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Editorial

Drug therapy in liver diseases

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One of the most frequently asked questions to medical doctors concerns the risks and proper use of drugs in patients with underlying liver disease. The liver plays a central role in the pharmacokinetics (absorption, distribution, and elimination) of the majority of drugs. It is well recognized that in the presence of impaired hepatic function a decrease of xenobiotic substances metabolism generally occurs. Hepatic injury is not the typical adverse reaction associated with the drugs used in patients with liver cirrhosis. The drugs used in this group of patients (particularly diuretics and centrally active drugs) much more often impair renal function and /or induce hepatic encephalopathy.

The effects of liver disease on pharmacokinetics and pharmacodynamics are highly variable.[1] Liver dysfunction reduces the blood/plasma clearance of drugs eliminated by hepatic metabolism or biliary excretion and affects plasma protein binding, which in turn could influence the processes of distribution and elimination. Moreover, portal-systemic shunting and transjugular intrahepatic portosystemic shunts (for management of portal hypertension complications), which are common in advanced liver cirrhosis, may substantially decrease the elimination of high extraction drugs following their oral administration, thus leading to a significant increase in the extent of absorption. The activity of drug-metabolizing CYP450 enzymes seems to be variably and non-uniformomly reduced in patients with cirrhosis. Glucuronidation is often considered to be affected to a lesser extent than oxidative drug metabolism.[2-4] Acute liver disease often affects drug elimination less than cirrhosis. Cholestasis tends to decrease drug biotransformation more for many drugs as compared to hepatocellular disease. Special attention should be made to the effect of enzyme induction or decrease in drug metabolism by other agents in the presence of liver disease (i.e. the effect of chronic ethanol use on the formation of a toxic metabolite of acetaminophen in liver and kidney).

Altered receptor sensitivity (tissue responsiveness to the pharmacological action-pharmacodynamics) has been observed with some drugs (sedatives,[5-7] opioids,[8] diuretics[9,10]) in cirrhosis. Patients with liver cirrhosis have been reported to be more sensitive to the central adverse effects of morphine and benzodiazepines,[5-8] whereas the sensitivity to the natriuretic effect of loop diuretics and the therapeutic effect of b-adrenoceptor antagonists are reduced. Considering benzodiazepines, substances with a long half-life should be avoided and those eliminated by conjugation only (e.g. oxazepan or lorazepam) should be preferred.[5-7] Another example is the greater susceptibility of such patients to the nephrotoxic potential of aminoglycosides which should not be used in cirrhotics.[11] Drugs may also interfere with adaptive physiological processes induced by liver disease. So, Angiotensin converting enzyme (ACE) inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) counteract the enhanced activity of the renin-angitensin system in cirrhosis thereby generating a high risk of excessive hypotension or acute renal failure respectively. These drugs should be avoided in cirrhotics. NSAIDs can precipitate renal failure in patients with cirrhosis and ascites because of abolishment of renal production of prostaglandins which are the main vasodilatory substances of renal arteries.[12] Moreover, it is prudent to avoid the use of selective cyclo-oxygenese inhibitors (coxibes) despite the absence of clinical data.

Patients with advanced cirrhosis often have impaired renal function and dose adjustment may, therefore, also be necessary for drugs eliminated by renal excretion (e.g. sotalol, disopyramide, procainamide). It should be taken into account that serum creatinine significantly overestimates glomerular filtration rate in these patients.

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Pre-existing liver disease and also enzume polymorphisms or specific HLA genotypes can represent risk factors for drug induced liver disease. Hepatotoxic drug reactions are divided into dose-dependent and dose independent. The dose-dependent group is predictable but can be altered under ill-removal of the drug resulting over a period of time in toxic concentrations (i.e. acetaminophen in chronic alcoholic patients). The presence of underlying liver disease may predispose to greater dose-dependent drug toxicity (methotrexate, isoniazid), if the drug dosage is not appropriately adjusted downward and if the margin of safety between therapeutic and toxic concentrations (the toxic threshold) is small. The overwhelming majority of drug-induced liver injury is dose independent. It appears to occur in highly selected individuals with a generic proclivity for generating an unusual metabolite or who develop an allergic response to such a derivative (idiosyncratic liver damage). The presence of prior hepatic dysfunction does not induce or worsen such liver damage but the liver defense systems can be altered due to chronic liver disease.

The development of drug-induced liver disease is heralded by the onset of new symptoms (fatigue, myalgias, nausea, abdominal pain, jaundice) and abnormal liver function tests. With the presence of underlying liver disease, recording of a baseline and frequent (monthly) clinical and biochemical follow-up of the patient may be needed to detect early drug-induced toxicity. A bilirubin level >3 mg/dl or a 10-fold increase of serum aminotrasferase levels are considered serious hepatotoxicity regardless of baseline value. Drugs capable of causing idiosyncratic hepatocellular jaundice (e.g. statins, isoniazid) are often associated with asymptomatic minor (less than 3 times the upper limit of normal values) increase of serum aminotrasnferase elevations. These laboratory abnormalities reverse even if drug therapy is continued (adaptation) and therapy should be continued.

The main problem with the drug use in cirrhotic patients is that we can not define with precision the degree of impairment of liver function relevant to elimination of a particular drug in a given patient. There is no single equivalent of the clearance creatinine test (as for renal disease) in patients with liver disease. Moreover, there is no simple endogenous marker to predict hepatic function with respect to the elimination capacity of specific drugs. Several quantitative liver tests that measure the elimination of marker substrates such as galactose, sorbitol, antipyrine caffeine erythromycin and midazolam have been developed and evaluated. Nevertheless, no single test has been accepted in everyday clinical practice to adjust dosage regimens for drugs in patients with hepatic dysfunction. The semi-quantitative Child-Pugh score is frequently used to assess the severity of liver function impairment, but only offers the clinician rough guidance for dosage adjustment because it lacks the sensitivity to quantitate the specific ability of the liver to metabolize individual drugs.

Impairment of drug elimination only occurs late in the evolution of chronic liver disease and thus modification of the drug regimen should be needed only in the presence of severe hepatic dysfunction (Child Pugh class 2 and 3). In cirrhosis, dosage reduction, adapted empirically, is essential for many drugs to avoid excessive accumulation of the drug and active metabolites which may lead to serious adverse reactions.[13,14] The use of drugs that must undergo liver biotransformation before they can become pharmacologically active (pro-drug) should also be avoided unless absolutely essential.[15-17] The most dangerous drugs in patients with liver cirrhosis are those with a low hepatic extraction and a narrow therapeutic range. If such drugs are administered orally, both initial and maintenance doses have to be reduced by >50% of the normal dose. If such drugs are administrated parenterally or other drugs metabolized by the liver are used only the maintenance dose has to be adjusted.[13-16] The use of only 2 gr acetaminophen (paracetamol) per day appears to be safe in cirrhotics.

Both the Food and Drug Administration (FDA[18]) and the European Medicines Agency (EMEA[19]) have published a guidance for industry on evaluation of pharmacokinetics of medicinal products in patients with impaired hepatic function. When no recommendations for dosage adjustment in patients with hepatic dysfunction based on their Child-Pugh score are available, the following general considerations will be helpful. A marked decrease in systemic and/or oral clearance and significant prolongation of the elimination half-life have been documented for carvedilol, lidocaine, propafenon and verapamil which should be counteracted by a 2-to 3-fold reduction of the dosage in patients with moderate to severe liver cirrhosis. Nifedipine can increase the portal pressure and moxalactam or cefamandole can cause hypoprothrombinemia related to inhibition of synthesis of vitamin K dependent clotting factors. Metoclopramide significantly blunted the natriuretic response to spironolactone and should be avoided in patients with cirrhotic ascites. Pefloxacin is the only quinolone that has been reported to have induced serious epileptic complications and needs careful monitoring and dosage adjustment in cirrhosis. Isoniazid and rifampicine can be used cautiously in cirrhotics at standard dosages. Liver biochemistry should be monitored very carefully

(monthly) during therapy. Ethambutol and streptomycin can be safely used. Ofloxacin can replace rifampicin use in cirrhotics with similar response rate. Interferon therapy should not be used in patients with decompensated HBV cirrhosis since it can cause a flare of the disease. Moreover, in cirrhotics, interferon therapy can be complicated by serious bacterial infections and by hematological side-effects (anemia, neutropenia, thrombocytopenia). Acute liver decompensation in chronic HBV liver disease can follow the withdrawal of antineoplastic or immunossupressive therapy. These patients should receive preemptive nucleoside/nucleotide therapy. Patients with impairment of liver function appear to be at risk of seizures and cardiac arrhythmias when they use theophylline. A reduction of the maintenance dose together with measurement of serum concentration is warranted. In patients with liver cirrhosis who have edema and/or ascites, the volume of distribution of hydrophilic drugs is increased. As a consequence, the loading dose of hydrophilic drugs may have to be increased according to bodyweight when a rapid and complete effect is needed (e.g. for b-lactam antibiotics or for digoxin). Guidelines for dose modification in cholestasis exist for many antineoplastic drugs (doxorubicin, etoposide, cyclophosphamide[18]) but are lacking for the drugs with biliary elimination.

In conclusion, drug therapy can be rationalized by taking into account the route of metabolism of drug its pharmacokinetics, the severity of liver disease, and changes in end organ response that occur in the presence of liver diseases. Drugs must be given with caution to patients with severe hepatic insufficiency such as in the case of decompensated cirrhosis. Before drug administration, the potential therapeutic benefits must be carefully counterbalanced with their risk for serious toxic reactions. This is especially true for drugs with a narrow therapeutic index and for sedatives, central analgesics and anxiolytics (they can precipitate hepatic encephalopathy). If these drugs are really needed, they should be started at a low dose which may subsequently be titrated to obtain the desired therapeutic effect. Further research is needed to develop more sensitive liver function tests to guide drug dosage adjustment in patients with hepatic dysfunction. However it is important to realize that the recommendations for dose adaptation remain general and cannot replace accurate clinical monitoring of patients with liver disease treated with drugs.

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