosinophilia [11, 12].

Factors such as systemic illnesses, concomitant drugs, chronic alcoholic abuse, fasting modulate the threshold toxic dose by influencing CYP2E1 (the main enzyme which converts acetaminophen to a reactive metabolite) or glutathione status (main detoxification factor) [11, 13].

Generally, more than 100 medicinal preparations have been reported to be toxic to the liver. The degree of evidence of toxicity is variable as for classical pharmaceutical agents. And potential hepatotoxicity was proved in drugs associated with alternative medicines such as herbal preparations and dietary supplements. Herbal medicines may cause a large spectrum of liver injury, affecting all cells present in the liver and biliary tree, and ranging from mild asymptomatic liver enzyme elevation to acute hepatitis, chronic hepatitis, cirrhosis, liver failure, acute and chronic cholangitis, with macrovesicular steatosis, and vascular lesions [9].

Also among the risk factors for the development of the DILI is age. The clinical cases of serious adverse drug reactions that has been reported rising with increasing the age of patients [10, 14]. Manifestations of DILI in older people are dose-related, and can be a result of ageing being associated with impaired drug clearance. In the Spanish DILI registry, 46% patients with DILI were ≥ 60 years old and according the US DILIN reported 16.6% of patients with DILI were 65 years or older. And it was mentioned that the effect of age on DILI incidence was also in parallel with increasing of using, suggesting that the elderly patients are taking more medications [10, 14].

The aim of the study was to analyze the differences in morphological preparations of liver tissue with different numbers of injections of 2% lidocaine hydrochloride solution into the head and neck region of experimental animals.

Object and methods of the research. Experimental studies were carried out on 10 male mild laboratory white mice in accordance with the requirements governing work with experimental animals. Laboratory animals were injected with a 2% solution of lidocaine hydrochloride according to our technique into the submandibular region (option of mandibular anesthesia by extra oral access) every 3-4 days (1st, 3rd, 7th, 11th, 15th days, totally 5 injections) at average therapeutic doses, that was based on clinical pharmacology data [5]. This experimental model corresponds to the conditions of real clinical practice [3, 15]. In the objects withdrawn from the experiment, liver tissue was taken for pathohistological examination with a time step of 3-4 days.

Experimental studies were conducted in compliance with the requirements of humane treatment of experimental animals, regulated by the European Convention for the Protection of Vertebrate Animals Used

for Research and Other Scientific Purposes (Strasbourg, 18.03.1986).

The results of the study and their discussion. During the examination of liver preparations after the first injection of 2% lidocaine hydrochloride, there were obtained multiple foci of necrosis of hepatocytes, different in shape and size, without or with a perifocal inflammatory reaction (a large number of eosinophils were visualized in the infiltrate).

After second times injection of the local there anesthetic, moderate parenchymal and interstitial edema, small foci of necrosis of hepatocytes, mainly centrilobular and near the central veins, with a perifocal cellular inflammatory reaction morphologically were observed. In single portal tracts, an inflammatory reaction and mild cholestasis are noted.

After third injection of local anesthetic, morphologically, in the liver it was revealed: plethora, foci of necrosis of hepatocytes with a perifocal inflammatory response (in the infiltrate there were lymphocytes, neutrophils, single eosinophils), focal inflammatory infiltration of a lot of portal tracts, moderate nuclear polymorphism, hepatocyte and fatty dystrophy (predominantly medium droplet).

After the fourth injection of the 2% solution of lidocaine hydrochloride in liver preparations we observed plethora, small and large foci of necrosis of hepatocytes with a perifocal inflammatory reaction (lymphocytes, neutrophils, eosinophils in the infiltrate), focal inflammatory infiltration of portal tracts, moderate nuclear polymorphism, fatty tissue.

After fifth injection of local anesthetic in the liver there were noted nuclear polymorphism, multiple, mainly large, foci of necrosis of hepatocytes with a perifocal inflammatory reaction (there are a large number of eosinophils in the infiltrate), inflammatory infiltration of the portal tracts, intraductal cholestasis, inflammatory infiltration around the central veins (infiltration with an admixture of a small number of eosinophils and single neutrophils), eosinophilic intranuclear inclusions were detected in individual nuclei, fatty degeneration of hepatocytes was determined.

These morphological changes should be regarded as a manifestation of drug injury stress to the liver, due to the pharmacological properties of a 2% solution of lidocaine hydrochloride, which is metabolized during the first passage through the liver (by 90-95%) under the action of microsomal enzymes by dealkylation of the amino group and rupture of the amide bond with the formation of active metabolites (monoethylglycinexyldine and glycinexyldine), which are active hepatotoxic metabolites [1, 5].

Conclusion. As a result of the study, it was revealed that even after the first injection of a 2% solution of lidocaine hydrochloride, hepatotoxicity was detected, and it increases with the number of injections of this local anesthetic in the head and neck region.

The prospects of further research. The research results will be introduced into practical healthcare.

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АНАЛІЗ ДОСЛІДЖЕННЯ ГЕПАТОТОКСИЧНОСТІ 2% РОЗЧИНУ ЛІДОКАЇНУ ГІДРОХЛОРИДУ ПРИ РІЗНОМУ ЧИСЛІ ВВЕДЕНЬ В ЕКСПЕРИМЕНТІ**Походенько-Чудакова І. О., Максимович Є. В., Кузнецов Я. О.**

Резюме. Вступ. До лікарських засобів, що володіють гепатотоксичним побічним ефектом, відносяться місцеві анестетики групи амідів, що широко застосовуються в стоматологічній практиці, зокрема 2% розчин лідокаїну гідрохлориду.

Мета дослідження – проаналізувати відмінності в морфологічних препаратах тканини печінки при різному числі введення 2% розчину лідокаїну гідрохлориду в ділянці голови та шиї експериментальним тваринам.

Об'єкти і методи. Експериментальні дослідження проведені на 10 самцях лабораторних білих мишей, яким вводили 2% розчин лідокаїну гідрохлориду за розробленою нами методикою в піднижньощелепну область (варіант мандибулярної анестезії позаротовим доступом) кожні 3-4 дні (1, 3, 7, 11, 15 добу, всього 5 ін'єкцій) в середніх терапевтичних дозах, виходячи з даних клінічної фармакології. У виведених з експерименту особин здійснювали забір тканини печінки для патогістологічного дослідження.

Результат. При дослідженні препаратів печінки, після першого введення 2% лідокаїну гідрохлориду виявлені множинні, різні за формою і розмірами вогнища некрозу гепатоцитів без або з перифокальною запальною реакцією. Після двох введення місцевого анестетика морфологічно спостерігався помірний паренхіматозний та інтерстиціальний набряк, дрібні вогнища некрозу гепатоцитів, переважно центральнобулярно та біля центральних вен, з перифокальною клітинною запальною реакцією. В одиничних портальних трактах відзначається запальна реакція і слабовиражений холестаза. Після трьох введення місцевого анестетика морфологічно в печінці виявлені: повнокров'я, вогнища некрозу гепатоцитів з перифокальною запальною реакцією, вогнищева запальна інфільтрація багатьох портальних трактів, помірний ядерний поліморфізм, жирова дистрофія гепатоцитів. Після чотирьох введення 2% розчину лідокаїну гідрохлориду в препаратах печінки спостерігаються повнокров'я, дрібні і великі вогнища некрозу гепатоцитів з перифокальною запальною реакцією, вогнищева запальна інфільтрація портальних трактів, помірний ядерний поліморфізм, жирова дистрофія гепатоцитів. Після п'яти введення місцевого анестетика в печінці відзначався ядерний поліморфізм, множинні, переважно великі, вогнища некрозу гепатоцитів з перифокальною запальною реакцією, запальна інфільтрація портальних трактів, внутрішньопротоковий холестаза, запальна інфільтрація навколо центральних вен, в окремих ядрах виявлялися еозинофільні внутрішньоядерні включення, визначалася жирова дистрофія гепатоцитів.

Висновок. В результаті проведеного дослідження виявлено, що вже при одноразовому введенні 2% розчину лідокаїну гідрохлориду виявляється гепатотоксичність, яка збільшується з числом введення даного місцевого анестетика в область голови і шиї.

Ключові слова: гепатотоксичність, 2% розчин лідокаїну гідрохлориду, експериментальні дослідження.

ANALYSIS OF THE STUDY OF 2% LIDOCAINE HYDROCHLORIDE SOLUTION HEPATOTOXICITY AT VARIOUS NUMBER OF INJECTIONS IN THE EXPERIMENT**Pohodenko-Chudakova I. O., Maksimovich E. V., Kuznetsov Y. O.**

Abstract. The aim of the study was to analyze the differences in morphological preparations of liver tissue with different numbers of injections of 2% lidocaine hydrochloride solution into the head and neck region of experimental animals.

Objects and methods. Experimental studies were carried out on 10 male laboratory white mice, which were injected with a 2% solution of lidocaine hydrochloride according to the technique developed by us into the submandibular region (a variant of mandibular anesthesia with an extraoral access) every 3-4 days (1, 3, 7, 11, 15 days, total 5 injection) in average therapeutic doses, based on the data of clinical pharmacology. Liver tissue was taken from the objects withdrawn from the experiment for pathohistological examination.

Results. In the study of liver preparations, after the first injection of 2% lidocaine hydrochloride, multiple foci of necrosis of hepatocytes with or without perifocal inflammatory reaction, different in shape and size, were revealed. After second injection of local anesthetic, moderate parenchymal and interstitial edema, small foci of necrosis of hepatocytes, mainly centrilobular and near the central veins, with a perifocal cellular inflammatory reaction were observed morphologically. In single portal tracts, an inflammatory reaction and mild cholestasis are noted. After third injections of local anesthetic morphologically, the liver we revealed: plethora, foci of necrosis of hepatocytes with a perifocal inflammatory reaction, focal inflammatory infiltration of many portal tracts, moderate nuclear polymorphism, fatty degeneration of hepatocytes. After fourth injections of a 2% solution of lidocaine hydrochloride in liver preparations, we revealed plethora, small and large foci of necrosis of hepatocytes with a perifocal inflammatory reaction, focal inflammatory infiltration of the portal tracts, moderate nuclear polymorphism, fatty degeneration of hepatocytes. After fifth injections of local anesthetic in the liver, nuclear polymorphism was noted, multiple, mainly large, foci of necrosis of hepatocytes with a perifocal inflammatory reaction, inflammatory infiltration of the portal tracts, intraductal, cholestasis, inflammatory infiltration around the central veins, eosinophilic intranuclear inclusions were detected in some nuclei hepatocytes.

Conclusion. As a result of the study, it was revealed that even after the first injection of a 2% solution of lidocaine hydrochloride, hepatotoxicity was detected, and it increases with the number of injections of this local anesthetic in the head and neck region.

Keywords: hepatotoxicity, 2% lidocaine hydrochloride solution, experimental studies.

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Стаття надійшла 30.01.2021 року*

DOI 10.29254/2077-4214-2021-2-160-323-326

UDC 617. 52/. 53 - 002. 34 - 089. 168. 1 - 003. 2

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COMPARATIVE ASSESSMENT OF DYNAMICS OF INFLAMMATORY INFILTRATE AREA IN PATIENTS WITH BOILS IN MAXILLOFACIAL AREA AND NECK WITH DIFFERENT APPROACHES TO COMPLEX POSTOPERATIVE TREATMENT¹Belarusian State Medical University (Minsk, Republic of Belarus)²Vitebsk State Medical University (Vitebsk, Republic of Belarus)³5th city clinical Polyclinic (Minsk, Republic of Belarus)⁴Association of Oral and Maxillofacial Surgeons of the Republic of Belarus (Minsk, Republic of Belarus)
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The connection of the publication with planned research works. The topic of scientific research work of the Department of Oral Surgery of the educational institution "Belarusian State Medical University" in 2018-2022 is "Prediction, diagnostics, treatment, prevention of complications and rehabilitation of patients with surgical pathology of the maxillofacial region" (State register No. 20180755 of 25.05.2018).

Introduction. The most common non-endogenous inflammatory diseases of the maxillofacial region include boils [1]. Questions related to the development of this pathology are relevant not only for dental surgeons, maxillofacial surgeons and otorhinolaryngologists, but also for general surgeons and dermatologists [2].

Special attention should be paid to the rehabilitation of patients with boils in the maxillofacial region and neck, since incisions during primary surgical treatment (PST) of the infectious and inflammatory focus are car-

ried out by external access. Taking this into account, it is necessary to strive for the most aesthetic result of surgical treatment in the shortest possible time, in order to prevent psychologic discomfort in this category of patients [3, 4].

At the same time, the issue of wound healing and treatment remains one of the most urgent in modern medicine. The big difficulties in the treatment of these patients are diagnosis, prediction of the course of the pathological process, determination of adequate tactics, subject to strict compliance with the basic principles of treatment of purulent wounds and wound infection. It should be emphasized that the limited possibility of using standard methods of treatment and prevention of complications is associated with an increase in the number of observations of allergic reactions in the population. This fact is the reason for attracting non-drug