World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-32, March 2024
ISSN: 2749-3644

NEW APPROACHES IN THE TREATMENT OF METABOLIC DISORDERS IN LIVER FAILURE

Sayfutdinova Z.A., Nurillayeva G.S.
Tashkent medical academy

Article history:
Received: January 24th 2024
Accepted: March 20th 2024

Abstract:

Hepatotoxicity is damage caused by exposure to a drug or non-pharmacological agents. Risk factors include: individual intolerance, age, gender, alcohol consumption, smoking, concomitant use of other drugs, liver disease, genetic and environmental factors. [1–3] Although most lipophilic drugs can cause hepatotoxicity , [4] antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants are the pharmacological groups that are the most common causes. [1, 5-9]. Among the drugs administered intravenously, antibiotics and neoplasia drugs are mostly associated with liver toxicity

Keywords: Hepatotoxicity, intolerance, age, gender, alcohol consumption, smoking, concomitant use of other drugs, liver disease, genetic and environmental factors. [1–3] Although most lipophilic drugs

Hepatotoxicity is damage caused by exposure to a drug or non-pharmacological agents. Risk factors include: individual intolerance, age, gender, alcohol consumption, smoking, concomitant use of other drugs, liver disease, genetic and environmental factors. [1–3] Although most lipophilic drugs can cause hepatotoxicity , [4] antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants are the pharmacological groups that are the most common causes. [1, 5-9]. Among the drugs administered intravenously, antibiotics and neoplasia drugs are mostly associated with liver toxicity. [10].

Hepatotoxicity can be divided into intrinsic and idiosyncratic reactions. The former are predictable, dose-dependent and reproducible, but have limited information about their frequency of occurrence. Idiosyncratic reactions are either immune or metabolic and are unpredictable, independent of dose and not reproducible, but they affect only a small amount of patients (between 1/1000 and 1/100,000 examined patients).

Intrinsic hepatotoxicity is less common than idiosyncratic hepatotoxicity [12, 18–20] Liver histology is ideal for identifying patterns of liver toxicity, but in clinical practice most hepatotoxic injuries are classified according to biochemical tests [21]. According to the international consensus of the Council of International Organizations of Medical Sciences (CIOMS), in liver damage, liver enzymes are present twice more than the upper limit of normal (ULN). On the other hand, types of damage are classified:

• Hepatocellular injury is defined as an isolated increase in alanine aminotransferase (ALT) of more than twofold or an ALT/alkaline phosphatase ratio of more than five. Chi's Law defines this type of injury as an ALT value greater than three times the TPL. [24, 25]

• Cholestatic damage is defined as a single increase in alkaline phosphatase greater than twice the EPL or a ratio of less than two.

• Mixed injury is defined as ALT and alkaline phosphatase levels greater than twice the upper limit of normal and a ratio greater than two but less than five.

Hepatotoxicity is associated with mitochondrial dysfunction, inhibition of cellular respiration or alteration of fatty acid β- oxidation [6, 27]. This leads to apoptosis , necrosis, autophagy and consequently cell death [28, 29].

Main clinicopathological manifestations of hepatotoxicity and histological data:

A. Acute hepatitis (characterized by inflammation of the parenchyma, necrosis in Kupffer cells and sinusoids)

b . Chronic hepatitis (fibrosis)

c. Fulminant hepatitis (necrosis and inflammation)

d. Cholestatic hepatitis (liver inflammation and damage)

e. Cholestasis (bile plugs in zone 3)

f. Vanishing bile duct syndrome (bile duct damage, cholestasis and inflammation)

g . Granulomatous hepatitis (granulomas in the portal tract or parenchyma)

h . Macrovesicular steatosis (lipid droplets in the cytoplasm of the hepatocyte)

i . Microvesicular steatosis (tiny droplets of lipids in the cytoplasm of the hepatocyte)

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-32, March 2024
ISSN: 2749-3644

j. Steatohepatitis (steatosis , lobular inflammation, accumulation of hepatocytes and pericellular fibrosis) [12, 29-31].

These manifestations are accompanied by nonspecific signs and symptoms such as fever, fatigue, nausea, pain, jaundice, dark urine, pruritus, ascites, encephalopathy and elevated transaminases [16, 32, 33].

Although approximately 1100 drugs, excluding substances found in natural products, have been associated with hepatotoxicity [19], identification of this adverse event is challenging.

Therefore, a thorough investigation is required to identify any substance and exclude other causes of liver disease (3, 8, 34). In addition, liver biopsy is fundamental to determine hepatotoxicity [35]. The chronological relationship between exposure to the suspected agent and the hepatotoxic reaction is key. To establish the likelihood that a drug is associated with hepatotoxicity , clinical scales such as the Roussel-Uclaf causality assessment method (RUCAM) and the Maria & Victorino (M&V) clinical scale have been developed. It is believed that the content of the RUCAM scale and criterion validity make it the most appropriate, and that it generates results consistent with medical judgment and expert judgment of hepatotoxicity . However, due to its high cost, the application has limitations in its usefulness in clinical practice [36–38].

In the absence of specific pharmacotherapy, treatment of hepatotoxicity is based on withdrawal of the suspected drug, treatment of symptoms and subsequent laboratory preliminary tests [39]. However, the use of N- acetylcysteine as an antidote for paracetamol toxicity and hepatotoxicity due to phenytoin and carbamazepine , and the use of drugs for the treatment of valproic acid poisoning [40]

An updated list of hepatotoxic drugs and associated factors may help optimize detection and prevent this adverse event. Therefore, the objectives of this review were to prepare an updated list of drugs associated with hepatotoxicity and to identify the drugs most likely to cause hepatotoxicity according to scientific evidence .

PubMed / Medline search was performed using the MeSH terms "liver disease" (drug exposure, injury, pathology) and "drug-induced liver injury." The search was filtered by published articles with keywords in the title or abstract up to December 2020 in English, Spanish and French and for which access to the full text was available. Articles were categorized as case reports, reviews, systematic reviews, clinical trials, clinical trials, controlled trials, randomized clinical trials, clinical trials, meta-analyses . Articles with evidence of hepatotoxicity due to medications only and those considered relevant to the subject were included

Mechanisms of hepatotoxicity, risk factors, clinical manifestations, management, outcome, measurements. Liver enzymes and drug dosages were also recorded.

Means and standard deviations were calculated for numerical values. Theoretical data such as liver enzyme values (aspartate , aminotransferase [AST], ALT, and total bilirubin [TB]) and dosages of drugs administered.

The research identified 610 articles, of which 402 met the inclusion criteria and were selected, whereas 208 did not meet the inclusion criteria and were excluded. Forty-six other articles considered relevant to the review were included.

A list of 181 drugs and 17 combination pharmacological dosage forms or therapeutic regimens that can cause hepatotoxicity. Six of these drugs (methotrexate , minocycline , vancomycin , everolimus , isoniazid , and tamoxifen) and one treatment regimen (isoniazid , rifampicin plus pyrazinamide) were classified as definite drugs and five combination dosage forms or therapeutic regimens were classified as probable, and 119 drugs and 11 combination dosage forms were classified as possible.

The type of injury caused by each drug has been identified, and hepatocellular injury is more common than cholestatic or mixed injury. Information was found for each drug with a certain probability, which was tabulated, type of hepatotoxicity , type of lesion, appearance, mechanism of hepatotoxicity , risk factors, clinical manifestations and results.

More cases of amiodarone have been reported and have been associated with increased hepatic enzyme synthesis in 15–55% of patients [46].

Antihypertensive drugs such as enalapril increase liver enzyme levels and produce jaundice and structural changes in the liver are confirmed by biopsy, which led to transplantation and death [48].

for methyldopa (probable) . and diosyncratic liver toxicity [17]. They had a pattern of hepatocellular injury, especially in women, showing jaundice, anorexia and nausea. In addition, liver biopsy revealed necrosis and inflammatory infiltrates [49, 50].

Hepatocellular lesions accompanied by elevated liver enzymes, jaundice, fever and asthenia have been associated with atorvastatin and ezetimibe [51, 52].

Propylthiouracil caused the death of one patient, a woman and a girl, causing symptoms such as jaundice, itching and weight loss; necrosis, fibrosis, inflammatory infiltrate and was found on liver biopsy.

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-32, March 2024
ISSN: 2749-3644

Four cases of elevated liver enzymes, weakness and jaundice were identified in patients taking methylprednisolone . Symptoms improved after drug withdrawal [54].

Among antibiotics, idiosyncratic reactions have been identified in combination with vancomycin [55], especially reverse transcriptase inhibitors, nucleoside analogues and protease inhibitors, which can cause dose-dependent hepatotoxicity . Efavirenz and nevirapine have been reported to have elevated transaminase levels and incidence rates ranging from 1% to 14% [9]. Coinfection with hepatitis B or hepatitis C virus may increase the rate of hepatotoxicity associated with antiretroviral treatment.

Chemotherapy increases life expectancy, but can cause liver damage, ranging from steatosis and steatohepa , to cirrhosis. The likelihood of hepatotoxicity for tamoxifen , everolimus and methotrexate is certain.

Drugs such as flutamide , etoposide , imatinib , ipilimumab , oxaliplatin , temozolomide , thioguanine , glatiramer , azathioprine and infliximab have been classified as probable causes of hepatotoxicity .

Women affected by minocycline from 16 to 57 years of age who were diagnosed with autoimmune hepatitis. Rifampicin caused hepatocellular lesions and particularly affects women [57, 58] the following antibiotics have been classified as probable causes of hepatotoxicity : nitrofurantoin (incidence 12% of cases, idiosyncratic), [59, 60], flucoxacillin (11 cases, idiosyncratic), [61] telithromycin (hepatocellular lesions with elevated transaminase levels and fever), [62] ciprofloxacin and trovafloxacin (withdrawn from the market).

Liver damage associated with the antifungal agents itraconazole , fluconazole , and ketoconazole has been improved with drug suspensions. [63].

NSAIDs have been identified as an important group that can cause liver damage, mostly idiosyncratic, in cases of abuse or overdose. Identified risk factors included age, female gender, chronic alcohol use, concomitant drugs, underlying diseases, obesity, type 2 diabetes and stroke. Pathogens include diclofenac , lumiracoxib and nimesulide . Acetaminophen is widely recognized as an intrinsic hepatotoxic substance due to its metabolites, causing liver necrosis.

When taking N- acetylcysteine and prednisolone, the condition improved in some patients.

Halothane was a general anesthetic that most likely caused liver toxicity. Genetic predisposition, repeated doses, obesity is a combination of isoniazid , rifampicin and pyrazinamide (definite possibility). Hepatotoxicity is manifested by elevated liver enzymes, abdominal pain, jaundice, asthenia, nausea, vomiting and necrosis and is confirmed by liver biopsy. In the case of combination pharmaceutical dosage forms of antibiotics such as trimethoprim / sulfamethoxazole and amoxicillin/ clavulanic acid, cases of hepatotoxicity were identified as idiosyncratic and classified as probable [57]. Hepatotoxicity was observed mainly in men and caused jaundice and pruritus. In some cases caused by amoxicillin/ clavulanic acid, the result was liver transplantation.

The antiretroviral regimen ritonavir , indinavir , darunavir , and fosamprenavir have been associated with hepatocellular injury and necrosis. Case reports of anticancer drugs 6-thioguanine, daunomycin and cytosine arabinose used as part of a therapeutic regimen for myeloid leukemia in children is indicated hepatomegaly , cirrhosis and veno-occlusive diseases.

Risk factors included age and advanced age. Women are more likely to experience liver damage, including hepatocellular damage, elevated liver enzymes, necrosis, fever, jaundice, and fatigue.

Among anticonvulsants , valproic acid was the most important in the number of cases of hepatotoxicity (hepatocellular type), which is manifested by elevated transaminases , jaundice and anorexia. In addition, microvesicular and macrovesicular steatosis , necrosis, and inflammatory infiltrates were found on liver biopsy. This medicine may cause liver damage in people younger than 30 years of age.

The identified cases of carbamazepine were mainly of the mixed type with the formation of granulomas.

LITERATURE

1. Carmeliet P, Dor Y, Herbert J, et al. Role of HIF-1α in hypoxia-mediated apoptosis, cell proliferation and tumor angiogenesis. *Nature.* 1998;394:485–490. [PubMed] [Google Scholar]
2. Chapman-Smith A, Lutwyche JK, Whitelaw ML. Contribution of the Per/Arnt/Sim (PAS) domains to DNA binding by the basic helix-loop-helix PAS transcriptional regulators. *J Biol Chem.* 2004;279:5353–5362. [PubMed] [Google Scholar]
3. Chen EY, Fujinaga M, Giaccia AJ. Hypoxic microenvironment within an embryo induces apoptosis and is essential for proper morphological development. *Teratology.* 1999;60:215–225. [PubMed] [Google Scholar]
4. Cramer T, Yamanishi Y, Clausen BE, et al. HIF-1α is essential for myeloid cell-mediated

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-32, March 2024
ISSN: 2749-3644

inflammation. *Cell.* 2003;112:645–657. [PMC free article] [PubMed] [Google Scholar]
5. Date T, Mochizuki S, Belanger AJ, et al. Expression of constitutively stable hybrid hypoxia-inducible factor-1α protects cultured rat cardiomyocytes against simulated ischemia-reperfusion injury. *Am J Physiol.* 2005;288:C314–C320. [PubMed] [Google Scholar]
6. Dery MA, Michaud MD, Richard DE. Hypoxia-inducible factor 1: regulation by hypoxic and non-hypoxic activators. *Int J Biochem Cell Bio.* 2004;37:535–540. [PubMed] [Google Scholar]
7. Donghoon Y, Pastore YD, Vladimir D, et al. HIF-1α-deficiency results in dysregulated EPO signaling and iron homeostasis in mouse development. *JBC Papers in Press.* 2006 [Google Scholar]
8. Сайфутдинова З.А., Каримов Х.Я., Саидов А.Б. Механизмы нарушений при токсическом повреждении печени и пути их коррекции с помощью нового аминокислотного раствора на основе сукцината натрия и маннитола // Журнал теоретической и клинической медицины-2021. - №3. –Б. 7-11.
9. Саидов А.Б., Курбонова З.Ч., Сайфутдинова З.А., Шомансурова Г.Е. Қон компонентларида биохимик кўрсаткичлар лаборатор ташхиси // Замонавий клиник лаборатор ташхиси долзарб муаммолари. – 2022. – №1. - Б. 158-159.
10. Сайфутдинова З.А. Современные представления о гипоксии-индуцибельном факторе-1 (hif-1) – важном звене в патогенезе ишемических повреждений тканей // Вестник Ташкентской медицинской академии-2021. - №3. –Б. 33-36.
11. Сайфутдинова З.А., Каримов Х.Я., Саидов А.Б. Патофизиологическое обоснование применения новой аминокислотной смеси при повреждении печени // Тиббиётда янги кун-2021. - №4. –Б. 93-96.
12. Сайфутдинова З.А., Каримов Х.Я. Сравнительная оценка эффективности нового аминокислотного кровезаменителя при экспериментальном токсическом гепатите // Вестник Ташкентской медицинской академии-2021. - № Выпуск посвящается 100-летию ташкентской медицинской академии. –Б. 217-220.
13. Сайфутдинова З.А., Каримов Х.Я., Саидов А.Б. Анализ эффективности применения новой аминокислотной смеси при гелиотриновом поражении печени по данным морфологических методов исследований // Медицинские новости- 2021. -№7· –Б. 57-59.
14. Huang LE, Gu J, Schau M, Bunn HF. Regulation of hypoxia-inducible factor 1α is mediated by an O2-dependant degradation domain via the ubiquitin-proteasome pathway. *Proc Natl Acad Sci USA.* 1998;95:7987–7992. [PMC free article] [PubMed] [Google Scholar]
15. Ivan M, Haberberger T, Gervasi DC, et al. Biochemical purification and pharmacological inhibition of a mammalian prolyl hydroxylase acting on hypoxia-inducible factor. *Proc Natl Acad Sci USA.* 2002;99:13459–13464. [PMC free article] [PubMed] [Google Scholar]
16. Iver NV, Kotch LE, Agani F, et al. Cellular and developmental control of O2 homeostasis by hypoxia-inducible factor 1 alpha. *Genes Dev.* 1998;12:149–162. [PMC free article] [PubMed] [Google Scholar]
17. Kido M, Du L, Sullivan CC, et al. Hypoxia-inducible factor 1-alpha reduces infarction and attenuates progression of cardiac dysfunction after myocardial infarction in the mouse. *J Am Coll Cardiol.* 2006;46:2116–2124. [PubMed] [Google Scholar]
18. Krick S, Eul BG, Hanze J, Savai R, Grimminger F, Seeger W, Rose F. Role of hypoxia-inducible factor-1α in hypoxia induced apoptosis of primary alveolar epithelial type II cells. *Am J Resp Cell Molec Bio.* 2005;32:395–403. [PubMed] [Google Scholar]
19. Laderoute KR, Amin K, Calaoagan JM, et al. 5'-AMP-activated protein kinase (AMPK) is induced by low-oxygen and glucose deprivation conditions found in solid-tumor microenvironments. *Mol Cell Biol.* 2006;26:5336–5347. [PMC free article] [PubMed] [Google Scholar]
20. Lakhani NJ, Sarkar MA, Venitz J, Figg WD. 2-Methoxyestradiol, a promising cancer reagent. *Pharmacotherapy.* 2003;23:165–172. [PubMed] [Google Scholar]
21. Lando D, Peet DJ, Whelan DA, Gorman JJ, Whitelaw ML. Asparagine hydroxylation of the HIF transactivation domain a hypoxic switch. *Science.* 2002;295:858–861. [PubMed] [Google Scholar]

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-32, March 2024
ISSN: 2749-3644

22. Mole DR, Maxwell PH, Pugh CW, Ratcliffe PJ. Regulation of HIF by the von Hippel-Lindau tumour suppressor: implications for cellular oxygen sensing. *IUBMB Life.* 2001;52:43–47. [PubMed] [Google Scholar]
23. Natarajan R, Salloum FN, Fisher BJ, Kukreja RC, Fowler AA. Hypoxia inducible factor-1 activation by prolyl 4-hydroxylase-2 gene silencing attenuates myocardial ischemia reperfusion injury. *Circ Res.* 2006;98:133–140. [PubMed] [Google Scholar]
24. Oda T, Hirota K, Nishi K, et al. Activation of hypoxia-inducible factor 1 during macrophage differentiation. *Physiol Cell Physiol.* 2006;291:C104–C113. [PubMed] [Google Scholar]
25. Page EL, Robitaille GA, Pouyssegur J, Richard DE. Induction of hypoxia-inducible factor-1alpha by transcriptional and translational mechanisms. *J Biol Chem.* 2002;277:48403–48409. [PubMed] [Google Scholar]
26. Pajusola K, Kunnapuu J, Vuorikoski S, et al. Stabilized HIF-1α is superior to VEGF for angiogenesis in skeletal muscle via adeno-associated virus gene transfer. *FASEB J.* 2005;19:1365–1367. [PubMed] [Google Scholar]
27. Papandreou I, Cairns RA, Fontana L, Lim AL, Denko NC. HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption. *Cell Metab.* 2006;3:150–151. [PubMed] [Google Scholar]
28. Rebar EJ. Development of pro-angiogenic engineered transcription factors for the treatment of cardiovascular disease. *Expert Opin Investig Drugs.* 2004;13:829–839. [PubMed] [Google Scholar]
29. Richard DE, Berra E, Pouyssegur J. Nonhypoxic pathway mediates the induction of hypoxia-inducible factor 1α in vascular smooth muscle cells. *J Biol Chem.* 2000;275:26765–26771. [PubMed] [Google Scholar]
30. Semenza GL. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. *J Appl Physiol.* 2000;88:1474–1480. [PubMed] [Google Scholar]
31. Shi YH, Fang WG. Hypoxia-inducible factor-1 in tumour angiogenesis. *World J Gastroenterol.* 2004;10:1082–1087. [PMC free article] [PubMed] [Google Scholar]
32. Trentin D, Hall H, Wechsler S, Hubbell JA. Peptide-matrix-mediated gene transfer of an oxygen-insensitive hypoxia-inducible factor-1 alpha variant for local induction of angiogenesis. *Proc Natl Acad Sci USA.* 2006;103:2506–2511. [PMC free article] [PubMed] [Google Scholar]
33. Vaupel P. The Role of Hypoxia-Induced Factors in Tumor Progression. *Oncologist.* 2004;9:10–17. [PubMed] [Google Scholar]
34. Vincent KA, Shyu KG, Luo Y, et al. Angiogenesis is induced in a rabbit model of hindlimb ischemia by naked DNA encoding an HIF-1α/VP16 Hybrid Transcription Factor. *Circulation.* 2000;102:2255–2261. [PubMed] [Google Scholar]
35. Wang GL, Jiang B, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. *Proc Natl Acad Sci USA.* 1995;92:5510–5514. [PMC free article] [PubMed] [Google Scholar]
36. Yang J, Zhang L, Erbel PJ, Gardner KH, Ding K, Garcia JA, Bruick RK. Functions of the Per/ARNT/Sim domains of the hypoxia-inducible factor. *J Biol Chem.* 2005;280:36047–36054. [PubMed] [Google Scholar]
37. Zagzag D, Zhong H, Scalzitti JM, Laughner E, Simons JW, Semenza GL. Expression of hypoxia-inducible factor 1α in brain tumors: association with angiogenesis, invasion, and progression. *Cancer.* 2000;88:2606–2618. [PubMed] [Google Scholar]
38. Zhang H, Gao P, Fukuda R, et al. HIF-1 inhibits mitochondrial biogenesis and cellular respiration in VHL-deficient renal cell carcinoma by repression of C-MYC activity. *Cancer Cell.* 2007;11:407–420. [PubMed] [Google Scholar]