HEPATOTOXIC EFFECTS DUE TO THE COMBINED CONSUMPTION OF OPIOID DRUGS AND ALCOHOL

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Summary

Introduction. Over the past 20 years, opioid consumption in the world has reached epidemic proportions, which has led to an increase in premature mortality and significantly changed the epidemiology of liver diseases [1-3]. Similar processes took place in Ukraine, where since the mid-2000s; a dangerous trend has emerged among drug users – the spread of synthetic opioids and their simultaneous consumption with alcohol. The most widespread combination was «street methadone» and alcohol. Mechanisms of hepatotoxic effects of synthetic opioids (heroin, methadone) and alcohol were previously studied in experiments on human cultured hepatocytes and rats [4, 5]. However, the peculiarities of the development of hepatotoxicity in the case of combined human consumption of modern synthetic drugs and alcohol have not been sufficiently studied.

Aim. The study of features of liver injury with combined consumption of opioid drugs and alcohol.

Materials and methods. A retrospective analysis of the medical data of 1,540 patients with the diagnoses of «Acute narcotic poisoning» and «Acute methadone poisoning» (ICD-10: T40.0-T40.3); 42 acts of forensic medical and forensic histological examination of death cases associated with illegal methadone and alcohol were considered. Clinical, biochemical, and pathohistological studies were used. Histological samples were examined using an Olympus CX 41 microscope in transmitted light, at magnifications of 100, 200, and 400 times. The SPSS Statistics 29.0.0.0 program was used, Pearson’s correlation analysis was used, p<0.05.

Results. According to the results of forensic and histological studies, pronounced infiltration of the liver tissue by small lymphocytes (r=0.471, p=0.002) was found in persons with a long history of illegal methadone and alcohol consumption, which was combined with portal fibrosis (r=0.333, p=0.021) and, in some cases, moderate proliferation of bile ducts (r=0.203, p=0.047). Morphometric analysis of liver biopsies revealed sinusoidal dilatation, inflammatory and fibrotic changes of the terminal hepatic venules (r=0.501, p=0.017); sclerotic changes were noted from the expansion of the portal tracts due to fibrosis and to the initial signs of a partial structure violation, which indicates the transition to cirrhosis.

Conclusions. The progressive spread of the practice of combined consumption of opioid drugs on the example of methadone and alcohol increases the risk of hepatotoxic effects, in particular, accelerating the development of fibrosis and cirrhosis.

Keywords: drug poisoning, methadone, alcohol, hepatotoxicity

INTRODUCTION

Over the past 20 years, opioid consumption in the world has reached epidemic proportions, which has led to an increase in premature mortality and significantly changed the epidemiology of liver diseases [1-3]. Similar processes took place in Ukraine, where since the mid-2000s; a dangerous trend has emerged among drug users – the spread of synthetic opioids and their simultaneous consumption with alcohol. The most widespread combination was «street methadone» and alcohol. Mechanisms of hepatotoxic effects of synthetic opioids (heroin, methadone) and alcohol were previously studied in experiments on human cultured hepatocytes and rats [4, 5]. However, the peculiarities of the development of hepatotoxicity in the case of combined human consumption of modern synthetic drugs and alcohol have not been sufficiently studied. The complexity of researching the mechanisms of toxic damage to the hepatobiliary system in drug users is due to the influence of several etiological factors: the duration of drug addiction; comorbidities; consequences of bacterial
and viral infections; drug dose and antiretroviral (ARV) therapy [6, 7, 10].

**AIM**

The study of features of liver injury with combined consumption of opioid drugs and alcohol.

**MATERIALS AND METHODS**

A retrospective analysis of the medical data of 1,540 patients with the diagnoses of «Acute narcotic poisoning» and «Acute methadone poisoning» (ICD-10: T40.0-T40.3) who were treated in the period 2010-2020 at the toxicological center of the Kyiv City Clinical Hospital was carried out emergency medical care. 42 acts of forensic medical and forensic histological examination of death cases associated with illegal methadone and alcohol were considered. After formalin fixation, alcohol wiring, and paraffin embedding, the sections were stained with hematoxylin and eosin. The preparations were examined using an Olympus CX 41 microscope in transmitted light, at a magnification of 100, 200, and 400 times. The statistical analysis of the obtained data was carried out using the IBM SPSS Statistics 29.0.0.0 program, the Spearman correlation coefficient was used – r \( \leq 0.05 \). The materials of scientific publications of Elsevier and PubMed electronic libraries on the topic of research were studied.

**RESULTS**

The relevance of the problem of distribution of opioid drugs in Ukraine is confirmed by the reports of the Center for Mental Health and Monitoring of Drugs and Alcohol of the Ministry of Health of Ukraine, operational data of the Security Service of Ukraine and the Ministry of Internal Affairs of Ukraine. National monitoring proves that the spectrum of toxic substances expands and changes noticeably every year, as evidenced by the data of the toxicology center of the Kyiv City Clinical Emergency Medical Hospital, where since the mid-2000s cases of poisoning by opioid drugs have been regularly registered: dipidolor, buprenorphine, pethidine, promedol, pentazocine, tramadol, oxycodone, methadone, morphine, heroin, fentanyl, etc. For example, during the research period, the number of positive tests for the content of methadone increased more than 150 times, for the content of morphine and Tramadol – 100 times, for the content of heroin – 6 times. At the same time, it is important to note that during the same period, the number of positive tests for the content of natural opium decreased by 7 times. Thus, today the most common drugs that cause poisoning (overdose) are semi-synthetic and synthetic opioids.

All patients with narcotic poisoning underwent clinical and laboratory tests, the results of which revealed various diseases of the gastrointestinal tract (table 1).

<table>
<thead>
<tr>
<th>№ п/п</th>
<th>Nosological structure/age group</th>
<th>16-19</th>
<th>20-24</th>
<th>25-29</th>
<th>30-34</th>
<th>35-39</th>
<th>40-44</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Viral hepatitis (in the anamnesis)</td>
<td>80,60</td>
<td>153,90</td>
<td>166,40</td>
<td>102,60</td>
<td>67,20</td>
<td>1,70</td>
</tr>
<tr>
<td>2</td>
<td>HIV (ARV therapy in history)</td>
<td>32,20</td>
<td>32,40</td>
<td>28,60</td>
<td>21,60</td>
<td>0,00</td>
<td>0,00</td>
</tr>
<tr>
<td>3</td>
<td>Ulcer disease</td>
<td>16,10</td>
<td>59,40</td>
<td>67,60</td>
<td>86,40</td>
<td>43,20</td>
<td>30,60</td>
</tr>
<tr>
<td>4</td>
<td>Gastritis, duodenitis</td>
<td>32,20</td>
<td>56,70</td>
<td>70,20</td>
<td>59,40</td>
<td>62,40</td>
<td>61,20</td>
</tr>
<tr>
<td>5</td>
<td>Non-infectious colitis</td>
<td>0,00</td>
<td>0,00</td>
<td>2,70</td>
<td>10,80</td>
<td>9,60</td>
<td>8,50</td>
</tr>
<tr>
<td>6</td>
<td>Hepatitis</td>
<td>0,00</td>
<td>51,30</td>
<td>72,80</td>
<td>113,40</td>
<td>91,20</td>
<td>22,10</td>
</tr>
<tr>
<td>7</td>
<td>Liver cirrhosis</td>
<td>0,00</td>
<td>0,00</td>
<td>0,00</td>
<td>113,40</td>
<td>91,20</td>
<td>22,10</td>
</tr>
<tr>
<td>8</td>
<td>Pancreatitis</td>
<td>0,00</td>
<td>13,50</td>
<td>28,60</td>
<td>70,20</td>
<td>105,60</td>
<td>34,00</td>
</tr>
</tbody>
</table>

It was found that chronic pancreatitis, persistent hepatitis and alcohol-associated liver cirrhosis at various stages were the most common among patients aged 35-44 years. Among patients over 44 years of age, diseases of the stomach, duodenum, and non-infectious diseases of the colon prevailed. Clinical and laboratory studies revealed liver function disorders among patients with long-term methadone use, which were accompanied by increased levels of GGT, AST, ALT, LDH, and alkaline phosphatase.

According to the results of forensic autopsies and forensic histological studies of 42 cases of hospital death that occurred as a result of poisoning (overdose) with methadone and alcohol, signs of long-term toxic damage to the liver were characteristic (fig. 1-4).
For example, 16 cases (38.1 %) had morphological signs of chronic hepatitis with manifestations of cytolysis and cholestasis. Signs of a chronic inflammatory process and lymphoplasmycotic infiltration were typical, which may be the result of the reaction of liver cells, including hypoxia, caused by the effect of methadone on the central nervous system, lungs, and myocardium. During the microscopic examination, dystrophic changes in the form of vacuolization were detected in the liver parenchyma, in some cases — phenomena of focal protein and small droplet fatty dystrophy, focal necrosis, and infiltration. Congestion of the central hepatic veins and interlobular venous branches of the portal vein in the interlobular triads was observed. Mixed and fibrin thrombi were found in the vessels. Swelling of endothelial cells; moderate expansion of perisinusoidal spaces were noted in the sinusoids. Pathohistological changes of the liver in 4 deceased drug users with concomitant viral hepatitis B (3 persons, 7.14 %) and C (1 person, 2.4 %) were characterized by the presence of fine droplet fatty and parenchymal protein dystrophy of hepatocytes, venous complete blood, as well as abundant lympho- and leukocytes infiltration of portal tracts.

Forensic and histological studies prove that repeated use of opiate drugs is accompanied by specific changes in the liver tissue, which mainly have the character of chronic persistent hepatitis with signs of portal mononuclear hepatitis with a significant content of lymphocytes and macrophages in infiltrates, or with the formation of lympho-macrophage granulomas in the liver parenchyma, sometimes with the appearance of germinal centers. It is important to note that in opium addicts who mainly consume natural opium (morphine, poppy straw), persistent hepatitis for a long time does not have signs of fibrosis of the portal tracts. However, the consumption of new synthetic drugs and/or the combined use of opioids with other narcotic substances and alcohol changes the nature of pathological manifestations in liver tissue. For example, in patients with a long history of methadone and alcohol consumption, pronounced infiltration of liver tissue by small lymphocytes (r=0.471, p=0.002) was found, which was combined with portal fibrosis (r=0.333, p=0.021) and in some cases moderate proliferation bile ducts (r=0.203, p=0.047). Morphometric analysis of liver biopsies revealed sinusoidal dilatation, inflammatory and fibrotic changes of the terminal branch of the hepatic venule (r=0.501, p=0.017). In addition, sclerotic changes were noted: from the expansion of the portal tracts due to fibrosis to the initial signs of a partial structure violation, which indicates the transition to cirrhosis. Fibrosis is
DISCUSSION

In the early 1990s, it was established on isolated human hepatocytes that the hepatotoxicity of heroin and methadone is manifested in the presence of ethanol; which reduces the rates of urea synthesis, glycogen metabolism and the accumulation of the intracellular pool of glutathione, which is accompanied by a simultaneous increase (up to 40%) in the level of cytochrome P-450 [4]. During the following years, the mechanisms of hepatotoxicity of methadone were studied in detail. It has been proven that methadone is mainly metabolized in the liver, and its metabolism occurs by hepatic microsomal enzymes, mainly by the P450 system. The conversion of methadone into the metabolite – 2-Ethylidene-1,5-Dimethyl-3,3-Diphenylpyrrolidine (EDDP) occurs with the help of liver microsomes, mainly CYP3A4 and possibly CYP2C9 and CYP2C19. Some authors note that the specified mechanism is directly related to the occurrence of hepatotoxic effects. By activating cytochrome P-450-dependent monoxygenases, opioids deplete the system of cytochromes and activate free-radical processes. In turn, the peroxidation of cell membrane lipids as a result of the action of free radicals leads to damage to the membrane of hepatocytes, which, in turn, can cause the loss of intracellular cytosolic components with the subsequent increase in the activity of plasmatic transaminases and a decrease in the pool of hepatocellular glutathione [3-5]. It has also been established that δ-opioid receptors, which are known to make a significant contribution to cellular development and are abundant in liver tissue, influence the initiation and progression of liver diseases in drug users [8].

The direct and indirect effects of opioids that can contribute to liver damage are varied. Opioid use is independently associated with an increased risk of liver fibrosis, independent of other substance use and HIV or viral hepatitis B and C [1, 2]. The exact mechanisms of opioid-induced liver fibrosis are not yet fully understood. Opioid use has also been associated with impaired cholesterol and bile acid metabolism, although the exact mechanism by which this occurs remains largely unknown. Elevations of biochemical markers including ALT, LDH, and lipid peroxides have been reported among chronic heroin users, which may indicate direct hepatotoxic effects mediated by these drug metabolites. It has also been proven that periportal infiltrates consisting of lymphoid, histiocytic, and neutrophilic elements are found in the liver samples of people with a long period of opioid consumption, accompanied by hepatocyte swelling, cholestasis, and haemorrhages. Confirmation of the depth of structural damage to hepatocytes is a moderate lymphomonocytic infiltration of the portal tracts, an increase in the number and activity of Kupffer cells, and degranulation of some cells [4].

Histopathologic examination of hepatocytes obtained from chronic opioid-treated rat models showed sinusoidal dilatation, perivenular ballooning degeneration, perivenular necrosis, haemorrhage, and focal microvascular steatosis. Animal studies demonstrate that long-term administration of opioids initiates the occurrence of dystrophic-inflammatory processes in the liver tissue, which are significantly intensified against the background of alcohol consumption and are manifested in the form of dilation or narrowing of sinusoids, hemostasis with the formation of blood clots and haemorrhages, hypertrophy, and eventually dystrophy of hepatocytes, in which hydropic dystrophy, lymphohistiocytic infiltration, focal necrosis and an increase in the number of altered apoptotic cells predominate [5].

However, the direct and indirect effects of opioids on liver disease remain an area that requires additional research as it is difficult to separate the effects of opioids from other factors. For example, approximately one-third of individuals with a history of opioid abuse or dependence are estimated to have co-occurring alcohol use disorders, a major negative factor, as evidenced by separate studies [2, 3, 9].

CONCLUSIONS

The progressive spread of the practice of simultaneous consumption of methadone and alcohol increases the risk of hepatotoxic effects, in particular, accelerating the development of fibrosis and cirrhosis. At the same time, taking into account the multifactorial impact caused by both the direct toxic effect of narcotic substances and indirect effects (hypoxia, bacterial and viral infections, the presence of concomitant diseases), the combined effect of synthetic opioids and alcohol on the formation of liver pathology remains an area that requires additional research.

Prospects for further research. The direct and indirect effects of opioids on liver disease remain an area that requires additional research as it is difficult to separate the effects of opioids from other factors (hypoxia, bacterial and viral infections, comorbidity).

FUNDING AND CONFLICT OF INTEREST

The studies were carried out as part of the planned research work (state registration No. 0112U001133); «Scientific substantiation of measures of toxicological safety of the human environment in the public health
The study did not require additional funding. The Authors declare no conflict of interest.

**COMPLIANCE WITH ETHICAL REQUIREMENTS**

In this study the authors adhered to the Ethical Principles for Medical Research Involving Human Subjects outlined in the World Medical Association’s Declaration of Helsinki (WMA, 1964 p.) and current Ukrainian regulations. The study protocol was approved by the ethics committee of the L. I. Medved’s Research Centre of preventive toxicology, food and chemical safety of the Ministry of Health of Ukraine. Animals were not used.

**REFERENCES**

Резюме

ГЕПАТОТОКСИЧНІ ЕФЕКТИ, ОБУМОВЛЕНІ КОМБІНОВАНІМ СПОЖИВАННЯМ ОПІОІДНИХ НАРКОТИКІВ І АЛКОГОЛЮ

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Вступ. Протягом останніх 20-ти років споживання опіоїдів у світі набуло масштабів епідемії, що призвело до збільшення передчасної смертності та суттєво змінило епідеміологію захворювань печінки.

Мета. Дослідження особливостей ураження печінки при комбінованому споживанні опіоїдних наркотиків і алкоголю.

Матеріали та методи. Проведено ретроспективний аналіз медичних даних 1540 пацієнтів з діагнозами «Гостре наркотичне отруєння», «Гостре отруєння метадоном» (МКХ-10: Т40.0-Т40.3), що лікувалися у період 2010-2020 рр. у токсикологічному центрі Київської міської клінічної лікарні швидкої медичної допомоги. Розглянути 42 акти судово-медичного і судово-гістологічного дослідження випадків смерті, асоційованих з нелегальним метадоном і алкоголем. Використовували клінічні, біохімічні та патогісто-логочні дослідження. Гістологічні зразки досліджували на мікроскопі Olympus CX 41 у прохідному світлі при збільшенні 100, 200, 400 разів. Статистичну обробку отриманих даних проводили за програмою IBM SPSS Statistics 29.0.0.0, використовували кореляційний аналіз Пірсона, р≤0,05.

Результати. За результатами судово-гістологічних досліджень у осіб з тривалим анамнезом споживання нелегального метадону і алкоголю була виявлена виражена інфільтрація тканини печінки лімфоцитами малого розміру (r=0,471, p=0,002), що поєднувалась з портальним фіброзом (r=0,333, p=0,021) та, в окремих випадках, помірною проліферацією жовчних каналців (r=0,203, p=0,047). Морфометричний аналіз біоптатів печінки виявив синусоїдальну дилятацію, запальні та фібротичні зміни термінальної печінкової вені (r=0,501, p=0,017); відмічалися склеротичні зміни від розширення портальних трактів за рахунок фіброзу і до початкових ознак порушення часткової будови, що свідчить про переход до цирозу.

Висновки. Прогресивне поширення практики комбінованого споживання опіоїдних наркотиків на прикладі метадону і алкоголю підвищує ризик виникнення гепатотоксичних ефектів, зокрема пришвидшує розвиток фіброзу і цирозу.

Ключові слова: наркотичні отруєння, метадон, алкоголь, гепатотоксичність