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ORIGINAL PAPER

Drug dosage recommendations in patients with chronic liver disease

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ABSTRACT

Chronic liver diseases (CLD) alter the kinetics of drugs. Despite dosage adjustment is based on Child-Pugh scores, there are no available recommendations and/or algorithms of reference to facilitate dosage regimens.

A literature review about dose adjustment of the drugs from the hospital guide –which are included in the list of the WHO recommended drugs to be avoided or used with caution in patients with liver disease– was carried out. The therapeutic novelties from the last few years were also included. In order to do so, the summary of product characteristics (SPC), the database DrugDex-Micromedex, the WHO recommendations and the review articles from the last 10 years in Medline were reviewed. Moreover, the kinetic parameters of each drug were calculated with the aim of establishing a theoretical recommendation based on the proposal of Delcò and Huet.

Recommendations for 186 drugs are presented according to the SPC (49.5%), DrugDex-Micromedex (26.3%) and WHO (18.8%) indications; six recommendations were based on specific publications; the theoretical recommendation based on pharmacokinetic parameters was proposed in four drugs.

The final recommendations for clinical management were: dosage modification (26.9%), hepatic/analytical monitoring of the patient (8.6%), contraindication (18.8%), use with caution (19.3%) and no adjustment required (26.3%).

In this review, specific recommendations for the practical management of patients with chronic liver disease are presented. It has been elaborated through a synthesis of the published bibliography and completed by following a theoretical methodology.

Key words: Liver disease. Liver dysfunction. Prescription drugs. Hepatic impairment. Dose-response relationship.

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INTRODUCTION

The liver plays a fundamental role in the metabolism of most drugs because hepatic and biliary excretion processes determine the rate of their elimination from the body, while bioavailability is affected by first-pass mechanisms.

Alterations affecting the kinetics of drugs in chronic liver disease (CLD) are mainly due to three mechanisms: reduction of portal blood flow which affects the pre-systemic elimination of high extraction drugs; decreased synthesis of transport proteins, mainly albumin and alpha-glycoprotein, which affect the bioavailability of drugs highly bound to plasma proteins; reduced drug-metabolizing hepatic enzymes, which affects the amount of plasma active metabolite, thus, the effectiveness and toxicity (1).

Chronic liver disease is assessed through Child-Pugh score system which is based on five variables: the presence of ascites and encephalopathy, plasma concentrations of bilirubin and albumin and prothrombin time. The Child-Pugh score indicates the level of chronic hepatic damage: score 5-6 is class A (mild); 7-9 corresponds to class B (moderate); and 10-15 is class C (severe) (2,3).

Another classification scheme such as MELD (Model for End stage Liver Disease) is based on serum bilirubin concentration, serum creatinine, the international normalized ratio (INR) of prothrombin time, and the underlying cause of liver disease (4). The MELD score was designed to predict 3-month mortality among patients on a liver-transplant waiting list and has been adopted to use for allocating priorities in patients awaiting liver transplantation (5). However, unlike in renal patients, where estimates of glomerular filtration rate (creatinine clearance,

inulin clearance) correlate with kinetic parameters of drug elimination such as renal clearance, these classification schemes lack the sensitivity to quantitate the specific ability of the liver to metabolize individual drugs. That is why it is not a frequently used classification scheme for pharmacological adjustment.

The recommendations for drug dosage adjustment in patients with CLD are based on Child-Pugh scores. Since 2003 and 2005 respectively, the regulating agencies Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require the performance of kinetic studies previous to the authorization of new drugs in patients with CLD in order to provide future dose adjustment recommendations (6,7). This information reflected in the summary of product characteristics (SPC) is highly useful. However, a great amount of drugs lack of this specific information because patients recruited in clinical trials show a good hepatic function (Child-Pug class A) and do not have an advanced liver dysfunction (Child-Pugh class C).

The complexity of hepatic metabolism has limited the development of tools allowing predictions of drug behavior in patients with chronic liver disease. Unlike in renal insufficiency, there are no guidelines and algorithms of reference to facilitate drug dosage in these patients. In this context, there is a growing need to check and expand the available information in the SPC. The review of recommendations from other sources and the application of calculation procedures based on the kinetic parameters of the drug are needed to establish practical dose recommendations in CLD for the frequently used drugs in the care environment.

The aim of this article is to provide dose adjustment recommendations for the most commonly used drugs in the hospital in patients with chronic liver disease.

MATERIALS AND METHODS

Drugs were selected from the list of medicines WHO recommends to avoid or to use with caution in patients with liver disease (8), selecting those included in the hospital Pharmacotherapeutic Guide (PG). The therapeutic novelties from over the last few years were also included.

A literature review about dosage recommendations in chronic liver disease was carried out for the selected drugs from the following sources: a) SPC; b) DrugDex Micromedex (9); c) WHO recommendations (8); and d) review articles published in the last 10 years in the Medline database with the following search strategy: "Hepatic"[Ti] OR "liver"[Ti]) AND ("Dose-Response Relationship, Drug"[Mesh]) AND (Review[ptyp] AND (English[lang] OR Spanish[lang]) AND "2001/02/27"[PDat]: "2011/02/24"[PDat]). The following search engines were used: "Scholar-google" and "Alquimia" (10) with the aim of finding bulletins published by centers of reference which include drug dosage recommendations in chronic liver disease.

Table I. Categorization and dose recommendation in IH patients. Categorization based on Huet et al. (11) and Krähenbühl et al. (12). Recommendation for initial dose adjustment and maintenance adapted from Delcò et al. (1)

Category	*E_H*	*F*	*PB*	*General recommendation*
1	High (≥ 60%)	≤ 40%	Any	Reduction Id and Md by: dose reduction = (Nd x F)/100
2	Intermediate (30 - 60%)	40-70%	Any	Id: start in the low range of normal Md: should be adjusted as described in low E_H and low PB
3	Low (≤ 30%)	≥ 70%	≥ 90% < 90%	Drug monitoring Md: CP A: 50% of Nd CP B: 25% of Nd CP C: drug monitoring
4	Unknown			

Id: initial dose. Md: maintenance dose. Nd: normal dose without liver disease. EH: hepatic extraction ratio. F: bioavailability. BP: fraction bounds to proteins. CP: Child-Pugh index.

The final dosage recommendations have been based on the SPC information and on the rest of the bibliography defined in the search strategy. In case they were not coincident, the most restrictive proposal was taken.

When no information was found, the adjustment recommendations were given according to the process defined by Delcò et al. (1), based on the method established by Huet et al. (11) and Krähenbühl et al. (12). This method classifies each drug according to three parameters: hepatic extraction ratio (E_H) –classified in 3 categories (high ≥ 60%, intermediate 30-60% and low ≤ 30%), bioavailability (F) and plasma protein binding (PB) (Table I). For the drugs with no E_H available information, E_H was calculated using the formula defined by Westphal et al. (11): $[E_H = (Q_0 \times CL_{syst})/Q_H]$. Q_0 values (extra renal drug moiety) and CL_{syst} (systemic or total clearance) were obtained from the literature, assuming a hepatic blood flow (Q_H) of 1.5 L/min.

In order to have supplementary information to the bibliography, the following parameters were registered for all drugs: E_H, bioavailability, plasma protein binding and the corresponding category according to the Huet classification (11).

RESULTS

The information of 191 drugs was reviewed: 56 of oncology therapy, 84 anti-infective agents [antibiotics

(35), anti-tuberculosis drugs (5), antifungal (15) and antiretroviral agents (29)], 13 of cardiovascular therapy and 38 of other pharmacological groups.

The final recommendation was established for 186 reviewed drugs and was defined according to the SPC in 92 (49.5%), 49 in DrugDex Micromedex (26.3%) and 35 in WHO (18.8%); the recommendations of 6 drugs (3.2%) were based on the publications of Azanza et al. (14), for the group of antimicrobials. In four drugs (2.2%) (dacarbazine, leuprorelin, maraviroc and zidovudine) no information in the previously mentioned databases was found nor in further bibliography searches. That is why a theoretical adjustment recommendation based on the proposal defined by Delcò et al. (1) and Huet et al. (11) was given. In five drugs (buserelin, dactinomycin, enfuvirtide, megestrol and trastuzumab) no information was found about dosage adjustment due to lack of data.

Depending on the type of recommendation the following was obtained: 48 drugs (25.8%) needed quantitative adjustment; 88 drugs (47.3%) had to follow qualitative recommendations divided into: 37 caution of use, 16 monitoring the patient and 35 contraindication; and 50 drugs (26.9%) did not require dosage adjustment, being 72% of them of low E_H (< 0.3).

Regarding the reviewed drugs, the established classification by Huet et al. (11) was the following respectively: 19 (10.2%) class 1; 28 (15.1%) class 2; 77 (41.4%) class 3 and 62 (33.3%) class 4.

From the 191 reviewed drugs, E_H was calculated with the Westphal et al. formula (13) in 103 drugs (53.9%); in 66 drugs (34.6%) it was not obtained due to lack of data; in 22 drugs (11.5%) E_H was obtained through the bibliography.

Some other registered parameters to justify dosage adjustment were: PB ≥ 90% in 66 drugs (34.6%), < 90% in 102 drugs (53.4%) and no data was obtained in 23 drugs (12.0%). The hepatic/biliary metabolism predominance with a score of $Q_0 > 0.4$ was found in 65 drugs (34.0%), it was less than 0.4 in 35 drugs (18.3%) and it could not be obtained in 91 (47.6%), which indicates that most of the drugs in which Q_0 was obtained are highly metabolized and/or are excreted through bile.

The dosage adjustment recommendation is shown in table II, it indicates the final recommendation in drugs requiring adjustment in chronic liver disease, drugs in which hepatic or analytic monitorization is recommended, contraindicated drugs in chronic liver disease, drugs used with caution and drugs not requiring adjustment in chronic liver disease. The category Huet and Krähenbühl and the E_H of every drug is also found in table II.

DISCUSSION

In this review, a dosage adjustment for 186 frequently used drugs in hospitals in patients with chronic liver disease is proposed.

There is not an established method available to assess hepatic failure which correlates with the hepatic clearance of drugs. Besides, the semiquantitive scale of Child-Pugh is not precise and it does not always quantify the specific capacity of the liver to metabolize different drugs. Drug adjustment to the hepatic function of the patient by using the Child-Pugh score has limitations because it was initially designed to stratify the risk of anastomosis or portocaval shunt in cirrhotic patients. However, it has been demonstrated that the Child-Pugh score shows also some relation with survival and with the development of complications in cirrhosis. The Child-Pugh score requires quantification of subjective variables such as ascites and encephalopathy, which vary among different observers and can be modified by medical interventions such as the lactulose and/or diuretics prescription in encephalopathy and ascites.

The Child-Pugh score is mostly used in the review articles which include drug dosage recommendations in patients with chronic liver disease through the application of an explicit methodological procedure (8,15-19). The bulletin written by Shapiro (20) compared the Child-Pugh scores with the Cockcroft-Gault equation used in the adjustment for renal insufficiency. In some studies, the adjustment based on the E_H with supplementary information such as plasma protein binding, hepatic cytochrome metabolism or transaminases among others (1,17,19) is proposed. However, general recommendations are proposed for most of the drugs.

To define the drugs that have to be adjusted in patients with chronic liver disease, the main parameter proposed by different authors is E_H. Kim et al. (21) proposes to establish three categories to adjust drugs depending on E_H in the hepatic first-pass effect, being those of high extraction the adjusted ones.

The recommendations of the Drug Information Service (22) propose that in the case of a severe liver dysfunction (albumin < 30 g/dL, INR > 1.2), drugs with a high E_H are still the ones which should have a higher adjustment despite it includes the possibility of dose reduction in the low extraction ones. Accordingly, Shlatter et al. (16) agree in the dosage recommendations based on E_H and/or pharmacological bioavailability, justifying adjustments of initial doses and maintenance.

The established recommendations about the possible dose adjustment in patients with hepatic insufficiency by Verbeeck et al. (19) are very similar to the ones by Delcò et al. (1) and Klotz (23). Both characterize the drugs depending on the hepatic extraction rate, plasma protein binding and their hydrophilicity. The difference with the previous authors is that the latest propose an initial and maintenance dose adjustment (1,19) of the drugs with a low level of extraction and a narrow therapeutic range. Pirmohamed (17) proposes to select those with a wide therapeutic range to ensure a lower hepatotoxicity. Some other authors such as Sloss et al. (18) establish the avoidance of use or the increase of administration intervals in

Table II. Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	E_H	*Metabolism*	Q_0	*PB (%)*	*Recommendation*
Abacavir* Prod Info Ziagen, 2008 (27)	1	> 0.6	Dehydrogenation and glucuronidation	0.9	50	Child-Pugh index 5-6: 200 mg/12 h Child-Pugh index ≥ 7 not recommended
Acetaminophen Prod Info Gelocatil, 2010 (27)	3	< 0.3	Extensive liver metabolism: glucuronidation and conjugation		10.0-30.0	Not exceed 2 g/24 h
Acetylsalicylic acid (9)	4	Not known	Hydroxylation and *glucuronidation*	0.65-0.94	50-80	Avoid Child-Pugh C index
Acyclovir* Prod Info Aciclovir Bexal, 1999 (27)	3	0.05	Inactive metabolite (9-carboxymethoxymethylguanine)	0.1-0.38	9.0-33	No adjustment required
Aldesleukin Prod Info Proleukin, 1999 (27)	4	Not known	–	–	–	Monitor liver function Contraindicated Child-Pugh C index
Allopurinol (8)	1	0.7	Oxidation (active metabolite) and allopurinol ribose	–	–	Dose reduction 50%
Amphotericin B Lipid Complex* (9)	2	0.31	–	0.9	–	In a HIV study in patients with cryptococcal meningitis was reduced to 50% in patients with significant hyperbilirubinemia (4 or 6 times the normal level) or elevation of transaminases (7 or 9 times the normal level)
Amphotericin B Liposome* (9)	3	0.012	–	0.9		No adjustment required
Amikacin (9)	4	Not known	–	0.02-0.1	4.0-11	Calculated based on total weight in ascitic patients. Determine and monitor the drug level nephrotoxicity
Amitriptyline* (9)	2	0.57	Hydroxylation (CYP2D6), Ndemethylation (CYP3A4 to nortriptyline), conjugation	1	95	Starting at 50% of normal dose and maintenance dose adjusted according to clinical effect and adverse effects
Amlodipine* Prod Info Astudal, 1992 (27)	3	0.083	Extensive liver metabolism: Oxidation	0.3	93-98	Precaution
Amoxicillin* Prod Info Clamoxyl, 2006 (27)	3	0.034	Partial liver metabolism	0.4	15-25	Monitor liver function
Amoxicillin/Clavulanic Acid Prod Info Augmentine, 2010 (27)	4	Not known	Partial liver metabolism	0.3-0.5	18-25	Monitor liver function (cholestatic jaundice)

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	*E_H*	*Metabolism*	*Q_0*	*PB (%)*	*Recommendation*
Ampicillin* Prod Info Ampilevel, 1999 (27)	3	0.037	–	0.2	17-20	Precaution
Ampicillin/sulbactam (9)	4	Not known	–	0.3	17	Precaution
Anastrazole Prod Info Arimidex, 2010 (27)	4	Not known	N-dealkylation, hydroxylation (CYP), glucuronidation	0.95	45	No adjustment required
Anidulafungin* Prod Info Ecalta, 2007 (27)	3	0.003	Not undergo hepatic metabolism	0.3	99	No adjustment required
Artemether/ Lumefantrine (8)	4	Not known	Artemether: CYP450 (CYP3A4/5, CYP2B6, CYP2C9, CYP2C19). Dihydroartemisinin (DHA), an active metabolite Lumefantrine: CYP450 (CYP3A4, CYP2D6)		95-99	Precaution in Child Pugh C index
Atazanavir Prod Info Reyataz, 2009 (27)	4	Not known	Extensive liver metabolism: CYP3A4. Metabolites are eliminated by the bile in free metabolites or glucuronidation The metabolic minor additional routes consist of N-desalquilation and hydrolysis. Metabolites lack antiviral activity	0.8	86	Not use in moderate to severe HI
Atripla® Prod Info Atripla, 2007 (27)	4	Not known	Efavirenz: cytochrome P450 (P450CYP3A4 and P450CYP2B6) Emtricitabina: Liver metabolism (13%) Tenofovir: none to negligible	0.6-8 (E); 0.14 (EM); 0.2-0.3 (T)	99.5-99.75 (E); 4 (EM); 0.7 (T)	Contraindicated Child-Pugh C index
Azathioprine Prod Info Imurel, 2007 (27)	2	0.4	Oxidation		30	Precaution
Azithromycin* Prod Info Zitromax, 1999 (27)	1	> 1	Liver metabolism around 35%	0.88-0.95	7.0-50	No adjustment required
Aztreonam (9)	4	Not known	Hydrolysis	0.3-0.4	56	No adjustment required
Bicalutamide* (9)	2	0.34	Oxidation (CYP), glucuronidation	1	98	Monitor liver function. If transaminases three times normal or bilirubin value is recommended to avoid treatment
Bleomycin* (9)	3	0.04	Hydrolysis	0.7		No adjustment required

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	E_H	*Metabolism*	Q_0	*PB (%)*	*Recommendation*
Bupivacaine* (8)	2	0.31	Glucuronidation	0.9	95	Avoid Child-Pugh C index
Buserelin	3	Not known	–			Not calculable
Busulfan* Prod Info Busilvex, 2008 (27)	3	0.21	Oxidation, sulfation	1	30	Precaution
Capecitabine* Prod Info Xeloda, 2001 (27)	1	2.7	Carboxylesterase, cytidine desaminase, phosphorylation	0.97	54	No adjustment required
Carbamazepine* (9)	3	0.062	Epoxidation to active epoxide metabolite by CYP 3A4, glucuronidation, further metabolism of active metabolite by epoxide hydrolase	1	75	Avoid worsening or active liver disease
Carboplatin* Prod Info Carboplatino Teva, 2009 (27)	3	0.012	–	0.25	20	No adjustment required. If overdose occurs hepatotoxicity
Caspofungin* Prod Info Cancidas, 2009 (27)	3	0.004	N-acetylation and hydrolysis	0.59	97	Child-Pugh index = 7-9: 70 mg administered the first day, then 35 mg/24 recommends continuing Child-Pugh index ≥ 10: initial and maintenance dose 35 mg/24 h
Cefazolin* Prod Info Cefazolina normon, 2002 (27)	3	0.008	Minimal liver metabolism	0-0.4	80-86	No adjustment required
Cefditoren Prod Info Spectracef, 2010 (27)	4	Not known	Extensive liver metabolism	0.78-0.82	88	Precaution
Cefepime* Prod Info Maxipime, 1999 (27)	3	0.012	Partial liver metabolism. 85% is excreted as unchanged	0.01-0.3	16-20	No adjustment required
Cefotaxime (9)	4	Not known	Desacetyl	0.15-0.5	27-38	No adjustment required
Cefoxitin* (9)	3	0.025	Minimal liver metabolism (2%): descarbamyl, inactive metabolite	0.1-0.15	41-75	No adjustment required
Ceftazidime* Prod Info Fortaz, 2006 (27)	3	0.007	Not undergo hepatic metabolism	0.04-0.1	5.0-17	No adjustment required
Ceftriaxone* (9)	3	0.04	Minimal liver metabolism	0.33-0.67	83-96	No adjustment required

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	*E_H*	*Metabolism*	*Q_0*	*PB (%)*	*Recommendation*
Cefuroxime* Prod Info Zinnat, 2008 (27)	3	0.048	Nonspecific esterases	0-0.34	50	No adjustment required
Chlorambucil (8)	3	< 0.3	Extensive liver metabolism	1	99	Precaution
Ciprofloxacin Prod Info Baycip, 2010 (27)	2	0.4	Hepatic metabolism results in 4 metabolites have been identified as desetilenciprofloxacin, sulfociprofloxacin, and formylciprofloxacin oxociprofloxacin. The first three have an antibacterial activity comparable to or lower than nalidixic acid. The last is largely equivalent to norfloxacin in their antimicrobial activity	0.43-0.7	20-40	No adjustment required
Cisplatin* (9)	3	0.002	–	0.65	90	No adjustment required
Cladribine Prod Info Litak, 2009 (27)	4	Not known	–		25	Contraindicated
Clarithromycin* (9)	3	0.29	Hydroxylation	0.6-0.8	> 90	No adjustment required
Clindamycin (8)	3	< 0.3	Extensive liver metabolism: Actives metabolites (N-dimethyland sulfoxide)	0.32-0.95	60-95	Monitor liver function. In Child-Pugh C increase interval doses or decrease dosing
Clomipramine* (8)	2	0.5	Hydroxylation by CYP2D6, demethylation to active metabolite (N-Desmethylclomipramine) by CYP3A4, CYP2C19 and CYP 1A2, glucuronidation	1	98	Avoid Child-Pugh C index
Cloxacillin* (8)	3	0.035	Liver metabolism around 12%	0.3-0.6	94-95	Precaution
Codeine (8)	2	0.52	Extensive liver metabolism (24- 89%). Glucuronidation	0.1	0	Avoid Child-Pugh C index and cirrhosis, produces sedation
Combivir® Prod Info Combivir, 2009 (27)	4	Not known	Zidovudine: metabolized in the liver (60%), forming an inactive glucuronide conjugate antiviral Lamivudine: minimal liver metabolism (5-10%)	0.1 (Z); 0.3 (L)	< 36-38	Recommend drugs separately. Avoid if acute dysfunction
Cyclophosphamide* (8)	3	0.04	Hydroxylation (CYPs 2B6, 2C19, 2C9, 3A4)	0.9	15	If total bilirubin ≥ 3 mg/ml reduce dose by 25% Monitor liver function

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	E_H	*Metabolism*	Q_0	*PB (%)*	*Recommendation*
Cyclosporin Prod Info Sandimmun neoral, 2010 (27)	1	0.72	Cytochrome P-450: CYP3AI	0.9	90	Precaution. Determine drug level
Cytarabine* (9)	2	0.55	Cytidine deaminase	0.9	13	If total bilirubin > 2 mg/ml reduce dose by 50% Monitor liver function
Dacarbazine*	3	0.04	Extensive liver metabolism causing some metabolites with cytotoxic activity, being eliminated in the urine 18-63%	0.3	5	** Maintenance dose: CP A: 50% of normal dose CP B: 25% of normal dose CP C: drug monitoring
Dactinomycin	4	Not known	Biliar excretion: 50-90%	0.7		Not calculable
Daptomycin* Prod Info Cubicin, 2006 (27)	3	0.002	Studies in vitro found that daptomycin was not metabolized by human liver microsomes	0.2	90-95	Precaution in Child-Pugh C index
Darunavir Prod Info Prezista, 2010 (27)	4	Not known	Oxidation (CYP3A4)	0.79	95	Child-Pugh index < 10 No adjustment required Child-Pugh index >10 not recommended
Daunorubicin (9)	4	Not known	Mainly liver: formation of a metaboli te with cytotoxic activity (daunorubicinol), glucuronide, sulfate and aglycones	0.9		If total bilirubin > 1.5-3 reduce 25% If total bilirubin > 3 reduce 50%
Diazepam* (9)	3	0.02	Extensive liver metabolism: N-demethylation (CYP2C19), hydroxylation (CYP 3A4), glucuronidation Ndesmethyldiazepam, oxazepam and temazepam are active metabolites	1	98	Reduce dose to 50% or use lorazepam
Didanosine* Prod Info Videx, 2009 (27)	2	0.55	Via the same pathways responsible for the elimination of endogenous purines	0.82	5	No adjustment required
Docetaxel* (9)	2	0.43	Oxidation (CYP3A4). Biliar excretion: 75%	1	95	If transaminase > 1.5 normal value or alkaline phosphatase > 2.5 normal value to reduce the dose by 25% Do not administered if serum bilirubin increased or transaminase > 3.5 normal value or alkaline phosphatase > 6 normal value
Doripenem* Prod Info Doribax, 2008 (27)	3	0.05	Dehydropeptidase I, leading to an open ring inactive metabolite	0.3	8.1	No adjustment required

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	E_H	*Metabolism*	Q_0	*PB (%)*	*Recommendation*
Doxorubicin* Prod Info Doxorubicin Hydrochloride, 2003 (27)	1	0.73	Plasmatic and liver metabolism (doxorubicinol), sulfation, glucuronidation Biliar excretion: 50-80%	0.95	80	Reduced dose: Serum bilirubin (mg/dL) Dose reduction(%) 1.2 - 3.0 50 3.1 - 5.0 75
Doxycycline (8)	3	< 0.3	Liver metabolism around 50%	0.55-0.45	80-93	Precaution, if hepatotoxicity, assess other antibiotics
Efavirenz (8)	4	Not known	Hydroxylation (CYP 450) and glucuronidation	0.16-0.6	99.5-99.75	Precaution
Emtricitabine* Prod Info Emtriva, 2008 (27)	3	0.036	Minimal liver metabolism (13%): Oxidation and glucuronidation	0.14	4	No adjustment required
Enalapril (8)	4	Not known	Liver metabolism around 60% (active metabolite: enalprilate)	0.33	50-60	Precaution
Enfuvirtide	4	Not known	Hydrolysis		92	Not calculable
Epirubicin* Prod Info Epirubicina Accord, 2010 (27)	1	0.89	Reduction Biliar excretion: 40%	0.9	85	Reduced dose: Serum bilirubin (mg/dL) Dose reduction (%) 1.2-3.0 50 3.1-5.0 75
Ertapenem* Prod Info Invanz, 2007 (27)	3	0.004	Renal metabolism: Dehydropeptidase I	0.2	85-95	Adjustment not required unless renal failure is accompanied
Erythromycin (14)	2	0.38	Extensive liver metabolism: demethylation	0.85-0.97	75-90	Child-Pugh A index = 0,5 g/8 h Child-Pugh B index = 0,3 g/8 h Child-Pugh C index = 0,3 g/8 h
Estramustine Prod Info Estracyt, 2006 (27)	4	Not known	Hydroxylation and glucuronidation	0.9	99	Precaution
Ethambutol* (14)	3	0.002	Partial liver metabolism (15% inactive metabolites)	0.1-0.5	10.0-30.0	No adjustment required
Etoposide* (9)	3	0.02	Extensive liver metabolism: CYP3A4, glucuronidation and sulfation. Biliar excretion: < 10%.	0.65	95	If total bilirubin or AST 1.5-3 mg/dL ≥ 60-180 U/L reduced by 50%. Contraindicated in patients with decompensated liver disease (total bilirubin > 3.1 and AST > 180) Monitor liver function is recommended.
Etravirine Prod Info Intelence, 2009 (27)	4	Not known	Completely metabolized by oxidation reactions in the liver by CYP3A4 and to a lesser extent by CYP2C. The metabolites formed then undergoes conjugation reactions with glucuronic acid, catalyzed by UDP-glucuronyl transferase	0.93	99.9	Child-Pugh index ≤ 7: no adjustment required Child-Pugh index > 7 not recommended

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	E_H	*Metabolism*	Q_0	*PB (%)*	*Recommendation*
Exemestane* Prod Info Aromasin, 2007 (27)	1	6.77	Oxidation (CYP3A) Aldocetoreductase followed by conjugation.Biliar excretion: 40%	1	90	Monitor liver function
Flucytosine (9)	4	Not known	–	0.1-0.35	4	No adjustment required
Fluconazole* (14)	3	0.002	Liver metabolism around 10%	0.2	11.0-12	Avoid in decompensated hepatitis
Fludarabine* (9)	3	0.06	–	0.35	10.0-30.0	No adjustment required
Fluorouracil* (9)	1	0.71	Dihydropyrimidine dehydrogenase	0.95	94	If total bilirubin ≤ 5 mg/dL: 100% dose If total bilirubin > 5 mg/dL: avoid In cirrhotic patients recommended starting dose of 50% and increase as liver toxicity
Fluoxetine* (9)	3	0.22	N- Demethylation (CYP2D6): active metabolite (norfluoxetine)	0.97	94	Reduce dose 50% in cirrhotics (without ascites) or use alternate days
Fluphenazine* Prod Info Modecate, 2009 (27)	2	0.47	Hydroxylation Glucuronidation, sulfation Demethylation biliar excretion and enterohepatic circulation	1	90	Avoid Child-Pugh C index
Flutamide (9)	4	Not known	Hydroxylation	1	95	No adjustment required
Fosamprenavir* Prod Info Telzir, 2004 (27)	2	0.57	Extensive liver metabolism: CYP3A4	0.86	90	Child-Pugh index 5-6: 700 mg /12 h + Ritonavir 100 mg/24 h Child-Pugh index 7-9: 450 mg /12 h + Ritonavir 100 mg/24 h Child-Pugh index 10-15: 300 mg /12 h + Ritonavir 100 mg/24 h
Foscarnet* Prod Info Foscavir, 2009 (27)	3	0.01	–	0.05-0.27	14.0-17	No adjustment required
Furosemide (8)	4	Not known	Liver metabolism around 10%	0.1-0.4	91-99	Monitor electrolytes
Ganciclovir* (9)	3	0.002	–	0.86	1.0-2.0	No adjustment required
Gemcitabine* Prod Info Gemcitabina Stada, 2010 (27)	1	0.9	Deamination Phosphorylation	0.9	1.0-12	Precaution
Gentamicin* (9)	3	0.01	Not undergo hepatic metabolism	0-0.3	0-30	No adjustment required
Glibenclamide Prod Info Micronase, 1997 (27)	4	Not known	Extensive liver metabolism	0.5	99	Start with 1.25 mg and monitor effect
Goserelin* Prod Info Zoladex, 2010 (27)	3	0.04	–	0.4	25	No adjustment required

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	*E_H*	*Metabolism*	*Q_0*	*PB (%)*	*Recommendation*
Griseofulvin (8)	4	Not known	Extensive liver metabolism	0.8		Avoid Child-Pugh C index
Haloperidol* (8)	2	0.55	N-dealkylation: CYP3A4, CYP2D6 Reduction: CYP 3A4, CYP 2D6 Glucuronidation. Biliar excretion: 15% Enterohepatic circulation	1	92	Reduce dose 50% (precipitated coma) and monitor effect
Heparin Prod Info Heparina Hospira, 2007 (27)	4	Not known	–			Monitor dose based on activated partial thromboplastin time APTT
Hydralazine (8)	4	Not known	Liver acetylation	0.2	88-90	Precaution, dose reduction is recommended based on their toxicity
Hydrochlorothiazide (9)	4	Not known	Not undergo hepatic metabolism	0.3-0.5	40	Monitor electrolytes
Ibuprofen* (8)	3	0.001	Extensive liver metabolism	0.2	99	Precaution
Idarubicin (9)	1	1	Extensive liver metabolism idarubicinol	0.4	96	If total bilirubin = 2.6-5 dose reduction 50% Do not administer if total bilirubin > 5 mg/dL
Ifosfamide* (9)	3	0.02	Liver metabolism: CYP3A	0.5		Monitor liver function
Imatinib Prod Info Gleevec, 2008 (27)	4	Not known	N-demethylation: CYP 3A Biliar excretion: 20%	0.95	95	In patients Child-Pugh C index reduce doses to 25%. Do not administer if total bilirubin > 3 normal or transaminases > 5 normal value
Imipenem* (9)	3	0.05	Renal metabolism: dehydropeptidase I	0.3-0.5	20	No adjustment required
Indinavir* Prod Info Crixivan, 2008 (27)	1	0.97	Extensive liver metabolism: oxidation (CYP3A4)	0.8	60	Child-Pugh index < 10 set to 600 mg/8 h Not studied in severe HI
Irinotecan* Prod Info Irinotecan Hospira, 2005 (27)	3	0.22	Esterases, glucuronidation, CYP3A4 Biliar excretion: 25%	0.75	65	Total bilirubin level Dose 1.1-1.5 normal value 350 mg/m^2 > 1.5 normal value 200 mg/m^2 > 5 normal value contraindicated
Isoniazid Prod Info Cemidon, 2004 (27)	3	< 0.3	Extensive liver metabolism	0.7-0.95	4.0-30.0	Monitor liver function Contraindicated in severe HI
Itraconazole* Prod Info Canadiol, 2010 (27)	2	0.4	Extensive liver metabolism (CYP 3A4) Enterohepatic circulation	0.55	99	Precaution
Ketoconazole (14)	4	Not known	Liver metabolism around 50%: oxidation	0.87	91-99	Monitor liver function. Avoid Child-Pugh C index

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	*E_H*	*Metabolism*	*Q_0*	*PB (%)*	*Recommendation*
Kivexa® Prod Info Kivexa, 2009 (27)	4	Not known	Abacavir: dehydrogenation and glucuronidation Lamivudine: minimal liver metabolism (5-10%)	0.16	36-50	Contraindicated
Lamivudine* Prod Info Epivir, 2006 (27)	3	0.08	Lamivudine: minimal liver metabolism (5-10%)	0.3	36	Adjustment not required unless renal failure is accompanied
Letrozole* (9)	3	0.03	Liver metabolism (CYP3A4, 2D6)	0.95	60	Patients with cirrhosis or with Child-Pugh C index reduced by 50% dose
Leuprorelin	3	0.05	–		46	** Maintenance dose: CP A: 50% of normal dose CP B: 25% of normal dose CP C: drug monitoring
Levofloxacin* Prod Info Levaquin, 2006 (27)	3	0.05	Minimal liver metabolism	0.13-0.39	24-38	Precaution, especially > 65 years old
Lidocaine* (8)	2	0.4	Liver metabolism around 90%	0.2	33-80	Avoid Child-Pugh C index
Linezolid* Prod Info Zyvoxid, 2010 (27)	3	0.06	Minimal liver metabolism	0.7	31	No adjustment required
Lopinavir/Ritonavir* Prod Info Kaletra, 2006 (27)	3	0.01	Lopinavir: extensive liver metabolism (CYP 3A) Ritonavir: extensive liver metabolism (CYP3A4)	0.2	98-99	Precaution
Maraviroc*	2	0.4	Liver metabolism around 58% (CYP3A4)	0.76	76	**Initial dose: start at the minimum of the normal dose Maintenance dose: same that low E_H and PB
Mefloquine * (8)	3	0.02	Extensive liver metabolism	0.9	98	Avoid Child-Pugh C index
Megestrol	4	Not known	Glucuronidation	1	18	Not calculable
Meglumine Antimonate (8)	4	Not known	–	0.1		Precaution
Melphalan* (9)	2	0.31	Hydroxylation	0.9	80	No adjustment required
Mercaptopurine* (9)	2	0.46	Extensive liver metabolism: xantino-oxidasa	0.9	19	Monitor liver function
Meropenem* Prod Info Meronem, 2010 (27)	3	0.05	–	0.3	2	No adjustment required

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	*E_H*	*Metabolism*	*Q_0*	*PB (%)*	*Recommendation*
Methadone (8)	3	< 0.3	Liver metabolism: P450 CYP3A4, CYP2B6, CYP2C19, CYP2C9, CYP2D6; N-demethylation		71-88	Avoid Child-Pugh C index
Metformin Prod Info Dianben, 2010 (27)	4	Not known	Not undergo hepatic metabolism	0.1		Avoid Child-Pugh C index
Methotrexate* (9)	3	0.005	Liver metabolism around 10%	0.05	50	Total bilirubin AST level reduce level < 3 mg/dL and AST < 180 UI: 0% 3.1-5 mg/dL or AST> 180 UI: 25% > 5 mg/dL: contraindicated
Methyldopa (8)	4	Not known	Liver metabolism around 50%	0.3-0.5		Precaution
Metoclopramide* (9)	3	0.04	Minimal liver metabolism: sulfation and glucuronidation	0.1	30	No adjustment required
Metronidazole* (14)	3	0.002	Liver metabolism around 50%: oxidation	0.2-0.4	< 20	Child-Pugh A and B index: unchanged Child-Pugh C index: 250 mg/8 h
Micafungin* (14)	2	0.36	Liver, extent unknown	0.71	99	Monitor liver function. Avoid Child-Pugh C index
Mitomycin Prod Info Mitomycin-C, 2007 (27)	4	Not known	Partial liver metabolism	0.9		Avoid
Mitoxantrone* Prod Info Novantrone, 2007 (27)	2	0.47	Biliar excretion: 25%	0.95	76	Adjust dose at 8 mg/m2 or avoided in patients with total bilirubin > 3.5 mg/dL or acute liver dysfunction
Morphine (8)	1	0.76	Liver metabolism around 50%: glucuronidation	0.1	20-36	Avoid Child-Pugh C index and cirrhosis, produces sedation
Nelfinavir* Prod Info Viracept, 2007 (27)	1	0.73	Extensive liver metabolism: CYP3A4, CYP2C19, CYP2C9 and CYP2D6	0.9	98	Avoid Child-Pugh B and C index
Nevirapine* (8)	3	0.003	Extensive liver metabolism: hydroxylation (CYP3A and CYP2B6) Glucuronidation	0.12	60	Precaution
Nifedipine (8)	2	0.33	Extensive liver metabolism: CYP3A4	0.2	90-96	Precaution, dose reduction is recommended based on their toxicity
Nitrofurantoin Prod Info Furantoína, 2010 (27)	4	Not known	Partial liver metabolism	0.6	90	Contraindicated severe HI

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	*E_H*	*Metabolism*	*Q_0*	*PB (%)*	*Recommendation*
Ofloxacin Prod Info Floxin, 2006 (27)	4	Not known	Minimal liver metabolism	0.1	20-32	Max. 400 mg/day
Oxaliplatin Prod Info Eloxatin, 2007 (27)	4	Not known	Nonenzymatic reduction Biliar excretion: 5%	0.5	75	No adjustment required
Paclitaxel* Prod Info Taxol, 2010 (27)	3	0.24	Extensive liver metabolism: CYP2C8, and lesser extent by CYP3A4 Biliar excretion: > 5%	0.95	95	Transaminase / Total bilirubin / Dose level 24 h infusion < 2 Nv / < 1.5 mg/dL / 135 mg/m² 2-10 Nv / < 1.5 mg/dL / 100 mg/m² < 10 Nv / 1.6-7.5 mg/dL / 50 mg/m² > 10 Nv / > 7.5 mg/dL / not administer 3 h nfusion < 10 Nv / < 1.25 Nv / 175 mg/m² < 10 Nv / 1.26-2 Nv / 135 mg/m² < 10 Nv / 2.01-5 Nv / 90 mg/m² > 10 Nv / > 5 Nv / not administer Nv: normal value
Piperacillin Sodium/ Tazobactam * Prod Info Tazocel, 2010 (27)	3	0.02	Partial liver metabolism	0.2-0.3	30	No dose adjustment is necessary, use with precaution
Phenytoin (9)	3	< 0.3	Hydroxylation: CYP2C9, CYP2C19 Glucuronidation	1	90	Determine drug level Increased toxicity risk
Phenobarbital * Prod Info Phenobarbital, 2005 (27)	3	0.002	Oxidation: CYP2C19 Glucuronidation	0.75	50	Avoid Child-Pugh C index
Posaconazole* Prod Info Noxafil, 2005 (27)	2	0.31	Liver metabolism: glucuronidation	0.85-0.86	98	Precaution
Prednisolone (9)	3	< 0.3	Extensive liver metabolism		70-90	No adjustment required
Procainamide (8)	4	Not known	Liver metabolism around 50%	0.1	10.0-20.0	Reduce by 25% or avoid in severe cirrhosis
Procarbazine (8)	4	Not known	–	0.3		Avoid Child-Pugh C index
Promethazine * (8)	1	0.76	Extensive liver metabolism: sulfoxides and glucuronyl conjugates	1	85	Avoid Child-Pugh C index
Propranolol Prod Info Sumial, 2009 (27)	1	0.75	Liver metabolism around 50-70%	0.9	93	Precaution

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	*E_H*	*Metabolism*	*Q_0*	*PB (%)*	*Recommendation*
Pyrazinamide (8)	4	Not known	Liver metabolism around 95%	0.3	5.0-10.0	Monitor liver function
Pyrimethamine (8)	4	Not known	–		87	Precaution
Raltegravir Prod Info Isentress, 2008 (27)	4	Not known	Liver metabolism around 30%	0.68	83	Child-Pugh index < 10: Adjustment not required Child-Pugh index ≥ 10: no data (Precaution)
Raltitrexed Prod Info Tomudex, 2002 (27)	4	Not known	Intracellular metabolism (polyglutamation)	0.5	93	Precaution
Ranitidine* (9)	2	0.48	Liver metabolism around 30-70%	0.3	15	Cirrhotic patients max. 150 mg/24 h
Ribavirin Prod Info Copegus, 2010 (27)	4	Not known	Phosphorylation (active metabolites)	0.6		No adjustment required Contraindicated in decompensated
Rifabutin* (9)	3	0.1	Liver and intestinal metabolism around 50% (active deacetylated metabolite)	0.47	85	No adjustment required
Rifampicin (8)	4	Not known	Liver metabolism around 60-80% (active metabolite desacetylrifampicin)	0.7-0.85	60-90	Max. 6-8 mg/kg twice a week
Ritonavir* Prod Info Norvir, 2010 (27)	3	0.08	Liver metabolism: CYP P450-3A4 and 2D6	0.86	98-99	Child-Pugh index < 10: Adjustment not required Child-Pugh index ≥ 10: Not recommended
Rituximab Prod Info Mabthera, 2010 (27)	4	Not known	–			Monitor liver function, especially if the HI is due to HBV
Saquinavir* (8)	1	0.9	Liver metabolism around 90% (CYP3A4)	0.81	97	Precaution
Simvastatin (8)	2	0.35	Extensive liver metabolism (CYP3A4)	0.6	95	Precaution
Sodium Nitroprussiate (8)	4	Not known	Metabolized by erythrocytes and tissues			Avoid Child-Pugh C index
Sorafenib (9)	4	Not known	Liver metabolism: oxidation (CYP3A4) and glucuronidation (UGT1A9)	0.8	24-48	Child-Pugh / Total bilirubin / Dose index A / 1-1.5 Nv / 400 mg/12 h B / 1.5-3 Nv / 200 mg/12 h C / > 3 Nv / 200 mg/72 h Nv: normal value Reduced 50% decrease in cholinesterase levels. Monitor effect

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	E_H	*Metabolism*	Q_0	*PB (%)*	*Recommendation*
Stavudine * Prod Info Zerit, 2006 (27)	3	0.23	Limited liver metabolism : Oxidation, glucuronidation and conjugation by N-acetylcysteine	0.6	0	No adjustment required
Sulfadiazine Prod Info Flammazine, 2007 (27)	4	Not known	Extensive liver metabolism	0.4	38-48	Precaution
Sulfamethoxazole/ Trimethoprim (8)	4	Not known	Liver metabolism: 70% sulfamethoxazole and 10% trimethoprim	0.7-0.9	70	Precaution
Sunitinib* Prod Info Sutent, 2007 (27)	2	0.37	Liver metabolism: CYP3A4	0.7	40-60	Child-Pugh A and B index: adjustment not required Child-Pugh C index. Monitor liver function
Suxamethonium Prod Info Anectine, 1995 (27)	4	Not known	Plasmatic metabolism (pseudocholinesterase)	0.9		Reduced 50% decrease in cholinesterase levels Monitor effect
Tamoxifen (9)	3	< 0.3	Hydroxylation, demethylation and conjugation	1	99	Monitor liver function in patients with preexisting liver disease
Teicoplanine* Prod Info Targocid, 2000 (27)	3	0.005	Minimal liver metabolism	0.42-0.58	90	No adjustment required
Telithromycin* Prod Info Ketek, 2004 (27)	3	0.11	Liver metabolism around 37% (CYP3A4 metabolizes approximately 50%)	0.75	60-70	Dose in patients with HI and renal insufficiency (GFR < 30 mL/min): 400 mg/24 h
Temozolomide Prod Info Temodal, 2009 (27)	4	Not known	–	0.9	15	Precaution in Child-Pugh index ≥ 10
Tenofovir* Prod Info Viread, 2010 (27)	3	0.04	Minimal liver metabolism	0.2-0.3	0.7-7.2	No adjustment required
Thiotepa* (9)	3	0.11	Extensive liver metabolism: triethylene phosphoramide active metabolite (TEPA)	0.5	99	Avoid in decompensated IH
Tigecycline Prod Info Tygacil, 2009 (27)	4	Not known	Liver metabolism around 20% (glucuronidation, N-acetylation and epimerization)	0.66	71-89	Child-Pugh A and B index: adjustment not required Child-Pugh C index: initial dose of 100 mg intravenous followed by 25 mg/12 h

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	*E_H*	*Metabolism*	*Q_0*	*PB (%)*	*Recommendation*
Tioguanine Prod Info Tioguanina Glaxosmithkline, 2007 (27)	4	Not known	Metabolism thiopurine methyltransferase	> 0.9	5.0-9.0	Monitor liver function
Tipranavir* Prod Info Aptivus, 2005 (27)	3	0.01	Extensive liver metabolism: CYP3A4	0.82	99	Child-Pugh index < 6: adjustment not required Child-Pugh index ≥ 7: contraindicated
Tobramycin * (9)	3	0.0002	Not undergo hepatic metabolism	0.15-0.4	0-30	No adjustment required
Topotecan* Prod Info Hycamtin, 2007 (27)	2	0.33	Hydrolysis Biliar excretion: 20%	0.6	35	No adjustment required
Trastuzumab	4	Not known	–	0.04		Not calculable
Trizivir® Prod Info Trizivir, 2009 (27)	4	Not known	Abacavir: dehydrogenation and glucuronidation Lamivudine: minimal liver metabolism (5-10%) Zidovudine: liver metabolism (60%), forming an inactive glucuronide conjugate antiviral	0.3	50 (A); < 36 (L); 34-38 (Z)	Contraindicated
Truvada®* Prod Info Truvada, 2008 (27)	3	0.08	Emtricitabine: minimal liver metabolism (13%) = oxidation and glucuronidation Tenofovir: minimal liver metabolism	0.14-0.2	4 (E); 0.7 (T)	No adjustment required
Valproic Acid* Prod Info Depakene, 2006 (27)	3	0.01	Extensive liver metabolism: glucuronoconjugation (50%) and β-oxidation (40%)	0.95	90	Reduce dose by 50%. Determine drug level
Vancomycin* (9)	3	0.0002	Not undergo hepatic metabolism	0.0-0.6	30-55	No adjustment required
Verapamil (9)	1	0.7	Liver metabolism around 65-80%	0.3	88-94	Child-Pugh C index reduced by 50% of intravenous dose or 20% of oral doses
Vinblastine (9)	4	Not known	Liver metabolism: CYP3A4 Biliar excretion: > 50%	1	75	Reduce dose by 50% if total bilirubin > 3 mg/dL
Vincristine* Prod Info Oncovin, 1999 (27)	3	0.09	Extensive liver metabolism: CYP3A4 Biliar excretion: 70%	0.9	75	Reduce dose 50% if total bilirubin > 3 mg/dL Avoid administration if total bilirubin > 3.1 and AST > 180 IU

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Table II (Cont.). Recommendations for drug dosage in patients with chronic liver disease

Drug (references)	*Huet and Krähenbühl (11,12) category*	E_H	*Metabolism*	Q_0	*PB (%)*	*Recommendation*
Vindesine (9)	4	Not known	Extensive liver metabolism: CYP3A4			50% reduction in hepatobiliary disease
Vinorelbine Prod Info Navelbine, 2001 (27)	4	Not known	Extensive liver metabolism: CYP3A4, leading to 4-O-diacetyl-vinorelbine (majority and active) and vinorelbine N-oxide (inactive). Biliar excretion: 50%	0.85	15	Total bilirubin (mg/dL) / Initial dose (%) < 2 / 100% 2.1-3 / 50% > 3 / 25%
Voriconazole Prod Info Vfend, 2008 (27)	4	Not known	Extensive liver metabolism: CYP2C19, CYP2C9 and CYP3A4	0.8	58	Child-Pugh A and B index: 6 mg/kg i.v. every 12 hours (administered two doses), then 2 mg/kg i.v. every 12 hours. For oral doses, administer 100 mg/12 h in patients weight > 40 kg and 50 mg/12 h in patients weight < 40 kg Child-Pugh C index: avoid administration or assess benefit / risk at doses of 2 mg/kg/12 h
Warfarin (9)	4	Not known	Extensive liver metabolism: CYP2C9 , CYP2C19, CYP2C8, CYP2C18, CYP1A2 and CYP3A4		99	Monitor prothrombin time (INR)
Zalcitabine* Prod Info Hivid, 2002 (27)	3	0.03	Minimal liver metabolism	0.15		Precaution
Zidovudine*	1	1.13	Liver metabolism (60%), forming an inactive glucuronide conjugate antiviral	0.85	38	**Initial dose and maintenance dose reduced by: dose reduction = (Normal dose x bioavailability)/100

IU: international units. *HE calculated by Westphal et al. (11). **Delcò theoretical recommendation (1).

drugs with a low therapeutic margin and high-medium E_H as measures to reduce the dose. Besides monitoring carefully the adverse effects and analyzing the possible pharmacological interactions. Finally, the article published by Azanza et al. (14) summarizes in tables the adjustments in the presence of renal insufficiency and/or of hepatic function failure from the antimicrobials according to the Child-Pugh score published in the literature. Drugs classified as "use with caution" are also another aspect to evaluate. The use of them should assess the balance of benefit/risk for each case because in all of them the adverse reactions in the hepatic level have been described, which could make the pathology worse in these subpopulation of patients. In the review, the lack of information and clinical studies with many drugs becomes clear. This is because until recent years, patients with Child-Pugh C were excluded in the development of new drugs for ethical reasons. Despite regulating agencies EMA and FDA recommend to study the research drugs in order to predict their behavior in patients with hepatic insufficiency and to being able to recommend dose adjustment, according to a recent survey, the number of drugs with specific

adjustment recommendations based on the hepatic function with Child-Pugh scores is still very limited (24), probably due to hepatic insufficiency as exclusion criteria in most of the clinical trials. This would explain the lack of data in many cases in the SPC about dosage adjustment in moderate-severe hepatic insufficiency.

Moreover, there is a confirmed lack of consistency in the different consulted sources. This situation is also found in the general dosage recommendations as well as in the available kinetic data of drugs, mainly in the E_H, as it happens in the adjustment for renal insufficiency (25).

In view of the discrepancies highlighted above, the more conservative model is followed; despite it has the risk of an under-dosage, in some cases. Moreover, no guidelines in case of concomitant renal insufficiency or hepato-renal syndrome have been developed which could show one of its own limitations. Despite the existence of theoretical general recommendations in the medical literature about drug dosage in patients with hepatic insufficiency taking into account the pharmacokinetic parameters of E_H, plasma protein binding and bioavailability (1,15-19,21,22), it has been considered more useful to individualize the recommendations for each drug and adjust them to adult patients with liver diseases. We wonder if the recommendations can be applied to all patients with hepatic disease or if, on the contrary, a limit between acute, chronic or multiorganic failure hepatic diseases should be established.

In clinical practice, patients should be carefully analyzed to determine the risks and benefits, taking many factors into account such as the severity of the disease, the consequences of not using the drug and the existence of equivalences or alternatives of different available treatments. When having the chance to choose among many drugs to treat the same disease, the less hepatotoxic should be selected through published reviews which would help to take the right one (26) and with a wide therapeutic range. In case of hepatic insufficiency, caution to manage the treatment is imposed as well as an effective follow-up to determine the intensity and duration of the desirable and undesirable effects, mainly if repeated or continuous administrations exist.

In conclusion, nowadays there are significant gaps in the necessary data for the safety in drug administration in patients with hepatic function failure. That is why in this review a contribution to the practical management of drugs to facilitate dosage recommendations to doctors/caregivers in patients with chronic liver disease is presented. It has been obtained through a synthesis of the published bibliography and completed by applying a theoretical methodology.

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