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DOSAGE ADJUSTMENT IN HEPATIC PATIENTS: A LITERATURE-BASED REVIEW

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Abstract

The liver is the principal metabolic organ in our body. Any dysfunction in this system may affect on drugs' activity and on the host. Therefore, the dosage of a particular drug, especially which is orally administered should be taken into careful consideration This paper depicts a scenario on the dosage adjustment in hepatic dysfunction patients. Databases such as PubMed, MedLine, ScienceDirect, and GoogleScholar have been used for the up-to-date published evidences. Dosage adjustment in patients with hepatic dysfunction based on Child–Pugh scores, MELD and PELD formulas, where the patients and child pugh classification has three classes of hepatic stages such as mild grade (score: 5-6), moderate grade (score: 7-9) and severe grade (score: 10-15). Special care should be taken for the adjustment of cardiovascular drugs, antibiotics, opioids, antiarrythmic and anticancer drugs, and so on. This paper might be helpful for the clinicians for the appropriate dosage adjustments for patients with hepatic dysfunction.

Keywords: *hepatic system; metabolism; dosage adjustment*

Introduction

The liver is an important part of the human body which plays important roles in the absorption, distribution and elimination of various drugs (Ueno and Komatsu, 2017). It is not only the most important biotransformation site, but also parameters such as liver blood flow, binding to plasma proteins, and biliary excretion, which can all potentially influence drug pharmacokinetics, depending on the normal functioning of it (Almazroo et al., 2017).

Patients with hepatic dysfunction may also be more sensitive to the effects (both desired and adverse) of several drugs (Verbeeck, 2008). Dosage adjustment in patients with liver dysfunction is therefore essential for many drugs to avoid excessive accumulation in our body, and possibly of active drug metabolite(s), which may lead to serious adverse reactions (Almazroo et al., 2017).

This paper aimed to sketch a scenario on the dosage adjustment in hepatic dysfunction patients on the basis of published reports in PubMed, MedLine, ScienceDirect, and GoogleScholar databases.

Hepatic pathophysiology

Any compound entering the body is eliminated by metabolism and excretion *via* the urine or bile/faeces. The liver is situated, which is called eliminating organ (hepatocellular uptake and metabolism, biliary excretion) between the upper gastrointestinal tract and the general circulation. Together with the small intestinal epithelium and liver is responsible for the presystemic elimination (first-pass effect) of many potentially harmful exogenous substances, including therapeutic agents, those are absorbed into the hepatic portal circulation from the small intestine after their oral ingestion (Pond and Tozer,1984).

The liver has a dual blood supply delivering approximately 1,500 mL/min in healthy adults partly *via* the hepatic artery (approximately 25%) and partly *via* the portal vein (approximately 75%). Hepatic disease, and in particular cirrhosis, results in numerous pathophysiological changes in the liver that may influence drug pharmacokinetics (Morgan et al., 1995; Reichen,1999).

Effect of liver dysfunction on pharmacokinetic processes

Dosage consideration in hepatic patients

Several physiologic and pharmacokinetic factors are relevant in considering dosage of a drug in hepatic patients (**Table 1**).

Active drug and the metabolite(s)

For many drugs, both the drug and the metabolite(s) contribute to the overall therapeutic response of the patients to the drug. The concentration of the active drug and the metabolite in the body should be known. When the phramacokinetic parameters of the metabolite and active drug are similar, the overall activity of the drug can become more or less potent as a result of a change in liver function; that is,

i. when the drug is more potent than metabolite , the overall pharmacological activity will increase in the hepatic impaired patient because drug concentration will be higher;

ii. when the drug is less potent than the metabolite , the overall pharmacological activity in the hepatic patient will decrease because less of the active metabolite is formed.

Changes in pharmacologic activity due to hepatic disease (**Table 2**) may be much more complex when both the pharmacokinetic parameters and the pharmacodynamics of the drug change as a result of the disease process (Shargel et al., 2012).

Pathophysiologic assessment

In practice, patient information about changes in hepatic blood flow may not be available, because special electromagnetic (Nuxmalo et al., 1978) or ultrasound technique are required to measure blood flow and are not routinely available. Various approaches have been used diagnostically to assess hepatic impairment. The child pugh score assesses the overall hepatic impairment as mild, moderate or severe (Lucey et al., 1997' Figg et al., 1995). The score employs five clinical measures of liver disease, including total bilirubin, serum

albumin, INR (International Normalized Ratio), ascites and hepatic encephalopathy (**Table 2** and **3**).

Hepatic drug clearance

Although measurements of the creatinine clearance level can be used for dose adjustments in cases of impaired renal function, there is no naturally occurring substance that can be used to estimate the hepatic clearance of drugs. The Child-Pugh score is composed of several clinical variables and is used widely for the assessment of prognosis in patients with liver cirrhosis.

$$Cl_{hep} = \frac{Q \times (f_u \times Cl_i)}{Q + (f_u \times Cl_i)} \qquad Cl_{hep} = Q \times E = Q \times \frac{C_{in} - C_{out}}{C_{in}}$$

$$E = \frac{f_u \times Cl_i}{Q + (f_u \times Cl_i)}$$

Hepatic blood flow and intrinsic clearance

The following equation may be used to measure the hepatic clearance of a drug after assessing changing in blood flow and intrinsic Cl_{int}:

$$Cl_h = QCl_{int}/Q+Cl_{int}$$

For severe liver dysfunction (albumin< 30 g/L, INR >1.2)

a. If the drug is a high clearance drug (liver blood flow dependent) reduce dose by 50%.

High clearance drugs	
Antipsychotics	Opioids most
Beta –blockers most	Tricyclic antidepressant
Lignocaine	Statains
Nitrates	SSRIs
(adjusted from: Shargel et al., 2012)	

b. If the drug is low clearance (Floe independent includes all other metabolized drugs
reduce dose by 25%.

Low clearance drugs	
Anticonvulsants most	Sulphonylureas
Spironolactone	Theophylline
Paracetamol	Warfarin
NSAIDs	Steroids
(adjusted from: Shargel et al., 2012)	

Absorption

Gastrointestinal dysfunction has been described in patients with liver disease and may contribute to the complications of cirrhosis (Quigley,1996). Although studies with orally administered test substances, such as sugars, show an increased intestinal permeability, the consequences for intestinal absorption of drug molecules are not clear (Zuckerman et al., 2004). The effect of chronic liver disease on the bioavailability of orally administered drugs is, however, mainly the result of reduced presystemic hepatic metabolism. As a consequence of the unique position of the liver in the circulatory system, all drugs absorbed from the gastrointestinal tract (with exception of the mouth and the lower part of the rectum) are exposed to the metabolizing enzymes and bile excretory transport systems of the liver before reaching the systemic circulation. Drugs with an intermediate to high hepatic extraction ratio will undergo an important presystemic elimination or 'first-pass effect' (Blaschke and Rubin,1979; Tam,1993) (**Table 4**). The fraction of an absorbed oral dose that escapes first-pass hepatic clearance, FH (Wilkinson, 1980), can be described by the following equation:

$$F_H = 1 - f_H * E_H$$
$$= Q_H + f_u * CL_{int}(1\text{-}fH)/ Q_H + f_u * CL_{int}$$

Where, f_H is the fraction of the mesenteric blood flow passing through the functioning liver.

Plasma protein binding and distribution

Since only the unbound drug is capable of entering and leaving the tissue compartments, the distribution of a drug within the body depends on its reversible binding to blood cells, plasma proteins, and tissue macromolecules (MacKichan,2006). Many drugs that are highly bound to albumin or α1-acid glycoprotein have a significantly higher f_u in patients with chronic liver disease (Blaschke, 1977; MacKichan, 2006).

According to MacKichan (2006), mechanisms for decreased binding of certain drugs to plasma proteins include-

(1) reduced albumin and α1-acid glycoprotein synthesis leading to low levels of these important binding proteins in plasma of patients with chronic liver disease,
(2) accumulation of endogenous compounds, such as bilirubin, inhibiting plasma protein binding of certain drugs, and
(3) possible qualitative changes in albumin and α1-acid glycoprotein.

As a result of the lower plasma binding, the distribution volume of certain drugs may be larger in these patients. Moreover, water-soluble drugs will have a significant increase in their volumes of distribution in patients with ascites possibly necessitating larger loading doses. For example, the apparent volume of distribution of the β-lactam antibacterial cefodizime was shown to be three times larger in patients with cirrhosis compared to healthy individuals (Touny, 1992). Chronic liver disease, such as cirrhosis, is more likely to be associated with altered drug binding than are acute conditions such as viral hepatitis (Blaschke, 1977)

The decrease in hepatic metabolic capacity, is obscured by a simultaneous increase in the fraction of unbound drug if total plasma clearance is the sole parameter used to assess hepatic metabolic function. The marked reduction (-60%) of naproxen in patients with alcoholic cirrhosis, however, shows that metabolism of this drug is significantly impaired in these patients. In the same study, a small increase in distribution volume of naproxen was found in the presence of alcoholic cirrhosis. Naproxen is a drug with a very small distribution volume of approximately 0.15 L/kg. For drugs with such small distribution volumes, important alterations in plasma protein binding will only be associated with relative unimportant changes in Vd (Tozer, 1986).

Metabolism

The liver is the main organ involved in drug metabolism. The hepatic intrinsic clearance (CLint) represents the ability of the liver to clear unbound drug from the blood when there are no limitations of flow. CLint depends on metabolic enzyme activity and the activity of sinusoidal and canalicular transporters (**Figure 1**) (Chandra and Brouwer, 2004; Liu and Pang, 2004). The importance of hepatic transport proteins in hepatobiliary drug disposition has been recognized only recently. Many aspects of this evolving field and the impact of pharmacotherapy remain to be elucidated. It has long been realized that chronic liver disease in general is associated with impaired metabolism of a number of drugs. Indeed, in chronic liver disease, a reduction in absolute liver cell mass or a decrease in enzyme activity due to alteration in the function of surviving cells may lead to impaired drug metabolism (Morgan and McLean, 1995; Reichen,1999). In addition, as a result of sinusoidal capillarization, the uptake of certain drugs and of oxygen across the capillarized endothelium may be impaired, which may contribute to reduced hepatic drug metabolism in chronic liver disease (Morgan and McLean, 1995; Reichen, 1999; Morgan and McLean, 1991).

The microsomal mixed function oxidase system, located in the smooth endoplasmic reticulum of hepatocytes, is responsible for phase I oxidative metabolism. This system consists of two enzymes: cytochrome P450 (CYP450) and NADPH-dependent cytochrome P450 reductase. These enzymes require two additional components to function: nicotinamide adenine dinucleotide phosphate (NADPH) and molecular oxygen. As a result, CYP450 enzymes are in general more sensitive than the phase II conjugating enzymes due to the lack of oxygen that results from shunting, sinusoidal capillarization, and reduced liver perfusion (Morgan and McLean, 1991; Reichen,1999) (**Figure 2**).

Studies assessing the protein content or the activity of important drug-metabolizing enzymes in livers from cirrhotic patients have shown that, in general, enzyme activities and protein content are reduced with increasing disease severity (George and Murrayet al., 1995; George and Liddleet al., 1995; Furlan et al., 1999; Elbekai et al., 2000; Villeneuve and Pichette, 2004). However, these studies also seem to indicate a selective regulation of the various drug metabolizing enzymes in patients with chronic liver disease. Indeed, chronic liver diseases are associated with variable and non-uniform reductions in CYP450 activities that do not correlate with reduced hepatic blood flow. For example, in the same cohort of patients with mild to

moderate chronic liver disease, the oral clearance of mephenytoin was significantly reduced (to 20% of the control value) whereas the oral clearance of debrisoquine was not affected (Adedoyin et al., 1998; Branch,1998). Among extensive metabolizers (all study subjects were extensive metabolizers), mephenytoin isalmostexclusivelymetabolizedbyCYP2C19 and debrisoquine is a probe for CYP2D6 activity. Similarly, Frye et al. used a validated cocktail approach to study the effect of liver disease on multiple CYP450 enzymes (Frye et al., 2006). A mixture of caffeine, mephenytoin, debrisoquine, and chlorzoxazone was orally administered to measure the in vivo activity of CYP1A2, CYP2C19, CYP2D6, and CYP2E1, respectively, in healthy subjects and patients with different aetiologies and severity of liver disease. The results confirmed that CYP450 enzyme activity is differentially affected by the presence of liver disease (Lin et al.,2002; Daly, 2006).

Although the results of several studies clearly indicate a selective regulation of activity of different CYP enzymes in the presence of chronic liver disease, the mechanisms responsible for this differential effect remain unknown. CYP3A is the most abundant CYP450 subfamily. It plays a major role in human drug metabolism catalyzing the biotransformation of more than 50% of drugs commonly used. While CYP3A4 is usually the most abundant CYP450 isoform in human liver, CYP3A5 is expressed in only a fraction of Caucasians and may constitute 17–50% of the CYP3A enzymes in those who express it (Lin et al., 2002; Daly, 2006). CYP3A4 and CYP3A5 have largely overlapping substrate specificity. Among patients with cirrhosis, several pharmacokinetic studies have shown a decrease in the clearance of drugs metabolized by CYP3A4/3A5 such as midazolam, nifedipine and everolimus (Kleinbloesem et al., 1986; Pentikäinen et al.,1989; Chalasani et al., 2001; Kovarik et al., 2001). Conjugation reactions such as glucuronidation are often considered to be affected to a lesser extent by liver cirrhosis than CYP450-mediated reactions (Hoyumpa and Schenker,1991; Levy et al.,1998; Elbekai et al., 2000). One of these theories suggests that there is an activation of latent UDP-glucuronosyltransferase (UGT) enzymes during liver injury. Examination of cirrhotic human livers revealed an up-regulation of UGT activity in remaining viable hepatocytes (Debinski et al., 1995). Another possible explanation for the relative sparing of glucuronidation in liver disease may be increased extrahepatic metabolism in case of cirrhosis. Extrahepatic glucuronidation seems to contribute substantially to the overall clearance of, for example, morphine and may be increased in patients with liver dysfunction (Mazoit et al.,1990; Hoyumpa and Schenker,1991).

Biliary excretion

Common bile duct stones, sclerosing cholangitis, or cancer of the biliary tree or the pancreas can obstruct bile flow and produce extrahepatic cholestasis. Intrahepatic cholestasis due to functional derangement of the hepato-canalicular bile secretory system may be induced by certain drugs such as erythromycin, phenol-thiazines, and anabolic steroids (Klaassen and Watkins,1984). Reduced formation or secretion of bile into the duodenum will lead to a decreased clearance of substances, both endogenous and exogenous, that are eliminated by biliary excretion.

Studies in patients undergoing surgery for obstruction of the common bile duct have clearly shown that the biliary excretion of antibiotics, such as ampicillin, piperacillin, certain cephalosporins, clindamycin, and ciprofloxacin, was markedly impaired in patients with obstructed biliary tract (Mortimer et al., 1969; Sales et al., 1972; Brown et al., 1976; Leung et al., 1990; van Delden et al.,1994; van den et al.,1996)

Drugs and drug metabolites normally excreted to a significant extent via the bile may therefore accumulate in patients with obstruction of the common bile duct. In addition, biliary obstruction may lead to hepatocellular damage with impairment of metabolic drug clearance. Indeed, the activity of several CYPs, for example CYP2C and CYP2E1, has been shown to be impaired in livers removed at transplantation for patients with end stage cirrhosis with and without cholestasis (George and Murray et al., 1995), whereas CYP3A protein was significantly reduced only in the cirrhotic livers without cholestasis. Consequently, drugs that depend to a significant extent on hepatic metabolism for elimination may require dosage adjustment in patients with cholestasis.

The reduced transporter expression may contribute to impaired excretory liver function in patients with cholestatic liver diseases (Zollner et al., 2001; Kullak-Ublicket al., 2002). However, recent experimental studies suggest, that, particularly with prolonged cholestasis, maintenance or even up-regulation of hepatocellular efflux pumps may reflect adaptive and compensatory mechanisms limiting hepatocellular accumulation of potentially toxic biliary constituents (Zollner and Fickert et al., 2003). How these potential alterations by chronic liver disease of hepatic uptake transporters and efflux pumps may affect the hepatic elimination of drug substances remains to be determined.

Mechanisms of impairment of hepatic drug elimination in chronic liver disease

Four different theories have been proposed to account for the effects of chronic liver disease with cirrhosis on hepatic drug elimination:

1. **The sick cell theory**: The sick cell theory envisages that there is a reduction in the content and activity of the hepatic drug metabolizing enzymes while blood flow is maintained (Branch et al.,1976).
2. **The intact hepatocyte theory:** The intact hepatocyte theory, first proposed by Branch et al. seems to have been interpreted in the following two ways. (a) Chronic liver disease is not associated with a reduction in the function of each cell, but with a reduced number of hepatocytes showing relatively normal function. Therefore, the intrinsic clearances of various drugs per individual hepatocyte do not differ between normal subjects and patients with chronic liver disease. (b) Effective hepatic blood flo.,v perfusing functional hepatic tis- sue and the intrinsic hepatic clearance of a drug both shows a proportional decrease in chronic liver disease including liver cirrhosis (Branch et al.,1976; Huet et al., 1983; Kawasaki et al.,1988).
3. **The impaired drug uptake theory:** The third theory, which may be termed the impaired drug uptake theory, proposes that the most significant feature of cirrhosis is the process of sinusoidal capillarisation. This results from loss of fenestration of the sinusoidal endothelium, development of basal laminae and deposition of complex macromolecules in the space of Disse. This theory envisages that hepatic drug elimination is impaired primarily because of impaired uptake of drug across the capillarised endothelium (Varinet al.,1988; Reichen et al., 1989; Morgan et al., 1991)
4. **The oxygen limitation theory:** Finally, there is the oxygen limitation theory, which envisages that it is the impaired uptake of oxygen, rather than that of the drug itself, across the capillarised endothelium that is responsible for the impairment of hepatic drug metabolism in cirrhosis (McLean et al.,1991; Morgan et al., 1991).

While some data in support of each of the first 2 theories have been published recently, a large amount of clinical data would appear to refute both of these theories,which regard the decreased permeability of the capillarised sinusoid as the critical feature in cirrhosis. Further work is required to determine the applicability of each of these theories (Morgan et al., 1995).

Liver function tests and the metabolic markers

Drug markers used to measure residual hepatic function may correlate well with hepatic clearance of one drug which correlate poorly with substrate metabolized by a different enzyme within the same cytochrome p-450 subfamily. Some Useful hepatic marker compounds are listed below:

1. **Aminotransferase (AST):** Normal AST value for males is 10-55 U/L; and for females is 7-30 U/L.
2. **Alkaline phosphatase (AP):** Normal AP values for males is 45-115 U/L and for females is 30-100 U/L , Marked AP elevations may indicate hepatic tumors or biliary obstruction in the liver.
3. **Bilirubin:** Normal value is 0-1 mg/dL. Unconjugated hyperbilirubinemia results from increased bilirubin production. Conjugated hyperbilirubinemia results from defects in hepatic excretion.
4. **Prothrombin time:** Normal value is 11.2-13.2 sec, with the exception of factor 8, all coagulation factors are synthesized by the liver; therefore

hepatic disease can alter the coagulation (Shargel et al., 2012).

Hepatic impairment

Hepatic impairment may not sufficiently alter the pharmacokinetic of some of the drugs to require dosage adjustment. Drugs that have the following properties are less likely to need a dosage adjustment in patient with hepatic impairment.

• The drug is metabolized in the liver to a small extent (<20%) and the therapeutic range of the drug is wide so that modest impairment of the drug directly or by increasing its interaction with other drugs.
• The drug is gaseous or volatile, and the drug and its active metabolites are primarily eliminated via the lungs.

For each drug case, the physician needs to assess the degree of hepatic impairment and consider the known pharmacokinetics and pharmacodynamics of the drug (Shargel et al., 2012). The sum of the five scores from the table is used to assign a "Child-Pugh grade" (also known as a Child's grade) of A, B or C to the patient's clinical condition at that point in time. This grade is used to gauge mortality using the **Table 5**:

The Child-Pugh score should be reassessed periodically since the patient's clinical condition may improve or deteriorate with time.

Formulas

An alternative method for assessing liver dysfunction is the Model for End-Stage Liver Disease (MELD) score. This may be a more accurate method, but is less accessible to most clinicians because it involves calculating the score.

1. **Model for end stage liver disease (MELD):** The model for end-stage liver disease (MELD) is a scoring system used to prioritise patients awaiting liver transplantation. Patients with a higher score are deemed to require a transplant more urgent than those with a lower score. Serum bilirubin, creatinine and INR are the parameters used to calculate a MELD score (Malinchoc et al., 2000).

MELD = 3.78* serum bilirubin (mg/dl) + 11.20 *lnINR+9.57*ln serum creatinine (mg/dl)+6.43(constant for liver disease etiology)

where, INR = International normalized ratio,

Note: if the patient has been dialyzed twice within the last 7 days then the value for serumcreatinine used should be 4.0.

2. **Pediatric end stage liver disease (PELD):** It is a disease severity scoring system for children under12 years of age.PELD uses the patient's values for serum bilirubin, serum albumin, the international normalized ratio for prothrombin time (INR), whether the patient is less than 1 year old, and whether the patient has growth failure (<-2 standard deviation) to predict survival. It is calculated according to the formula proposed by Russell et al. (2001).

PELD = 4.8*[ln serum bilirubin (mg/dl)+ 18.57[ln INR]- 6.87[ln albumin (g/dl)+ 4.36(<1 year old)+ 6.67(growth failure)

Dosage adjustment in patients with hepatic dysfunction based on Child–Pugh scores

Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) have published a guidance for industry on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function (FDA, 2003; EMEA, 2005). These guidelines recommend that a pharmacokinetic study be carried out during development of a medicinal product that is likely to be used in patients with impaired hepatic function and when hepatic impairment is likely to significantly alter the pharmacokinetics of the drug substance or its active metabolite(s). The primary objective of such a study is to identify patients at risk and to assess whether a dosage adjustment is required for patients with impaired hepatic function. These guidelines recommend that the Child-Pugh classification be used to categorize patients according to their degree of hepatic impairment.

Moreover, in many cases when the pharmacokinetics of a medicinal product are studied during development, patients with a Child-Pugh classification C, i.e., with severe hepatic disease, are not included. However, the practical and ethical problems associated with giving investigational drugs that have no potential to confer benefits to patients with severe liver disease merit careful consideration. 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. It is assumed that the drug is mostly eliminated by hepatic mechanisms (metabolism, biliary excretion) (Hebert, 1998).

1. Drugs with a relatively high hepatic extraction ratio:
The oral bioavailability of these drugs can be drastically increased in patients with chronic liver disease, and the dosage should be reduced accordingly. Systemic administration (iv, im, sc, etc.), the plasma clearance may be reduced if hepatic blood flow is decreased.

2. Drugs with a low hepatic extraction and high plasma protein binding (>90%):
The oral and intravenous clearance of these drugs is determined by the intrinsic capacity of the hepatic elimination mechanisms and the unbound drug fraction in blood or plasma. The intrinsic clearance will be reduced to a degree determined by the functional status of the liver and the specific metabolic pathway(s) involved in the elimination of the drug. Because the unbound fraction of drug in blood or plasma may be significantly increased in patients with chronic liver disease, pharmacokinetic evaluation should be based on unbound blood/plasma concentrations, and dosage adjustment may be necessary even though total blood/plasma concentrations are within the normal range.

3. Drugs with a low hepatic extraction ratio and low plasma protein binding (<90%):
The oral and intravenous clearance of these drugs is determined by the intrinsic capacity of the hepatic elimination mechanisms and the unbound drug fraction in blood or plasma. The intrinsic clearance will be reduced to a degree determined by the functional status of the liver and the specific metabolic pathway(s) involved in the elimination of the drug.

4. The elimination of drugs that are partly excreted in unchanged form by the kidneys will be impaired in patients with the hepato-renal syndrome. It should be taken into account that creatinine clearance significantly overestimates the glomerular filtration rate in these patients.

5. The volume of distribution of hydrophilic drugs may be increased in patients with chronic liver disease who have edema or ascites. As a consequence, the loading dose may have to be increased in these patients if a rapid and complete effect of the drug is required. Since many hydrophilic drugs are eliminated primarily in unchanged form by the kidneys, renal function should be taken into consideration.

6. Extreme caution is recommended when using drugs with a narrow therapeutic index in patients with liver disease and when administering any drug to patients with severe liver dysfunction (Child-Pugh class C).

Dose adaptation of opioid drugs in patients with liver disease

The findings of the research to date and attempts to give some practical advice. The choice of the most appropriate drug and dose, however, depends on the individual situation of the patient and the kind of pain to be treated (**Table 10**).

Dose adaptation of antineoplastic drugs in patients with liver disease

Antineoplastic drugs, there is a discrepancy between the general commendations of how drugs should be administered to patients with liver disease and the available kinetic data for these drugs. The most important these data should be available for all substances for gaps extraction and of kinetic studies for critical drugs in patients with impaired liver function (**Table 11**).

PPIs dose adjustment in patients with advanced liver disease

The pharmacokinetics of omeprazole,lansoprazole, and rabeprazoleare ex- tensively altered in patients with moder- ate hepatic impairment; little information is available on their pharmacokinetics in patients with severe hepatic impairment (Geraldine et al., 2001) (**Table 13**).

Final concideractions

Drugs must be given with caution to patients with severe hepatic insufficiency, especially who have liver cirrhosis. Before administering drugs that are largely eliminated by hepatic mechanisms, their potential therapeutic benefits must be carefully counterbalanced with the risk of serious toxic reactions. This is especially true for drugs with a narrow therapeutic index and for sedatives, central analgesics, and anxiolytics, which may precipitate and cause hepatic encephalopathy. If these drugs are needed by the cirrhotic patients, they should be started at a low dose which may subsequently be titrated to obtain the desired therapeutic effect. A guide to a drug dosage in hepatic disease describing the effect of (mostly) cirrhosis on the pharmacokinetic behavior of more than 100 drugs, including recommendations for dosage adjustment has been published by Hebert. It constitutes a valuable information base when selecting a drug and its proper dosage regimen for a hepatic malfunction patient. In addition, more recent review articles have described the effect of liver disease on the pharmacokinetics of drugs, some of which focused on specific drug classes, such as opioids, cardiovascular drugs, antiretroviral agents, and antineoplastic drugs. For the safe use of antineoplastic drugs in patients with liver disease, the authors of the review article conclude that not enough data are available in the databases. They recommend that pharmaceutical companies should provide pharmacokinetic data in patients with impaired liver function, especially for drugs that are primarily eliminated by metabolism, to allow quantitative advice for dose adaptation.

Conflict of interest

None declared.

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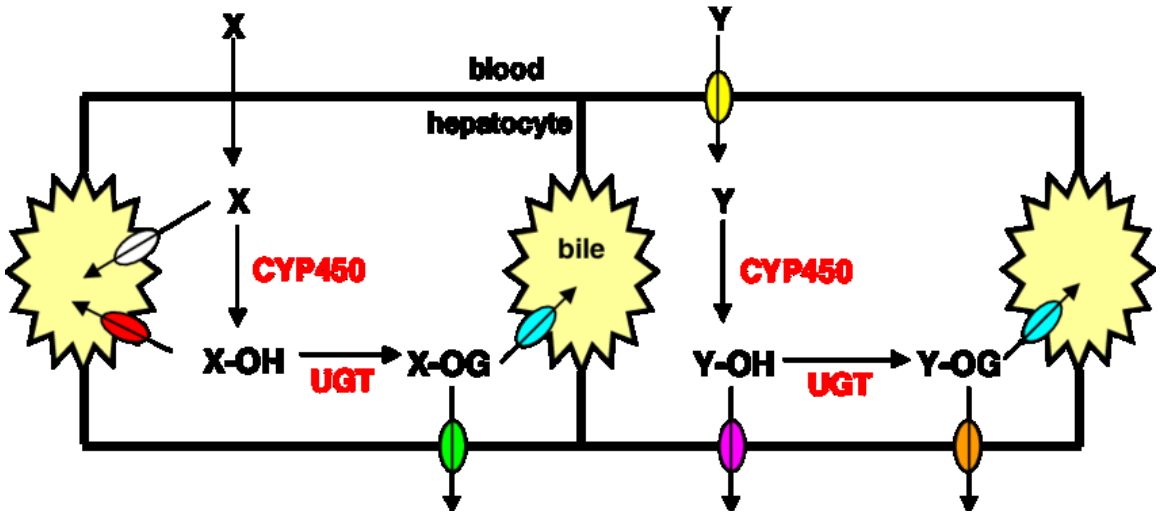

Figure 1. Schematic diagram showing two adjacent hepatocytes and bile canaliculi. [Hepatic uptake of drugs is mediated by SLC-type transporters (e.g., OATPs, OATs, OCTs, NTCP) in the basolateral (sinusoidal) membrane of hepatocytes. ABC transporters such as MRP2, MDR1, BCRP, BSEP, and MDR2 in the bile canalicular membrane of hepatocytes mediate the efflux (excretion) of drugs and their metabolites against a steep concentration gradient from hepatocyte to bile. Some ABC transporters are also present in the basolateral membrane of hepatocytes and play a role in the efflux of drugs and their metabolites back into the blood.]

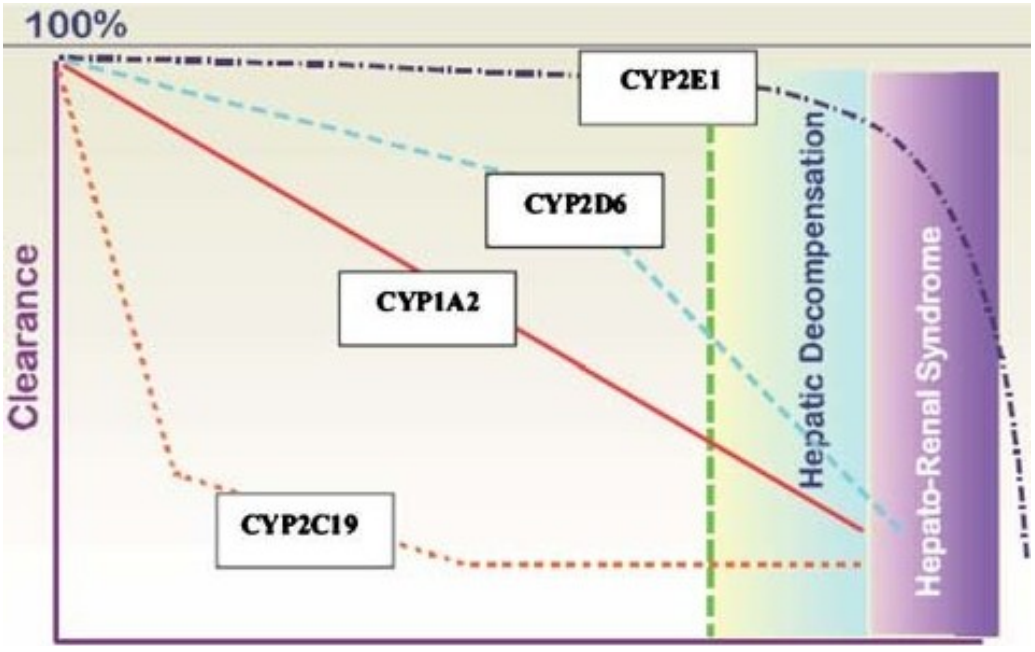

Figure 2. Sequential progressive model of hepatic dysfunction. [The ordinate shows how plasma clearance, starting at 100% when hepatic function is normal (normal HF), decreases for substances eliminated predominantly by metabolism via individual CYP450 isoforms in the liver. CYP450 enzyme activity in general decreases as liver function decreases. However, some CYP450 isoform enzyme activities show relative preservation as liver function deteriorates (e.g., CYP2E1 and to a lesser extent CYP2D6), whereas others (e.g., CYP2C19) are particularly sensitive to the presence of liver disease. In general, patients with hepatic decompensation suffer from the hepato-renal syndrome. (Reprinted with permission from the American Society for Clinical Pharmacology and Therapeutics from Frye et al. (2006).]

Table 1. Consideration of dosing patient with hepatic impairment (Shargel et al., 2012)

Parameters	Remarks
Nature and severity of liver disease	Not all liver diseases affect the pharmacokinetics of the drugs to the same extent.
Drug elimination	Drug eliminated by liver >20% are less likely to be affected by liver disease. Drugs that are eliminated mainly *via* renal route will be least affected by liver disease.
Route of drug administration	Oral drug bioavailability may be increased by liver disease due to decreased first pass effects.
Protein binding	Drug protein binding may be altered due to alteration in hepatic synthesis of albumin.
Hepatic blood flow	Drug with flow dependent hepatic clearance will be more affected by change in hepatic bold flow
Intrinsic clearance	Metabolism of drugs with high intrinsic clearance may be impaired
Biliary obstruction	Biliary excretion of some drugs and metabolites, particularly glucuronide metabolites
Pharmacodynamics changes	Tissue sensitivity to drug may be altered
Therapeutic range	Drugs with a wide therapeutic range will be less affected by moderate hepatic.

Table 2. Child-Pugh classification of the severity of liver disease (Trey et al., 1966)

Parameters	Points		
	1	2	3
Serum bilirubin (mg/dL)	<2	2–3	>3
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (s > control)	<4	4–6	>6
Encephalopathy (grade)	None	Grade 1 or 2	Grade 3 or 4
Ascites	Absent	Slight	Moderate
	<1.8	1.8- 2.3	>2.3

Table 3. Severity of Child-Turcotte classification schemes for liver disease (Brouwer et al., 1992)

	Grade A	Grade B	Grade C
Bilirubin(mg/dl)	<2.0	2.0-3.0	>3.0
Albumin (g/dl)	>3.5	3.0-3.5	<3.0
Ascites	None	Easily controlled	Poorly controlled
Neurological Disorder	None	Minimal	Advance
Nutrition	Excellent	Good	Poor

Table 4. Oral bioavailability is substantially increased in cirrhosis for drugs with a moderate to high hepatic extraction ratio

Drugs	Normal	Cirrhosis	Fold increase	References
Propranolol	0.36	0.60	1.7	Branch et al., 1977
Labetalol	0.33	0.63	1.0	Homeida et al.,1978
Meperidine	0.48	0.87	1.8	Neal et al.,1979
Pentazocine	0.18	0.68	3.8	
Chlormethiazole	0.10	1.16	11.6	Pentikäinen et al.,1980
Metoprolol	0.50	0.84	1.7	Regårdh et al., 1981
Verapamil	0.10	0.16	1.6	Somogyi et al., 1981
Nifedipine	0.51	0.91	1.8	Kleinbloesem et al., 1986
Carvedilol	0.19	0.83	4.4	Neugebauer et al., 1988
Nisoldipine	0.04	0.15	3.8	van Harten et al.,1988
Midazolam	0.38	0.76	2.0	Pentikäinen et al.,1989
Morphine	0.47	1.01	201	Hasselström et al.,1990

Table 5. Percentage survival in cirrhotic liver disease

Child-Pugh grade	Child-Pugh Score	Indication	1 Year Survival	5 year Survival	10 year Survival
A	5-6	Indicates a well-functioning liver	84 %	44 %	27 %
B	7-9	Indicates significant functional compromise	62 %	20 %	10 %
C	10-15	Indicates decompensation of the liver	42 %	21 %	0 %

Table 6. Medications requiring dosing adjustments based on Child–Pugh scores
(Figg et al., 1995; Kochaneket al., 2004; Lethbridge-Cejkuet al., 2005; FDA 2006; FDA 2007)

Drug and Manufacturer	Mild Disease (Score, 5 or 6)	Moderate Disease (Score, 7–9)	Severe Disease (Score, 10–15)
Anagrelide (Leukemia)	. . .	Start with 0.5 mg/day	No data, use with caution
Atomoxetine ADHD	. . .	Decrease to 50% of normal dose	Decrease to 25% of normal dose
Darifenacin Antimuscarinic)	. . .	Do not exceed 7.5 mg once daily . . .	Not recommended Start with 1 mg
Eszopiclone(sedative Hyp)	. . .	Do not exceed 16 mg	Not recommended
Galantamine	. . .	. . .	Do not exceed 8 mg/day
Ondansetron	. . .	Start with 5 mg twice daily and increase as tolerated	Not recommended
Pilocarpine	. . .	. . .	Not recommended
Sildenafil	Start with 25 mg	Do not exceed 5 mg	Not recommended
Solifenacin	. . .	Starting dose of 5 mg, maximum 10 mg	Not recommended
Vardenafil	. .	Reduce dose by 50%	Reduce dose by at least 50%, may need further reduction
Venlafaxine	. . .		

Table 7. Medications of cardiovascular drugs is requiring dosing adjustments based on Child–Pugh scores (Sokol et al., 2000)

Drug and Manufacturer	Mild Disease (Score, 5 or 6)	Moderate Disease (Score, 7–9)	Severe Disease (Score, 10–15)
Antiplatelets**(Clopidogrel)**	Not recommended	Not recommended	Caution needed
Thrombolytic **(Alteplase)**	Adjustment require	Adjustment require	Adjustment require
Inotropic Agents **(Digitoxin)**	Dose should be reduced	….	….
Centrally Acting Antihypertensives	Dose should be reduced	….	…..
Diuretics **(frusemide)**	No dose adjustment require		
Vasodilator **(nitroglycerin)**	Lower dose is require	Not recommended	…..
Fanoldopan	Not recommended	a low dose of 2.5 mg is recommended	…….
Alpha-Adrenergic Agonist **Midodrine**	…	dose reduction needed	not altered
Alpha-Adrenergic Blockers **Prazosin**	….	dose reduction needed	…….
Terazosin	….	dose decreased	dose reduction needed
Calcium channel blockers	….	no dose adjustment	dose reduction needed
Beta-Adrenergic Blockers	….	lower dose needed	…
Angiotensin II Receptor Antagonist		….	Drug should be administered caution
Angiotensin-Converting Enzyme (ACE) Inhibitors	…..	Lower initial dose	….
	….	Initiate with lower do	….

Table 8. Effect of liver cirrhosis on the elimination of **antiarrhythmic** drugs, and suggested reductions in dosage (Ulrich Klot, 2007)

Drugs	Effect on t1/2	Effect on CL	Estimated dosage reduction
Amiodarone	ND	ND	No recommendation
Carvedilol	↑	↓	By a factor of 4–5
Diltiazem	↑	(↓)	Probably by a factor of 2 (limited data)
Disopyramide	ND	↓	Probably 25% (limited data)
Flecainide	↑	↓	60%
Lidocaine	↑	↓	By a factor of 2–3
Metoprolol	↑	↓	By a factor of 2–3
Mexiletine	↑	↓	70%
Procainamide	ND	(↓)	Probably no reduction (limited data)
Propafenone	↑	↓	By a factor of 2–3
Quinidine	↑	↔	Probably no reduction (limited data)
Sotalol	↔	↔	Probably no reduction
Verapamil	↑	↓	By a factor of 2

CL = clearance; ND = no data; t1/2 = elimination half-life; ↑ indicates increase; ↓ indicates decrease; ↔ indicates no change.

Table 9. Antiretroviral dose recommendation in patients with hepatic dysfunction (Figg et al., 1995; Kochanek et al., 2004; Lethbridge-Cejku et al., 2005; Panel et al., 2006; FDA, 2006, 2007)

Antiretroviral (trade name)	Normal dosage	Dosing recommendations in hepatic impairment
Abacavir		Child-pugh score 7-9 200mg bid Child –Pugh score>9 Not recommendation
Amprenavir (Agenerase) oral solution	1400mg PO bid	Child-pugh score 7-9 450mg bid Child –Pugh score>9 300mg bid
Atazanavir (Reyataz)	400mg PO (treatment –naive patients only) 300mg + rotonavir 100mg PO	Child-pugh score 7-9 300mg Child –Pugh score>9 Not recommendation
Darunavir (Prezista)	Darunavir 600mg + ritonavir 100mg PO bid	No dosage recommendation; use with caution
Fosamprenavir (Lexiva)	700mg +ritonavir 100mg PO bid 1400mg PO bid 1400mg + ritonavir 200mg PO (treatment –naive patients only)	Child –Pugh score 5-6: 700mg bid or 700mg bid + ritonavir 100mg Child-Pugh score 7-9: 700mg bid or 450mg bid + ritonavir 100mg Child-Pugh score 10-12 350mg
Indinavir (Crixivan)	800mg PO q^{8h}	Mild to moderate hepatic insufficiency because of cirrhosis:600mg q^{8h}
Nelfinavir (viracept)	1250mg PO bid	Use with caution
Ritonavir(Norvir)	600mg PO bid or 100mg PO for pharmacokinetic enhancement with another PI	Mild hepatic impairment :no dosage adjustment Moderate to severe impairment: no data :use with caution

bid = twice daily; od = once daily; PO = orally; q8h = every 8 hours; tid = three times daily.

Table 10. Recommendation dose for prescribing in patient with hepatic insufficiency (Irmgard et al.,1999)

Drug	Problem in liver disease	Suggested action
Alfentanil	Reduced protein binding,CL decreased by 50% & $t_{1/2\beta}$ is prolonged.	Reduce dose in patient with severe liver damage.
Codeine	O-Demethylation, form morphine,reduce the active compound	Do not use for analgesia
Dextroprppoxyphene	Increase the F of oral dextroprpopoxyphene.	Avoide in patient with liver disease .
Fentanyl	Pharmacokinetics of a single intravenous dose remain unaltered	Normal single dose can be used .But with continuous administration recovery time after termination of the infusion may be prolonged .
Methadone	Prolongation of $t_{1/2\beta}$ & increase of Vd in patient with sever hepatic dysfunction. Chronic alcohol abuse may increase methadone metabolism.	Normal dose can be used in mild to moderate liver diseases. In severe liver dysfunction accumulation may occur.
Morphine	Reduced hepatic glucuronidation lead to an increase in oral F, decrease CL & prolonged $t_{1/2\beta.}$	Use with care in patient with severe liver cirrhosis & reduced the oral dose.
Remifentanil	Pharmacokinetics altered	Normal dose can be used .
Sufentanil	Pharmacokinetic altered & reduced protein binding with alkalosis associated with an increased Vd& $t_{1/2\ \beta}$.	Normal dose can be used . Use with care when plasma pH is elevated .
Tramadol	Reduced generation of the main metabolic O-demethyl-tramadol,that appears to be responsible to some of the analgesic action .$t_{1/2\beta}$ of tramadol & O-demethyl-tramadol approximately doubled .	Prefer alternative analgesic until analgesic activity of tramadol in patient with liver diseases is confirmed.

CL = clearance .F = oral bioavailability, $t_{1/2\beta}$ = terminal elimination half life .Vd = volume of distribution

Table 11. Dose adjustment recommendations for the use of antineoplastic drugs with in patients with liver disease

Drugs	Dose dependent adverse reaction	Dose adjustment recommendation	Ref erences
Amsacrine	Myelosuppression, cardiotoxicity (arrhythmia), hypotonia, nausea, vomiting, alopecia,	Recommendation: 50% dose reduction if serum bilirubin level >34 µmol/L. Dose reduction (70% of normal dose) in patients with severe liver disease.	Morant et al.,2004 and Koren et al .,2002
Bicalutamide	Blocked androgenic action (hot flushes,breast tenderness, diarrhea gynaecomastia	Recommendations: stop treatment if levels transaminase >3 × ULN or in patients, reduced libido with hyperbilirubinaemia	Morant et al., 2004
Dactinomycin	Myelosuppression, nausea and steatosis, vomiting, diarrhoea, mucositis,	Recommendation: 50% dose reduction in patients with hyperbilirubinaemia. Increase gradually while monitoring dose-dependent toxicity	Dollery et al.,1999
Imatinib	hepatocellular injury myalgia, fatigue	Recommendations: stop treatment if serum bilirubin level >3 × ULN or transaminase levels 5× ULN	Morant et al., 2004
Letrozole	Unknown	Dose : severe condition 2.5 mg every other day	Kochaneket al., 2004

Table 12. Antibiotic dose adjustment in patients with advanced liver disease

Drug and Manufacturer	Mild Disease (Score, 5 or 6)	Moderate Disease (Score, 7–9)	Severe Disease (Score, 10–15)	References
Linezolid (LNZ)	…	…	PK data are not available	Esposito et al., 2008; Steenbergen et al., 2009; Carpenteret al., 2011
Daptomycin (DAP)	…	…	Caution is advised	Carpenter et al.,2004; Steenbergen et al., 2005
Ofloxacin	…	…	Maximum of 400 mg/day	Figg et al., 1995; Kochanek et al., 2004; Lethbridge-Cejku et al.,2005; FDA, 2006, 2007
Tygecycline (TGC)	…	…	25 mg every 12 h.	Mazzei et al.,2008; Falagas et al., 2009
Rimantadine	…	…	100 mg/day	Figg et al., 1995; Kochanek et al., 2004; Lethbridge-Cejku et al.,2005; FDA, 2006, 2007
Caspofugin	…	Oropharyngeal candidiasis: 35 mg/day Invasive aspergillosis: 70-mg loading dose, then 35 mg/ day maintenance dose	…	
Sirulimus	Reduce dose by 1/3	Reduce dose by 1/3	Reduce dose by 1/3	
Voriconazole	Start with 1/2 maintenance dose	Reduce maintenance dose by 1/2	Not recommendation	

Table 13. PPIs dose adjustment in patients with advanced liver disease

Drug and Manufacturer	Mild Disease (Score, 5 or 6)	Moderate Disease (Score, 7–9)	Severe Disease (Score, 10–15)	References
Pantoprazole	Not require	Not require	Unknown	Huber et al., 1996
Esomeprazole	Not require	Not require	Maximum of 20 mg /day	Lethbridge-Cejku et al., 2005