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Review Article

Drug-Induced Liver Diseases in Children and Adolescents

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Abstract: Many drugs (now it's known more than 1200) are associated with hepatic side effects. Children (especially newborns and infants) are unique population with specific characteristics of absorption, metabolism and elimination of drugs that can predispose to hepatotoxicity. Aim of this review is to estimate risk factors of hepatotoxicity related to the patients' peculiarities and drug itself, also to describe some mechanisms and types of drug-induced liver disease (DILD) and beside this to offer some methods of the treatment and prevention of hepatotoxicity. In children the most often mentioned drugs caused DILD are antibiotics, psychotropics and NSAIDs and the main type of DILD is acute hepatitis with mortality of 10%. To conclude it's highly important to monitor activity of hepatic enzymes (ALT, AST, AP) during treatment by potentially hepatotoxic drugs in patients from risk groups (early age, any liver disease, diabetes mellitus, obesity, poor nutritional status) in order to timely withdraw offending drug and prescribe hepatoprotectors or even perform liver transplantation.

Keywords: Drug and Liver Disease, Risk Factors of Hepatotoxicity, Mechanisms and Types of DILD, Hepatoprotectors, Prevention of DILD

1. Introduction

Definition. Drug-induced liver diseases (DILD) – heterogeneous group of clinical and morphological liver changes caused by pharmacological treatment.

Actuality of this problem: Frequency of the drug-induced liver diseases is up to 25% of all adverse reactions related to pharmacological treatment and is on the third place following viral and alcohol related liver diseases. Prevalence of DILD is between 1,27 and 40,6 cases in 100 000 patients per year. Besides the quantity of DILD increased in 30 times during last 10-15 years perhaps due to introduction in clinical use of new drugs and increased aggressiveness of pharmacological treatment. Not rarely liver toxicity is the main cause for marketing license withdrawal as it was a case for 17 non-steroidal anti-inflammatory drugs (NSAID). Among hospitalized patients the frequency of DILD is 0,7-1,4% but among patients admitted with jaundice – it's nearly 5% [1].

Now it's known more than 1200 drugs of almost all pharmacological classes that could cause DILD at the same time the frequency of liver injury for each drug is changed from 1:1000 till 1:100 000. In children the most often mentioned drugs caused DILD are antibiotics (AB) contributing to nearly 50% of all cases of liver toxicity [2]. The most hepatotoxic AB are considered ampicillin and ceftriaxone, azithromycin and clarithromycin, tetracycline, co-trimoxazol, ciprofloxacin. Comparing the liver toxicity of AB of different groups the lowest risk of DILD belongs to penicillins and the highest – to fluoroquinolones. The second place in frequency of DILD in children belongs to psychotropics (40% of all DILD) – anticonvulsants, antidepressants, agents for treatment of hyperactive child syndrome with attention deficiency [3-5]. In accordance with data [6-8] NSAIDs are also part of the leader group of drugs caused DILD but it's necessary to notify that ibuprofen together with paracetamol are the main antipyretic drugs in children.

The frequency of hospitalizations caused by different signs of drug-induced hepatotoxicity are 1,9-6,2% and even 20% in some centers, and the frequency of fatal outcome in DILD achieve 7,4-11,9% [9-12]. The frequency of acute liver failure (ALF) could achieve 20% and fatal outcome - 31% in children

and adolescents while drug-induced hepatotoxicity is rather lower than in this population (nearly 1% of all adverse drug reactions) in accordance with [3]. Today DILD are the main reason for ALF requiring liver transplantation [6, 13].

Nevertheless the real number of patients with DILD are not specified due to different reasons: 1) wide over-the-counter availability; 2) seasonal fluctuation of drugs intake – more intensive use of antipyretic drugs and antibiotics (AB) in autumn and winter; 3) absence of evident clinical signs of DILD in some cases; 4) underreporting ("even though know but keep silent"); 5) absence of similar reports in literature; 6) present liver injury does not correlate with chemical and pharmacological characteristics of the drug; 7) unidentified cases of DILD or wrong interpretation of causality of liver injury mainly due to underestimation of possibility of drug-induced pathology in general.

2. Risk Factors of DILD

Probability of hepatotoxicity depends on the different associated factors that could be divided in two groups:

i) Causing by patient's characteristics (genetic predisposition – basic enzyme liver activity providing metabolism, detoxification and drug transport, nutritional status, age, gender, background liver and renal diseases, multiple morbid status and its related polypharmacy), smoking status, alcohol and drug abuse;

ii) Causing by the drug itself (chemical characteristics of the drug, duration of use, dosage, combination of two or more drugs with hepatotoxic effect).

2.1. Risk Factors of Hepatotoxicity Related to the Patient's Characteristics

2.1.1. Risk of Development of Drug-Induced Hepatitis

Risk of development of drug-induced hepatitis in case of use of tuberculostatic agents significantly determined by the genetic polymorphism of isoenzyme CYP2E1 and in particular its homozygous state (CYP2E1c1/c1) resulting in increasing this enzyme activity and high hepatotoxic risk [38].

Slowing acetylation causing by N-acetyl transferase 2 deficit contributes to hepatitis development in case of treatment by sulfonamides, hydralazine.

Toxic hepatitis caused by valproates is developed due to disturbances of valproic acid beta oxidation (genetically determined mitochondrial deficit in hepatocytes) and toxic metabolites formation. It's developed mainly in children under 2-3 years old that could be explained by factors including insufficient level of glucuronidation typical for this age group and as a result decreased effective valproates elimination [14, 15]. Valproate hepatitis develops in several weeks or months after start of treatment having a frequency as 1:10 000 but in combination with other anticonvulsants (especially with phenobarbital and phenytoin) – in 1,5 times frequently. In addition it's necessary to emphasize that children of early age are more prone than adults to disturbances of mitochondrial functioning at the time of drug use caused including the restricted capacities for synthesis of carnitine and also its loss in case of renal diseases [16].

Genetically determined deficit of glutathione synthetase increases the risk of hepatotoxic effect of drugs including paracetamol. Increasing of paracetamol hepatotoxicity is also observed in patient with obesity and protein diet deficiency (e.g. in strict vegetarians). In such a case it's revealed the increased activity of isoenzyme CYP2E1 and raised formation of toxic metabolite of paracetamol – N-acetyl-p-benzokinonimone (NAPQJ) simultaneously with its disturbed inactivation. Disturbed inactivation of NAPQJ could also be observed in children with obesity or poor nutritional status due to reduced glutathione exhaustion (less than 70% of normal range) [12]. Moreover the activity of 3A4 (main enzyme of mono-oxygenase system) decreases in obesity [17]. Toxic effect of paracetamol in neonates and children of early age could be enhanced by lower glucuronidation of this drug comparing to adolescents and also reduction of its pre-systemic metabolism in 50% and clearance in case of liver cirrhosis [18].

2.1.2. Age-Dependent Characteristics of Liver Metabolic Activity

The essential role in development of DILD in children belongs to age-dependent maturation of cytochrome P450 system (initially its activity corresponds to 50% of adults level) and in particular its isoenzyme 3A4 that participates in metabolism of 50% of all drugs [4] including those that have evident hepatototoxic effect - erythromycin, co-trimoxazol. In addition the activity of 3A4 being insufficient in children decreases in condition of acid-base balance disturbance and hypoxia and also in case of use of inhibitors of this enzyme – clarithromycin, fliconazole or omeprazole [18].

The liver metabolic activity is decreased in neonates especially in prematurely born also due to other enzymes. It relates to different types of esterase enzymes (acetylcholinesterase, pseudocholinesterase, arylesterase) as its maturation achieves adult level up to 12 months of life. It's mentioned also the decreasing hydroxylation of phenytoin and phenobarbital [19]. Insufficient age-dependent liver metabolic acitivity in case of long-term drug use could be accompanied by its accumulation with corresponding consequences.

Besides some other age-dependent clinicopharmacological specificities in children could contribute to development of drugs hepatotoxic effect. In infants mainly in neonates and especially in prematurely born the protein binding capacity of some drugs is decreased for example for phenobarbital and phenytoin with corresponding increasing of their uncombined fractions. On one side this is explained by decreased total protein level in plasma (including albumin) and on the other side increased fetal albumin level that has low capacity to bind weak acids (NSAID, anticonvulsants) and presence of endogenous ligands (uncombined fatty acids and bilirubin) that compete with drugs for proteins binding [15].

2.1.3. Gender Role

Gender role in development of DILD is different from one study data to others: in one study [4] such dependency was low due to a little bit bigger number of boys (58%), but in the

other study [5] – girls were significantly predominant (70%).

2.1.4. Treatment Anamnesis

Risk of development of DILD is higher in patients having in the past adverse drug reactions for this drug or its analogue. Moreover possibility of DILD development depends on allergic predisposition of the child.

2.1.5. Background Liver Diseases

Presence of any acute or chronic liver disease increases the possibility of DILD development for example re-activation of hepatitis B during treatment by methotrexate or infliximab. However not rarely the addition of drug-induced injury is unrecognized as it's considered as exacerbation of primary disease. Among other diseases with increased risk of DILD the most important are rheumatoid arthritis, HIV infection, inflammatory intestinal diseases, celiac disease, diabetes mellitus and renal diseases. The latter is significant for drugs eliminating by kidneys with its possible accumulation and hepatotoxic effect group of penicillins [20].

2.1.6. Adolescents

Smoking (socially acceptable phenomenon) is independent risk factor of death caused by liver insufficiency at the background of paracetamol use. But socially rejected narcotics like cocaine and ecstasy could contribute to the development of fulminant liver insufficiency [21].

2.2. Risk Factors of Hepatotoxicity Resulting from the Drug Itself

1) The highest hepatotoxic potential is proper to the drugs that metabolized intensively (>60%) in liver i.e. those substances with high hepatic clearance: NSAID, anticonvulsants, oral contraceptive drugs, paracetamol, anabolic steroids, rifampicin.

2) Pharmacokinetic drug-drug Interaction in case of compulsory polypharmacy caused by multiple morbid status of the patient, for example enhanced hepatotoxicity of paracetamol in patients taking barbiturates, and also in oncology patients at the background of polychemotherapy exhausting glutathione stores.

3) Or summation of toxicity in case of poly-therapy of anticonvulsants for resistant form of epilepsy (West syndrome, Lennox-Gastaut syndrome) in children of early age [14]. It was revealed the phenomenon of cross-sensitivity of drugs within one pharmacological class: if any drug of the concerned pharmacological class has already demonstrated hepatotoxic effect it could be highly probable affirmed that the other drug of the same class would have liver damage effect up to acute liver insufficiency.

3. Mechanisms of DILD

It could be classified the following mechanisms of DILD development: toxic, immunoallergic and idiosyncrative [12, 22].

3.1. Toxic Liver Damage

Toxic liver damage – direct injury of cell structures by the drug itself or its metabolites (metabolic type). As a rule it's dose-dependent event (and therefore predictable) and it is caused by liver overload in detoxification of xenobiotics. In this case it matters both the value of one dose (for paracetamol >20 g) and the cumulative dose (for methotrexate >1500 mg). It is supposed that hepatotoxicity of antimycotics (in particular ketoconazole and itraconazole as the most toxic) in case of exceeding dose is caused by disturbances of sterol synthesis in membranes of hepatic cells and (or) degradation of hepatic enzymes – catalase and peroxidase - that is accompanied in children by decrease activity of CYP3A4 that is responsible for metabolism of such drugs. The development of hepatotoxic effect of NSAID is mainly resulting from mitochondrial injuries and depression of cyclooxygenase of 1 and 2 types by reactive metabolites [6].

The following two mechanisms are not dose-dependent and therefore are less predictable.

3.2. Idiosyncrative Reaction

Idiosyncrative reaction (pharmacogenetic mechanism) is resulting from absence or decreased activity of hepatic enzymes participating in reactions of I and II types of drug biotransformation (oxidation and conjugation). Generated toxic metabolites of valproic acid (VPA) and paracetamol act with hepatotoxic effect while not being inactivated. For VPA it is determined by disturbed or limited beta-oxidation in mitochondrions presented in children of early age, but for paracetamol – due to glutathione deficit.

3.3. Immunomediated Reactions

Immunomediated reactions with liver involvement are developed in case of recurrent drug introduction after 1-5 weeks of interruption. In such a case there are also extrahepatic signs like fever, rash, eosinophilia. Such reactions could be caused particularly by sulfonamides, nitrofurans, acetylsalicylic acid, phenythoin, cordarone, NSAID, halothane. Having this mechanism of liver damage the drug itself or its metabolites (e.g. for cytostatic drugs [23]) binding with the hepatic proteins acts like hapten that conjugated to Kupffer's cells provokes to immune response through main histocompatibility complexes of I and II type. Humoral or cellular response (inherited or adaptive) causes inflammation proceeding with the pro-inflammatory cytokines like interleukin 1, tumor necrosis factor α, interferon γ. Sometimes the mechanism of liver damage could be considered as complex.

4. Types of DILD

Taking into account the diversity of types of DILD [1, 24] they are greatly divided into followings: hepatocellular (cytotoxic), cholestatic, mixed type, vascular, neoplastic and liver steatosis [9]. There is some relationship between certain

classes of drugs and peculiarities of liver injury.

4.1. Hepatocellular Type

Thus iron therapy and general anesthesia (halothane), NSAID, hydralazine, most of anticonvulsants and β-lactams in children cause cytotoxic effect (*hepatocellular type*) with sometimes fatal outcome.

4.2. Cholestatic Type

Neuroleptics, most of antithyroid agents (except of propylthiouracil), fluoroquinolones, macrolides, glucocorticosteroids, nitrofurans and phenothiazines cause predominantly *cholestatic disturbances*. Liver damage of cholestatic type could be resulted from: 1) selective intervention into substance excretion in biliary tracts; 2) direct injury of biliary tract by xenobiotics or its metabolites; 3) some drugs damage adenosine triphosphate (ATP)-dependent proteins that transport bilious acids.

4.3. Mixed Hepatocholestatic Injury

Mixed hepatocholestatic injury is usually the result of immunomediated reaction with disturbance of parenchyma and portal inflammation or insufficiency of canalicular pomps that lets toxic bilious acids accumulate causing secondary hepatocytes disturbance. In accordance with data [25] the significant part of patients have relationship between II class HLA and cholestatic (mixed) type of DILD (for example using amoxicillin\clavulanic acid) that proposes its genetic basis.

4.4. Vascular Liver Damage

Oral contraceptive, azathioprine cause hepatotoxicity resulting from endothelium injury and block of outgoing blood flow – thrombosis of hepatic veins or occlusion of hepatic venulas (venous occlusive disease) with development of stagnant hepatopathy and not cirrhotic portal hypertension or dilation of hepatic sinuses with formation of cavities full of blood (peliosis hepatitis).

4.5. Neoplastic Type

Some drugs (sex and anabolic hormones) could damage deoxyribonucleic acid (DNA) (mutagenic effect) causing development of benign (adenoma, nodular hyperplasia) or malignant (hepatic carcinoma) neoplasms in liver.

4.6. Liver Steatosis

Development of liver steatosis (accumulation of fatty acids in hepatocytes) is related to use of amiodarone and tetracycline (dose-dependent effect) or long-term use of prednisolone at the background of autoimmune hepatitis (time-dependent effect).

5. Diagnostics of DILD

Definite and doubtless DILD is diagnosed rarely due to different reasons and mainly due to underestimation of drug-induced pathology in general and also because the same liver pathology could be caused by different reasons. The doctor could be confused or take a wrong way of thinking if there are extrahepatic signs (rash, fever, arthralgia) observed at immunomediated DILD (hypersensitive syndrome). As a results (in accordance with data [25]) nearly 60% of patients with DILD of any type continue to take drugs after symptoms of liver injury revealed.

Probable DILD diagnosis are based on exclusion of other possible reasons (viral or autoimmune hepatitis, Wilson's disease, steatohepatitis in children with obesity), history of drug intake, time interval between start of treatment and manifestation of hepatic symptoms, correlation with other similar cases, laboratory (AST/ALT > 3 times the upper limit of normal (ULN), total bilirubin > 2 times ULN, alkaline phosphatase (AP) > 2 times ULN and morphological findings, risk factors [8, 26-29]. However the most convincing argument in favor of DILD is cessation of the signs after "suspected" drug withdrawal and its recurrence (at least transaminases increasing in two times) related to the repeated drug intake after interruption (re-challenge – gold standard).

Dynamics of hepatotoxicity is very likely related to the drug if the activity of hepatic enzymes decreases at least at 50% from the initial values during 8 days or presumably if the level of hepatic enzymes decreases at least at 50% during 30 days for hepatocellular type and during 180 days for cholestatic type of DILD [30]. It's evident from these data that cholestatic changes tend to longer involution that hepatocellular type possibly because of cholangiocytes are slower restored and regenerated than hepatocytes. Due to this reason the patients with cholestatic or mixed type of liver damage are more prone to chronicity than patients with hepatocellular type of DILD.

Drug use anamnesis has to include data on drugs intake both prescribed and in particular taken out of prescription including herbal drugs, food supplements, forbidden remedies and also information of the tolerance of the taken drug in the past.

Latent period – time between start of the drug intake and manifestation of the clinical and laboratory signs of hepatotoxicity, it could be very various – from several hours till a year that makes difficult to diagnose DILD. For example hepatotoxicity of such antibiotics like amoxicillin\clavulanic acid, erythromycin could be revealed within 7 days just after first intake. In addition it's supposed [30] that new macrolides together with erythromycin have cholestatic effect that means group effect for these drugs with frequency 1-2:50 000. Significantly longer latent period is specific for tricyclic antidepressants, anticonvulsants, chlorpromazine, metoclopramide, sulfasalazine (> 30 days) and diclofenac (nearly 3 months). In some cases (erythromycin, amoxicillin\clavulanic acid) could be occurred suspended reaction – development of hepatotoxicity already after stop of drug intake – 20 and more days after. This phenomenon could be related to slower development of immunological reaction or long-term retention of the drug in the body (slow metabolizers). It is emphasized that amoxicillin itself has rather weak hepatotoxic potential and in particular the

addition of clavulanic acid (750 mg per day) makes this drug hepatotoxic [4].

Clinical and Laboratory Signs of DILD

The symptomatology of DILD is general for all types of DILD and is characterized at manifestations by nausea (vomiting), pain in right upper quadrant of abdomen, complaints of influenza character, increased liver size, sometimes by jaundice and itch. Among early symptoms the predictor (biomarker) of hepatotoxicity is increasing lien size.

1) However the main clinical signs of DILD in children is acute hepatitis (hepatocellular type – 78%) with mortality of 10%, and ALT > 3 times ULN (sometimes > 10 times ULN) or R ≥ 5 (R=ALT/AP) [5, 31-33].

2) The main symptoms of DILD appropriate for acute cholestasis type that is usually not life-threatening are jaundice and itch with significant increase of AP, cholesterol and mainly direct bilirubin, but R>2. In some cases during observation for the patients with DILD the hepatocellular type tends to convert into cholestatic type [25].

3) Mixed hepatocholestatic type is sometimes similar to atypical hepatitis with not high level of transaminases and AP but 2<R<5 [26].

4) Liver injury of steatosis type is usually associated with steatorrhea and sometimes with pancreatitis.

5) Vascular reactions (venous occlusive disease) manifest with severe pain in right hypochondrium, ascites, signs of portal hypertension, moderate increase of enzymes.

6) Appearance of liver tumors (first of all – malignant) usually manifests with moderate pain in right hypochondrium, increased liver size, reduced appetite, positive tumor markers.

7) DILD is considered having mild severity if it is followed only by laboratory changes and having serious severity if it is required hospitalization or its prolongation, treatment changing or is life-threatening.

8) Regarding the type of course DILD could be considered as *acute* (including fulminant liver insufficiency) and *chronic* – changes of laboratory parameters more than 3 months for hepatocellular type and more than 6 months for cholestatic or mixed types [8].

9) The specific *ultrasound markers* of chronic liver disease independently of the etiology are the following: 1) increase of left liver lobe; 2) increase of lien area; 3) dilatation of lien vein [31, 33]. Moreover in children with liver diseases of viral and non-infectious causality there is increase of collagen synthesis and slowing of the process of its degradation in accordance with serum markers (level of collagen IV, C-terminal telopeptides).

6. Management of the Patients with DILD

Regarding the therapy of DILD it's necessary to admit that up to now there are no resources or methods that could influence seriously this pathology. The treatment is performed using standard scheme and targeted to the withdrawal of the suspected drug with desirable pre-evaluation of its blood concentration. In cases of mild severity the dose of drug is simply decreased. In case of severe hepatotoxicity (ALT/AST > 3 times ULN, total bilirubin > 2 ULN, AP > 1,5 ULN) preferably all drugs eliminated by liver have to be stopped with the possible changing to those eliminating by kidneys [28]. Some authors [34] propose to attempt keep the current treatment if the level of ALT is not higher than 5 normal ranges and such symptoms like nausea, vomiting, pain in right hypochondrium, increase liver size, extrahepatic signs are absent. Half of the patients have ALT level spontaneously normalized (phenomenon of "adaptation"). However in accordance with Hy's law the forecast of hepatotoxicity in case of hepatocellular type of DILD (level of ALT and total bilirubin more than 3 ULN) is pessimistic: mortality is more than 10%.

Hepatoprotectors: LIV.52®, silymarin, essential phospholipids recover hepatocytes' membranes (liver consists of 80% from membranes) and have choleretic and antifibrotic effects. These drugs have universal mechanism of action [12, 13, 35-37].

There are only three antidotes: folic acid defends liver against metothrexate, L-carnitine – against VPA, acetylcysteine (ACC) – against paracetamol. At the same time it is noticed in some reports that the treatment by acetylcysteine is successful for acute liver insufficiency caused by sulfasalazine. Theoretically ACC could be useful also for other cases of possible drug-induced hepatotoxicity (chemotherapy treatment – CT) as it is donator of glutathione (exhausted in case of CT). Besides ACC acts like antioxidant (creation of active oxigen forms is one of the mechanisms of hepatotoxicity), decreases the inflammation by reduction of chemotaxis of leukocytes and also increases the synthesis of nitrogen oxide [10, 24]. Ademetionine as well as ACC increases level of glutathione and other thiols (cysteine, taurine) and also sulfates that are main detoxicants. It has to be prescribed before or in parallel with potential hepatotoxic drugs intake in patients from high risk group and the treatment has to be performed quite long (as a rule more than 30 days) – until the normalization of hepatic parameters. In addition ademetionine has one more important quality – antidepressive action (depression is frequent concomitant disease in patients with severe liver disorders).

It is noticed that ursodeoxycholic acid (UDCA) has normalized action for apoptosis that is universal mechanism of DILD. The timelines for cytolysis elimination in accordance with ALT level in children group who has received UDCA are in 2 times quicker than in patients received standard treatment. Positive results of UDCA impact to cholestasis were demonstrated. The obtained data allow to recommend UDCA for treatment and possibly for prevention of liver damage in case of CT [38].

Glucocorticoids (GC) are recommended for patients with acute drug-induced hepatitis of high grade of activity – ALT/AST > 8-10 normal values or increase total and conjugated bilirubin in combination with 3 and more times increase of ALT and/or AST especially in case of presence of biomarkers of autoimmune hepatitis (LKM and LM-antibodies, increase gamma-globulins) [13]. It's considered that use of such treatment is justified in case of

microvesicular steatosis caused by methotrexate, warfarin and also in case of chronic hepatitis with delayed improvement. Besides nearly 1/3 of patient with acute hepatic failure has concomitant suprarenal glands insufficiency that is obviously required prescription of GC [5, 9, 10, 22].

In case of significant cholestasis UDCA could be effective in combination with duphalac and in case of severe itch – with cholestyramine with titration of its dose up to regression of itch or appearance of diarrhea. Unfortunately apart from bile acids (source of itch) cholestyramine could bind with other drugs. That's why intake of these drugs has to be adjusted – before 1 hour or after 6 hours after colestyramine intake.

In case of inefficiency or poor tolerance of colestyramine rifampicin 600 mg\day could be used. Regression of itch usually occurs in 1-3 weeks and is possibly caused enzyme induction and increase clearance of bile acids.

Although antihistamines and phenobarbital used for the same reason facilitate itch but have sedative effect in parallel. One intravenous injection of Ondansetron 8 mg alleviates itch within 24 hours possibly due to block of serotonin receptors (5-HT3) at the sensory nerve endings.

By common opinion appearance of acute liver failure due to drug intake is considered as direct indication for urgent liver transplantation as the alone measurement to keep patient's life because in case of development of fulminant hepatitis and hepatorenal syndrome mortality could achieve 80%.

7. DILD Prevention

1) Patients from high risk group should avoid hepatotoxic drug intake or they are prescribed the drugs with lower hepatotoxic potential, for example among NSAIDs these are celecoxib or naproxen.

2) Patients have to be warned not to take any drugs on their own except those prescribed by the doctor, follow strictly regimen of dosage and inform the doctor about any discomfort signs

3) To avoid polypharmacy including prescription of so-called safe herbal drugs and food supplements.

4) It's necessary to control the concomitant diseases – obesity, diabetes mellitus, poor nutritive status.

5) It's mandatory to monitor activity of transaminases and AP in case of treatment of potentially hepatotoxic drugs.

6) Patients from risk group who have compulsory intake of hepatotoxic drugs (for example in case of CT) have to be prescribed by hepatoprotectors as concomitant drugs in order to avoid interruption in treatment [23, 39].

Therefore drug-induced hepatotoxicity is serious challenge for pharmacological industry and for doctors. Introduction to practice of the new technologies like pharmacogenomic (determination of genetic polymorphism of enzymes responsible for metabolism of drugs) and methabonomic (determination of abnormal metabolites in blood and urine) will significantly increase the opportunities of identification of risk factors and revelation of pathogenesis of idiosyncratic reactions of hepatotoxicity.

8. Conclusion

Drug-induced liver disorders (DILD) are the diverse group of clinicomorphological types of liver injury caused by drug intake. during last 10-15 years the number of DILD increased in 30 times. In adults DILD has the third place after viral and alcohol liver diseases. But in children to our opinion DILD has to take second place just after viral and parasitic hepatitis. Up to date it's known more than 1200 drugs of different pharmacological classes are able to cause DILD. In children the leading positions are placed by antibiotics, antipsychotics, NSAID as a reason for DILD. There are more than 10 types of DILD, the main of them are hepatocellular, cholestatic, mixed, vascular, neoplastic and steatosis. The diagnostics of DILD is difficult (usually it's diagnosis of exclusion). The most serious arguments in favor of DILD are involution of the symptoms after stop of the "suspected" drug intake and resumption of the signs after repeated drug intake. The treatment of DILD aims to withdrawal of all drugs having active hepatic metabolism/clearance, introduction of hepatoprotectors. In order to prevent DILD it's recommended to analyze anamnesis thoroughly and carefully, control of concomitant diseases (obesity\poor nutritive status, diabetes mellitus), prescription of drugs with minimal potential hepatic toxicity, to keep from polypharmacy, control of biochemical markers of liver injury (aminotransferases), in some cases (patients from high risk groups) preventive hepatoprotectors intake (concomitant treatment).

Conflict of Interest

All the authors do not have any possible conflicts of interest.

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