



Drug-induced hepatotoxicity, risk drugs in hepatic dysfunction

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Learning outcomes

- *The student recognizes different types of drug-induced liver injury.*
- *The student is able to define information relevant to the evaluation of drug-induced hepatotoxicity.*
- *The student will outline the general management of drug-induced liver injury.*
- *The student will identify potentially risky medications for various types of hepatic dysfunction.*

Drug-induced hepatotoxicity

- Drug-induced liver injury (DILI)

- Aspects:

- Clinical presentation, symptoms

- Hepatocellular, cholestatic, combined pattern

- Asymptomatic, acute/chronic liver failure, new-onset icterus without signs of biliary pathology; immune reaction

- Manifestation hours-days vs. days-months

- Mechanism, pathophysiology

- Dose-dependent adverse effect

- Idiosyncratic reaction – allergic, non-allergic

- Histopathology

- Acute vs. chronic

- Hepatocellular injury, cholestasis, steatosis

Drug-induced hepatotoxicity – examples

hepatocellular	direct toxic effect; cells, membranes dysfunction	isoniazid, diclofenac, paracetamol, statins, phenytoin
cholestasis	canalicular membrane damage, interaction with transporters	chlorpromazine, phenothiazines, corticosteroids, amoxicillin-clavulanate, estrogens, androgens
immunologically-mediated	cytotoxic lymphocyte response against hepatocytes membranes, other autoimmune components	nitrofurantoin, isoniazid, methyldopa
granulomatous	lobules infiltration by macrophages, lymphocytes	sulphonamides, sulfonyleurea derivatives, phenytoin, diltiazem, allopurinol
microvesicular steatosis	mitochondrial dysfunction, impaired β -oxidation, triacylglycerols accumulation	valproic acid, amiodarone, NSAIDs (ibuprofen, aspirin), NRTIs, tetracyclines, tolcapon,
steatohepatitis		amiodarone, tamoxifen, methotrexate, irinotecan, 5-fluorouracil, corticosteroids
fibrosis		methotrexate, methyldopa, vit. A overdose
vascular	ischemia, hypoxia	nicotinic acid, azathioprine, cyclophosphamide, MDMA, hormonal contraceptives
oncological	benign liver adenomas	hormonal contraceptives, anabolics

Drug-induced hepatotoxicity

– Management:

- Differential diagnosis, careful history taking
- Withdrawal of the suspected drug
 - Latency, withdrawal (de-challenge), re-exposure (rechallenge), time to resolution
 - [LiverTox.nih.gov](https://livertox.nih.gov) (Clinical and Research Information on Drug-Induced Liver Injury)
- Specific therapy
- Symptomatic therapy
- (drug reintroduction after DILI management)

Risk drugs in terms of hepatic insufficiency

- Drugs with high extraction ratios – examples:

- morphine, fentanyl, sufentanil, naloxone, metoprolol, propranolol, verapamil, diltiazem, nitroglycerin, bupropion, buspirone, imipramine, sertraline, venlafaxine, quetiapine,...

- Drugs with low extraction ratios – examples:

- alprazolam, oxazepam, diazepam, phenytoin, valproic acid, carbamazepine, lamotrigine, levetiracetam, topiramate, theophylline, ibuprofen, indomethacin, naproxen, paroxetine, fluoxetine, citalopram, trazodone, warfarin, lansoprazole, pantoprazole, aripiprazole, risperidone,...

Risk drugs in terms of hepatic insufficiency

- Drugs with high plasma protein binding – examples:
 - valproate, oxacillin, ceftriaxone, phenytoin, NSAIDs, warfarin, diazepam, clozapine, olanzapine, risperidone, haloperidol, flupentixol, telmisartan, sulfonyleureas, furosemide, ertapenem,...
- Drugs eliminated unchanged by bile/biliary excretion – examples:
 - cefoperazone, buprenorphine, telmisartan, trandolapril, ceftriaxone, meropenem, ciprofloxacin,...

Risk drugs in terms of hepatic insufficiency

- Drugs with enterohepatic circulation – examples:
 - contraceptives, valproate, ampicillin, amoxicillin, ezetimibe, mycophenolate, indomethacin, levothyroxine,...
- Drugs requiring the presence of bile for absorption – examples:
 - vit. A, vit. D, vit. E, vit. K, ...

Take home message

- Dose-dependent hepatotoxicity is typical for paracetamol and is observed within hours, max. days after exposure; idiosyncratic drug-induced hepatotoxicity is most commonly associated with antimicrobials.
- In differential diagnosis, it is useful to know the hepatotoxicity profile of a particular drug. The reintroduction of a suspected drug is related to the expected benefit-risk ratio.
- Depending on the nature of the liver dysfunction, the entire pharmacotherapy of the patient should be re-conciliated, not only screened for hepatotoxic drugs.

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