

Drug-induced liver injury with cholestasis in the neurologist and psychiatric practice

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Among drug-induced liver injuries (DILI), the cholestatic type is second in frequency (from 20 to 40%), the most common is the hepatocellular variant (up to 78%). For this reason, practitioners of various specialties, including neurologists and psychiatrists, do not monitor cholestasis parameters, and drug-induced liver injury with cholestasis (DILIC) remains unrecognized. The urgency of this problem is great, because the frequency of deaths in DILIC is only slightly lower than in the hepatocellular type; in addition, it DILIC is much more likely to become persistent increasing the risk of chronic liver injury.

Among the drugs used in neurology and psychiatry, the "leaders" in terms of the number of DILIC are antidepressants, both tricyclic (amitriptyline, imipramine) and selective serotonin reuptake inhibitors (SSRIs: paroxetine, sertraline, fluoxetine, citalopram, escitalopram), antidepressants, antipsychotics (chlorpromazine, fluphenazine), anticonvulsants (mainly carbamazepine).

If the patient has a history of DILI caused by any of the forementioned medications, the agent should be switched to another drug from the same group with a minimal risk of DILI. If there is a history of DILI associated with antidepressants, it is recommended to choose SSRIs. It is necessary to monitor not only the activity of transaminases and bilirubin, but also the cholestasis parameters (alkaline phosphatase, γ -glutamyl transpeptidase) during treatment.

Keywords: drug-induced liver disease; drug-induced liver damage with cholestasis; antidepressants; antipsychotics; anticonvulsants.

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One of the most frequent adverse drug reactions (ADRs) is drug-induced liver injury (DILI), which accounts for almost 10% of all side effects of drugs [1, 2]. DILIs can be divided into the following types [3]: hepatocellular, cholestatic, and mixed. The cholestatic variant is characterized by an increase in the level of alkaline phosphatase (ALP) exceeding the upper limit of the norm (ULN) by two times or more or by the ratio of alanine aminotransferase (ALT) / alkaline phosphatase (ALP) ≤ 2 [3]. The same drug can cause different DILIs [4–6]. The cholestatic type ranks second in frequency of occurrence (20–40% of all DILIs), the hepatocellular type is the most common (40–78%) [7, 8]. That's probably the reason why doctors of various specialties, including neurologists and psychiatrists, monitor the levels of hepatic transaminases (ALT, aspartate aminotransferase – AST) to a greater extent, ignoring the indicators of cholestasis (ALP, gamma-glutamyltransferase – GGT); thus, drug-induced cholestatic liver injury (DILCI) often remains unrecognized. This problem is very relevant since the frequency of deaths caused by DILCI is only slightly lower than in the hepatocellular type of DILI; moreover, the risk of developing chronic liver injury because of DILCI is higher [3, 4].

Symptoms of cholestasis include skin itching, jaundice (however, jaundice-free forms are also possible), constipation, bitterness in the mouth, pain in the right hypochondrium, dark urine color, and fecal discoloration. Hypersensitivity symptoms (immunological features) may be present: fever, rash, eosinophilia. Cholestasis evaluation includes determining increased bilirubin, ALP, GGT, total cholesterol, bile acids in the blood serum [1–3].

In neurological practice, the use of many classes of drugs, such as antidepressants, antipsychotics, and antiepileptic drugs, is associated with the development of DILCI. Possible mechanisms of DILCI associated with these drugs, as well as the degree of probability of the relationship "Drug – DILI" are summarized in the table [5–11].

Antidepressants

Among tricyclic antidepressants (TCA), amitriptyline and imipramine are associated with the development of DILCI (see Table) [10–13]. Both drugs are associated with an asymptomatic increase in the liver enzymes (up to 20% of cases); however, in rare cases, they can cause acute liver injury with clinical symptoms [6, 13]. The onset of symptoms during imipramine treatment usually occurs from the 1st to the 8th week after the start of therapy, while during the treatment with amitriptyline, this period is highly variable – from 1 to 14 months after the start of treatment [6]. Hypersensitivity symptoms are common but usually mild and transient. Acute liver damage caused by these TCA, as a rule, is curable, but progressive and even fatal cases of acute cholestatic hepatitis and long-lasting DILCI with jaundice, resembling the so-called vanishing bile ducts syndrome, have been reported [13–15]. Usually, repeated administration of amitriptyline or imipramine quickly leads to relapse of acute liver injury, which can be fatal; therefore, repeated administration is not recommended. Also, there may be cross-reactivity with other TCAs, but not in all cases [6]. Therefore, if there is a history of DILI associated with any TCA, it is better to choose an antidepressant from another class, preferably SSRIs, with a minimal

risk of DILI. However, if there is still a need for TCA administration, one should choose a drug with a low risk of DILI, start therapy with minimal doses, and strictly monitor clinical symptoms and laboratory parameters of liver function [2, 5, 9].

SSRIs. In this group, the development of DILI is associated with *paroxetine, sertraline, fluoxetine, citalopram, escitalopram* [6, 7, 9]. Deviations in laboratory parameters characterizing liver function occur in less than 1% of patients receiving the listed drugs from the SSRIs group, are usually insignificant and rarely require a dose reduction or drug discontinuation. However, some rare cases of acute liver injury with clinical symptoms (icteric and anicteric types), usually mild or moderate, have been described; due to the treatment with paroxetine and sertraline, severe cases with the development of liver failure were also registered [6, 16]. Symptoms of hypersensitivity are rare. The clinical and laboratory manifestations of DILI usually occur 2–10 weeks after the start of therapy with citalopram, 2–12 weeks after fluoxetine, 2–16 weeks after paroxetine; the most variable time of onset of DILI symptoms is associated with sertraline intake – from 2 to 24 weeks. In patients treated with paroxetine, the development of chronic DILI has been described. In the case of DILI with clinical manifestations, immediate withdrawal of the inducer drug is necessary. The clinical symptoms and laboratory signs usually disappear within a few days. In the case of re-prescribing antidepressants, it is essential to consider that people with intolerance to one drug from the SSRI group may have similar reactions to other SSRIs [2, 6, 16]. Nevertheless, in the case of DILI development due to SSRIs, the best tactic is to prescribe another drug from this group with a lower risk of DILI, taking certain precautions: starting therapy with a minimum dose, slow titration, and careful monitoring of clinical and laboratory symptoms. Replacement with antidepressants of other classes is not recommended since the risk of developing DILI is the lowest with the SSRIs class.

MAO inhibitors.

Among the antidepressants of this group, individual clinical cases of DILI have been described due to the treatment with *phenelzine* and *tranylcypromine*. However, they usually cause a hepatocellular variant of DILI [6, 17]. In the case of DILI associated with any drug from this group, replacement with SSRIs or TCA is recommended since cross-adverse reactions (ARs) with the development of DILI with other MAO inhibitors have been noted [6].

Other antidepressants include trazodone and bupropion [16, 18]. At least more than 10 cases of acute clinically apparent episodes of liver injury with a

pronounced increase in liver enzyme levels with or without jaundice have been reported in patients treated with trazodone; such descriptions are rare in patients treated with bupropion [6]. In the case of DILI due to trazodone, the time of onset of clinical symptoms varies greatly – from several days to 6 months; in the case of bupropion therapy, it ranges from 1 to 3 months. In several cases, there were minimal immunoallergic manifestations. However, there are reports of single cases of fatal acute liver failure and chronic hepatitis during treatment with both drugs [16, 19].

Antipsychotics

The most well-known drug in neurological practice that causes DILI is *chlorpromazine*. Usually, jaundice develops 1–5 weeks after the start of chlorpromazine therapy, which can last very long (up to 7% of cases of cholestasis), and in this case, it is associated with vanishing bile ducts syndrome [6, 20]. In isolated cases, allergic manifestations, such as fever, develop; they are characterized by a mild course and resolve on their own [6]. In the case of an asymptomatic increase in liver enzyme levels asso-

Table. Drugs, associated with DILI [5–11]

| Drug | Comment | Possible mechanism of hepatotoxicity | Level of evidence |
|-------------------------------|---|--|-------------------|
| Antidepressants | | | |
| Tricyclic antidepressants | | | |
| Amitriptyline | Cases of DILI with clinical manifestations are rare. Types of DILI differ. There are descriptions of cases of acute cholestatic hepatitis with the development of vanishing bile ducts syndrome | Toxic effects of metabolites | B |
| Imipramine | Individual clinical cases are described. Type of DILI differ. | Hypersensitivity to the products of its metabolism in the liver | B |
| MAO inhibitors | | | |
| Phenelzine | A typical variant of DILI is hepatocellular, but individual clinical cases of DICLI are described | Direct toxic effects of metabolites or hypersensitivity reaction | C |
| Tranylcypromine | | Direct toxic effects of metabolites | D |
| SSRIs | | | |
| Citalopram, escitalopram | Individual clinical cases are described. Types of DILI differ. | Toxic effects of metabolites | C |
| Fluoxetine | | | C |
| Paroxetine | | | B |
| Sertraline | | | B |
| Other antidepressants | | | |
| Trazodon | Individual clinical cases are described. Usually the type of DILI is hepatocellular, but cases of mixed and cholestatic DILI have been described | Toxic effects of metabolites | B |
| Bupropion | Individual clinical cases are described. Types of DILI differ. | « « | C |
| Antipsychotics (neuroleptics) | | | |
| Haloperidol | Usually cholestatic or mixed type of DILI | « « | B |
| Chlorpromazine | The most well-known drug associated with DILI. The type of DILI is cholestatic or mixed. The development of vanishing bile ducts syndrome is described | Hypersensitivity reaction | A |
| Prochlorperazine | Individual clinical cases are described | Unknown, it is assumed that it is the same as in other drugs of this class | Not classified |

| | | | |
|---|--|---|----------------|
| Fluphenazine | The type of DILI is cholestatic or mixed. Cases with a prolonged course and the development of vanishing bile ducts syndrome are described | Hypersensitivity reaction | C |
| Thioridazine | Individual clinical cases are described. The type of DILI is usually cholestatic, but also can be mixed and hepatocellular | Toxic effects of metabolites | Not classified |
| Trifluoperazine | Individual clinical cases are described. The type of DILI is usually cholestatic, but also can be mixed | Hypersensitivity reaction | Not classified |
| Asenapine | A single clinical case of DICLI is described | Unknown | D |
| Clozapine | The type of DILI is usually hepatocellular or mixed, but also can be cholestatic | « « | B |
| Olanzapine | Types of DILI differ | Toxic effects of metabolites | Not classified |
| Risperidone | The type of DILI is usually cholestatic, but other types are also possible | Unknown | C |
| Antiepileptics | | | |
| Carbamazepine | The type of DILI is usually cholestatic or mixed. Lethal cases are described. The type of DILI is usually mixed, but also can be cholestatic and hepatocellular | Hypersensitivity reaction and/or immunological reaction to the complex "drug – protein", which is generated during metabolism (metabolites act as a hapten) | A |
| Oxcarbazepine | | | D |
| Phenobarbital | | | A |
| Gabapentin | Individual clinical cases are described; very rare - increased levels of hepatic enzymes as in the cholestatic type | Unknown | C |
| Phenytoin | More than 100 clinical cases have been described; frequency ranges from 1 in 1000 to 1 in 10,000, depending on race and ethnicity. Mixed type of DILI is the most common, cholestatic type can occur in rare cases | Hypersensitivity reaction | A |
| Pregabalin | Individual clinical cases are described. Types of DILI differ, including the cholestatic type | Idiosyncratic: immune-mediated reactions involving various enzymes | C |
| Zonisamide | Several clinical cases have been described, including one case of the development of vanishing bile ducts syndrome | Hypersensitivity reaction | D |
| Benzodiazepines Chlordiazepoxide Clonazepam Diazepam Flurazepam Triazolam Clonazepam Alprazolam | Several clinical cases have been described. The type of DILI is usually mixed or cholestatic, but also can be hepatocellular | Probably, the reaction to the intermediate products of the metabolism of drugs of this group | D |

Note. MAO – monoamine oxidase; SSRIs – selective inhibitors of serotonin reuptake. Levels of evidence [6]: A – a well-established (proven and documented) cause of liver injury with clinical manifestations; B – a very probable cause of liver injury with clinical manifestations; C – probable cause of liver injury with clinical manifestations; D – possible cause of liver injury with clinical manifestations; E – an unlikely cause of liver injury with clinical manifestations; E* – an unproven but suspected cause of liver injury with clinical manifestations.

ciated with chlorpromazine administration, there is usually no need to adjust the dose of the drug or discontinue it. Acute cholestatic hepatitis associated with chlorpromazine is typically benign and usually resolves independently, but in this case the

drug should be discontinued. Many patients with chronic cholestasis eventually recover, but they often have a persistent increase in liver enzymes and may develop biliary cirrhosis. Fatal cases of chlorpromazine-induced DILI are described [20]. Restarting this drug, as a rule, quickly leads to a relapse of acute liver injury, so it should be avoided [6]. Patients with DILI caused by chlorpromazine may have cross-sensitivity to other phenothiazines, but they respond well to other neuroleptics [6].

In 40% of patients who receive fluphenazine therapy for a long time, there is an increase in liver enzymes; however, this increase is usually asymptomatic, rarely exceeds ULN by 3 times, and even with continued fluphenazine therapy these indicators return to normal values by themselves [6]. Several cases of acute liver injury due to fluphenazine intake are described. The onset of clinical and laboratory manifestations of DILI due to phenothiazine intake usually occurs 1–4 weeks after the treatment start [6, 20]. Immunoallergic symptoms are rare and resolve on their own. The most significant fact is that jaundice caused by phenothiazine is usually prolonged and resembles vanishing bile duct syndrome [6].

Treatment with *prochlorperazine*, *trifluoperazine*, and *thioridazine* may result in a slight increase in laboratory parameters characterizing liver function, which does not require any dose adjustment or drug discontinuation. Jaundice develops 1–4 weeks after the treatment onset; however, there are cases when jaundice occurs a few months after the start of thioridazine administration [6]. Acute liver injury caused by these drugs usually ends in recovery; however, very prolonged and progressive jaundice has been reported, resembling vanishing bile duct syndrome; in such situations, liver transplantation may be required [6].

Haloperidol treatment usually causes an asymptomatic increase in liver enzymes, which occurs in 20% of cases, but does not require discontinuation of the drug or correction of its dose [6, 21]. The onset of symptoms usually occurs 2–6 weeks after the start of therapy [6]. Signs or symptoms of hypersensitivity are rare, mild, and transient [22, 23].

However, isolated cases of acute liver failure and at least one case of chronic cholestasis resembling vanishing bile duct syndrome have been reported [24, 25].

Clozapine, an antipsychotic of the second generation, is associated with DICLI. After this drug administration, approxi-

mately 2/3 of patients have an asymptomatic increase in liver enzyme levels, which does not require dose adjustment or drug withdrawal after 6–12 weeks. However, cases have been described where increased enzyme levels were accompanied by weakness, nausea, and discomfort in the epigastric region [6, 26]. In this case, it is recommended to stop the therapy with clozapine or start a sequential reduction of the drug dose. Acute liver injury, accompanied by a significant increase in liver enzymes and jaundice, occurs in about 1 out of 2000 cases, usually in the interval from several days to several weeks after the start of therapy with clozapine [26]. In addition, symptoms of hypersensitivity may develop, but they are usually mild [6, 27]. Acute liver injury caused by clozapine usually ends in recovery; however, there is evidence of progressive cases of acute cholestatic hepatitis, which required liver transplantation [6, 28].

Changes in laboratory parameters of liver function usually occur in 30% of patients during the first 8 weeks after the start of risperidone therapy; an increase in ALT levels is typically moderate, transient, and may disappear even with continued use of the drug. Several causes of acute liver injury with jaundice, occurring several months or even years after the start of risperidone treatment, have also been reported. Immunoallergic manifestations are rare, mild, and transient [6]. Cases of acute liver failure or vanishing bile duct syndrome due to treatment with risperidone have not been described. Since cross-reactivity with quetiapine may occur, if there is a history of DILI on any of these drugs, it is better to choose an antipsychotic from another class in the future. However, this does not occur in all cases.

Isolated cases of increased levels of liver enzymes in patients treated with *asenapine* and *olanzapine* are described.

Antiepileptics

Among antiepileptics, *carbamazepine* is mainly associated with the development of DILI. Numerous studies show that a significant proportion of patients taking carbamazepine have a temporary increase in serum aminotransferase levels (from 1% to 22%). This increase is benign and usually resolves even if the drug is continued at the same dose. In addition, most patients receiving carbamazepine can develop a mild to moderate increase in GGT levels [6]. Clinically pronounced hepatotoxicity of carbamazepine is relatively rare; however, a total of several hundred such cases have been described in the literature [6]. Carbamazepine hepatotoxicity most often occurs because of the development of hypersensitivity syndrome to anticonvulsants: 1–8 weeks after the treatment onset, fever appears, followed by rash, facial swelling, lymphadenopathy, increased levels of eosinophils (the so-called DRESS syndrome – Drug Rash with Eosinophilia and Systemic Symptoms). The most common form of the systemic lesion in the DRESS syndrome is liver damage, the severity of which varies from mild (temporary increase in levels of liver enzymes in blood serum) to severe (acute hepatitis-like syndrome), fatal cases have been described [29, 30]. When examining liver biopsies, cholestatic lesion with focal hepatocellular necrosis is detected, and in fatal cases, submassive or massive necrosis [6]. Other systemic manifestations of DRESS syndrome associated with carbamazepine intake include myositis, nephritis, and pneumonitis. In terms of carbamazepine hepatotoxicity, several cases of vanishing bile ducts syndrome have been described, in which patients developed severe cholestatic hepatitis with other immunoallergic manifestations, while cholestasis with itching, jaundice, and a noticeable increase in the level of ALP persisting for a long time [6].

In most cases, carbamazepine hepatotoxicity is reversible after the drug discontinuation; improvement occurs quickly, within 5–7 days [6]. However, in severe acute liver injury, progression to acute liver failure and death may occur [6, 30]. Repeated intake of carbamazepine leads to a rapid and more severe relapse of the disease, so it should be avoided. Possible cross-reaction with other anticonvulsants (phenytoin, phenobarbital, primidone, oxcarbazepine, and lamotrigine) can occur; therefore, it is not recommended to prescribe these anticonvulsants to patients with hepatotoxic ARs due to carbamazepine treatment, it is worth considering initiating therapy with drugs such as benzodiazepines, valproate, levetiracetam, gabapentin or pregabalin [6].

The development of DILI is also associated with *oxcarbazepine* and *phenobarbital*. Data from prospective studies show that an increase in aminotransferase levels in blood plasma occurs in less than 1% of patients taking these drugs [6]. This increase is rarely clinically significant and usually does not require dose adjustment or drug withdrawal. Liver damage is generally mild, but in patients receiving oxcarbazepine, a sudden onset of hepatitis-like syndrome is possible, which can be severe and even fatal [31]. Symptoms of hypersensitivity are rare, transient, and well-tolerated [6]. A cross-reaction with carbamazepine, phenytoin, and lamotrigine is possible; therefore, in this clinical situation, it is recommended to give preference to other drugs (benzodiazepines, valproate, levetiracetam, gabapentin, or pregabalin).

More than 100 descriptions of cases of liver injury associated with *phenytoin* have been published [6]. The estimated incidence of DILI ranges from 1 in 1000 to 1 in 10,000 and, apparently, depends on the race and ethnicity of patients [6]. The onset of the disease typically occurs 2–8 weeks after the start of phenytoin therapy with the development of fever, rash, facial edema, and lymphadenopathy, followed by jaundice and urine darkening a few days later. Clinical symptoms and signs may mimic acute mononucleosis or even lymphoma (pseudolymphoma syndrome). Almost all cases of phenytoin hepatotoxicity occur in the context of anticonvulsant hypersensitivity syndrome or DRESS syndrome. Other manifestations may include Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anemia, thrombocytopenia, neutropenia, nephritis, and pneumonitis [6]. Acute hepatitis with jaundice associated with phenytoin is a severe AR since the mortality rate exceeds 10% [6]. In this regard, if jaundice or other clinical symptoms develop in a patient receiving phenytoin treatment, the drug should be stopped immediately. In patients with severe hepatotoxic ARs for phenytoin, glucocorticoid therapy is often used, and, according to reports, the response to such treatment is rapid, and its effectiveness is high. Chronic liver injury due to phenytoin hepatotoxicity is rare; however, there are several reports of long-existing jaundice resembling vanishing bile duct syndrome [6]. Repeated administration of phenytoin causes a rapid and usually more severe relapse of DILI, which can lead to a fatal outcome, and should be avoided. There may also be a cross-sensitivity with other anticonvulsants (phenobarbital, carbamazepine, lamotrigine, and ethosuximide), although not in 100% of cases. Nevertheless, it seems reasonable to avoid the administration of these anticonvulsants and switch to such drugs as valproate, gabapentin, levetiracetam, topiramate, or benzodiazepines [6].

DILI is a relatively rare AR of *gabapentin*. Although there are several reports of liver injury due to gabapentin therapy, the

causal relationship was not always apparent [6, 18, 32]. Very modest data are available on the hepatotoxicity of *pregabalin*. Most cases of DILI were mild and were not accompanied by jaundice. Symptoms of liver injury manifested within 3–14 days after the start of pregabalin therapy [6, 33]. There were no symptoms of hypersensitivity. Isolated cases of severe jaundice due to pregabalin are described, but after the drug withdrawal, all symptoms completely resolved [6]. There are also minimal data on the hepatotoxicity of *zonisamide*. Since this drug is usually used with other anticonvulsants, its role in DILI is challenging to assess. DILI due to zonisamide usually occurs 3–8 weeks after the treatment initiation [6]. A single case of cholestatic hepatitis associated with the development of vanishing bile duct syndrome is described, which eventually resolved [34].

Benzodiazepines

Among the benzodiazepines, DILI is a relatively rare phenomenon; the severity is usually mild to moderate. There can be a slight increase in liver enzyme levels, usually asymptomatic, which does not require reducing the drug dose or its discontinuation [6]. Signs or symptoms of hypersensitivity are not described. There was no cross-reactions with other benzodiazepines.

DICLI prevention

Although there are no specific means to prevent DICLI caused by the above-listed drugs, the following measures can be recommended:

- avoid prescribing drugs with a high risk of DICLI, especially if there is a history of a similar AR, as well as prescribing two or more drugs, associated with DILI, if possible, optimize the number of drugs administered to the patient;
- pay special attention to possible interactions between drugs that increase the risk of DICLI;
- monitor the level of biochemical markers of liver function in blood serum (ALT, AST, GGT, ALP, bilirubin).

Conclusion

Thus, DICLI caused by antidepressants, antipsychotics, antiepileptics is a frequent complication of pharmacotherapy in the neurological practice, which can occur in patients prescribed with any drug of these classes (especially often – amitriptyline, chlorpromazine, carbamazepine). Therefore, timely detection of this type of DILI, discontinuation of the inducer drug, and compliance with preventive measures will contribute to improving patients' condition and quality of life.

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