Drug treatment in patients with hepatic impairment

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Disposition

- Introductory slides on basic liver function and factors influencing drug metabolism
- The pharmacokinetic view including regulatory perspective.
- An overview of the clinical implications of hepatic impairment on some common pharmaceutical groups/products.

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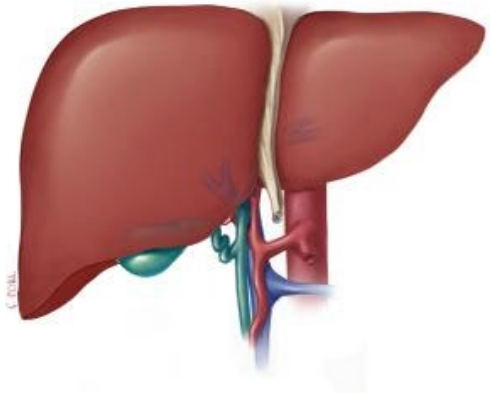
Drug treatment in patients with hepatic impairment-hepatologists clinical perspective

Mari Thörn MD, PhD

The liver-a complex organ with several functions

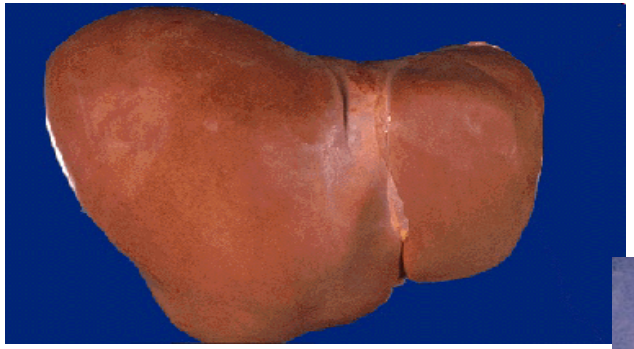
- **Synthesis**-endocrine and exocrine function hormones, bile, coagulation factors, protein- lipid- and carbohydrate metabolism
- **Storage**- iron, vitamins (B12)
- **Elimination**-ammonium->urea, detoxification/metabolism of toxins/drugs

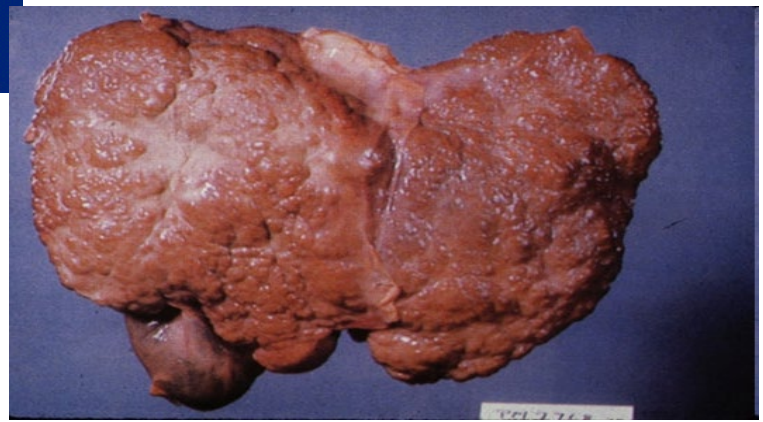


Regeneration

- A large ability to regenerate after damages- For example-to stop drinking alcohol that has led fat accumulation and inflammation may lead to normalization of the liver histology
- In surgery for liver malignancy a large part can be resected without problem if the liver is healthy the tissue regenerates within weeks
- Illustrated here by the Titan Prometheus

Liver cirrhosis





Clinical picture (examples)
-jaundice
-portal hypertension
with risk for bleeding
Ascites
Hepatic associated kidney impairment

Drug treatment in patients with liver disease

- Does the specific drug pharmacokinetic properties change with lower liver clearance?

- Can the drug be harmful for the liver and worsen the liver disease?

Decision-making in drug treatment of patient with liver disease

- In patients with mild liver disease eg Primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) with normal bilirubin and no signs of cirrhosis there is no general need to reduce the dosage of a drug.
- In patients with severe liver disease many drugs must be given in a lower dose and some medications should be avoided.

Hepatic impairment- implications on pharmacokinetics

- Severity of liver disease
- Hepatic blood flow/Shunting. Alterations in hepatic blood flow related to portal hypertension may lead to increased bioavailibility by decreased lower first pass extraction but also indirectly patients with ascites, portal gastropathy and decreased renal blood flow.
- Hepatic metabolism of drug. Changes in cytochrome P450 metabolic activity
- Hypoalbuminemia as a result of impaired production and fluid retention may lead to more unbound drug in plasma of high protein binding drugs.
- Cholestasis can impact drug clearance in drugs excreted in the bile.

Decision-making in drug treatment of cirrhosis

- Indication (Severity of the disease, long-term therapy)
- Pharmacokinetics of the individual drug (e.g.hepatic metabolism)
- Safety- alternative medications?
- Co-existing conditions (renal impairment)
- Concomitant medication (drug interactions)
- Severity of liver disease (clinical definition compensated vs decompensated cirrhosis, MELD or Child Pugh

Assessment of hepatic impairment

Child Pugh classification

Points	1	2	3
Encephalopathy	None	Grade 1-2	Grade 3-4
Ascites	None	Mild	Severe
Bilirubin	<35 mikrogram/l	35-51 mikrogram/l	>51 mikrogram/l
Albumin	>35 g/l	28-35 g/l	<28 g/l
PK/INR	<1,7	1,7-2,3	>2,3

Child A 5-6p Child B 7-9p Child C 10-15p

Assessment of hepatic cirrhosis other methods

- MELD (model of end stage liver disease score) based on INR, bilirubin and creatinine. Prognosis for survival on short-term (3 months)
- NCI-Index –national cancer institute. Developed for oncologic patients based on AST and bilirubin. Total bilirubin most important. Correlates with the CP score
- Radiologic methods (ultrasound, CT)

Other causes for hepatic impairment
(except cirrhosis)

- ALD-acute liver deficiency
- Acute on chronic liver disease
- Malignancy in the liver (primary or metastasis)

Regulatory pharmacokinetics

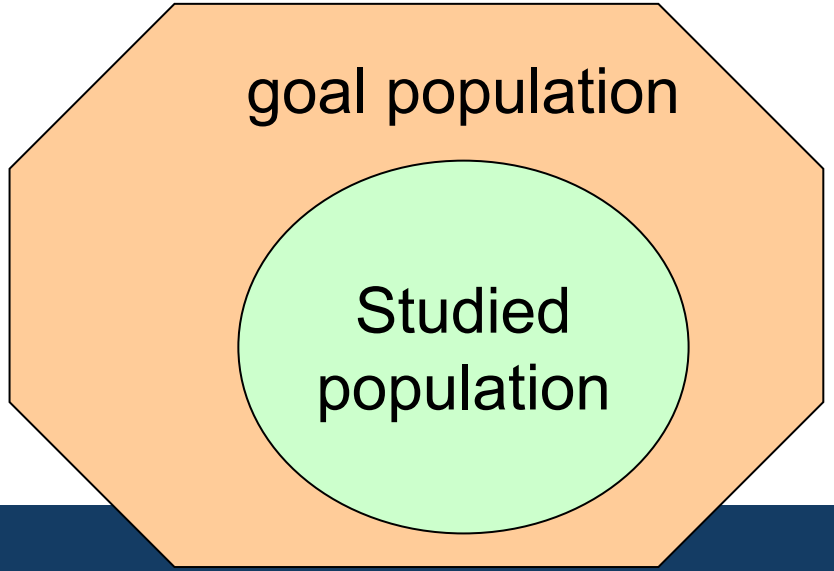
Special populations (e g elderly, persons with impaired organ function, interacting drugs) are often not included in the pivotal trials.

Pharmacokinetics

as a bridge

Same exposure →

Same efficacy and safety



Patients with hepatic impairment may have lower clearance of drugs

- A large fraction of drugs are hepatically eliminated (metabolism, biliary excretion)
- Patients with hepatic impairment may get higher exposure of these drugs → dose adjustments may be needed to reach the same plasma exposure.
- Severe liver disease more likely to impact PK

- Of note: Sometimes drugs cause hepatic toxicity or patients with hepatic impairment may be more vulnerable for other reasons - then dose adjustments based on PK may not be applicable.

What is done in drug development?

European Medicines Agency
Evaluation of Medicines for Human Use

London, 17 February 2005
CPMP/EWP/2339/02

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE EVALUATION OF THE PHARMACOKINETICS OF MEDICINAL PRODUCTS IN PATIENTS WITH IMPAIRED HEPATIC FUNCTION.

Objectives of the guideline is to give recommendations to companies about:

- In what situations studies of pharmacokinetics should be performed in subjects with impaired hepatic function
- The design of pharmacokinetic studies in subjects with impaired hepatic function
- Data presentation, analysis, and evaluation of results
- Reflection of these results in the SmPC in terms of dosing schemes, contraindications, special precautions and warnings for use and description of pharmacokinetic properties.

Limitations with PK studies in hepatic impairment

- The influence of liver disease on the pharmacokinetics of different drugs is complex
- There is a lack of specific markers of decreased liver function that gives a good measure of drug elimination capacity

When is a PK study in patients with HI recommended for a new drug?

- When the drug is likely to be used in patients with impaired hepatic function
- Hepatic impairment is likely to significantly alter the pharmacokinetics (especially metabolism and biliary excretion) of the drug and/or its active metabolites and
- A posology adjustment may be needed for such patients taking into account the PK/PD relationship.

A standard phase I hepatic impairment study

- Normally includes otherwise healthy subjects (often subjects with viral hepatitis or alcoholic liver disease). Sometimes patients e g for anticancer drugs.
- Subjects normally classified in groups (mild, moderate, severe HI) with matched controls (age, gender, weight, relevant genotypes)
- Number of subjects should be enough to detect clincally relevant pharmacokinetic differences (normally 5-8/group is seen)
- Normally single dose (if no dose or time dependency)
- Sampling for parent compound and any active or toxic metabolites
- If highly bound to plasma proteins, unbound concentrations should be measured

How is hepatic impairment classified in HI studies?

- Usually Child Pugh Classification is used
- Abnormalities in lab parameters (albumin, prothrombine time, bilirubin) are better related to elimination capactiy than encephalopathy and ascites, patients in studies must have adequate range of abnormalities in lab parameters.

- For cancer drugs, NCI criteria may be used. Should be mentioned in SmPC.

Alternative ways to estimate the effect of hepatic impairment on PK

- Using data from phase 2/3 if patients with hepatic impairment have been included. Normally in population PK analysis.

Often difficult, hepatic impairment is not very common and measures of hepatic function may not have been properly collected in the clinical trials.

- Physiologically based pharmacokinetic modelling (PBPK), attempts to predict the effect of HI based on previous physiological knowledge and data on elimination of the drug. Cannot replace HI study at present.

Example Drug X

- A drug in the oncology area

→ Contraindications should be avoided, drug may be life saving

- Metabolised by CYP3A4 to a metabolite M, which is also a CYP3A4 substrate
  Main elimination pathway metabolim → HI study relevant
- Metabolite M is active but less active than parent compound

→ Metabolite should be followed in HI study

- Protein binding of X 99,4 % and for metabolite M 98,8 %

→ Plasma protein binding is high and should be followed in HI study

- Smaller increases in exposure can be handled with dose adjustments based on toxicity, but large over exposures compared to the phase III population should be avoided

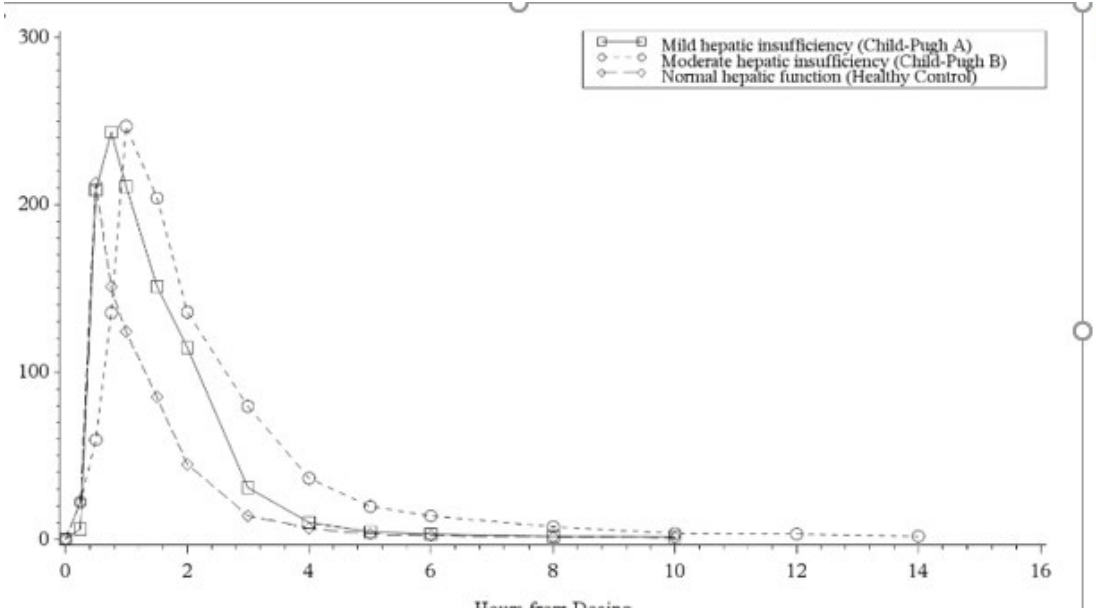
→ Dose adjustments or SmPC restrictions may be relevant if exposure increases by 2-fold or more

First a study in mild and moderate HI was performed

This was a 2-part, non-randomized, open label, single-dose study. Part 1 of the study compared the PK of X in subjects with mild and moderate hepatic insufficiency (based on the Child-Pugh classification) to healthy (mean) matched control subjects for age and weight. In Part 1, 6 subjects with mild hepatic insufficiency (a score of 5 to 6, on the Child-Pugh scale), 6 subjects with moderate hepatic insufficiency (a score of 7 to 9, on the Child-Pugh scale) and 6 healthy control subjects matched to the hepatic insufficiency groups according to mean age (± 10 years) and mean weight (± 20 %) were enrolled

The primary PK endpoints included AUC0-inf and Cmax, for X administered in hepatic impaired subjects and healthy control subjects.The PK parameters AUC0-last, AUC0-24, AUC%extrap, Tmax, Tlastz, t½, CL/F and Vz/F, as appropriate, for study drug was also computed.Unbound PK parameters were to be computed.Relationship between X PK parameters and hepatic function tests (bilirubin levels, albumin levels, and Child-Pugh score) were investigated

Only minor effects on PK was observed, similar in mild and moderate HI group



Mild 1.9-fold (n=6)
Moderate 1.5- fold (n=6)

higher AUC compared with controls

Subjects included were not very much affected in lab components of CP

→ Questionable whether data for moderate HI was representative

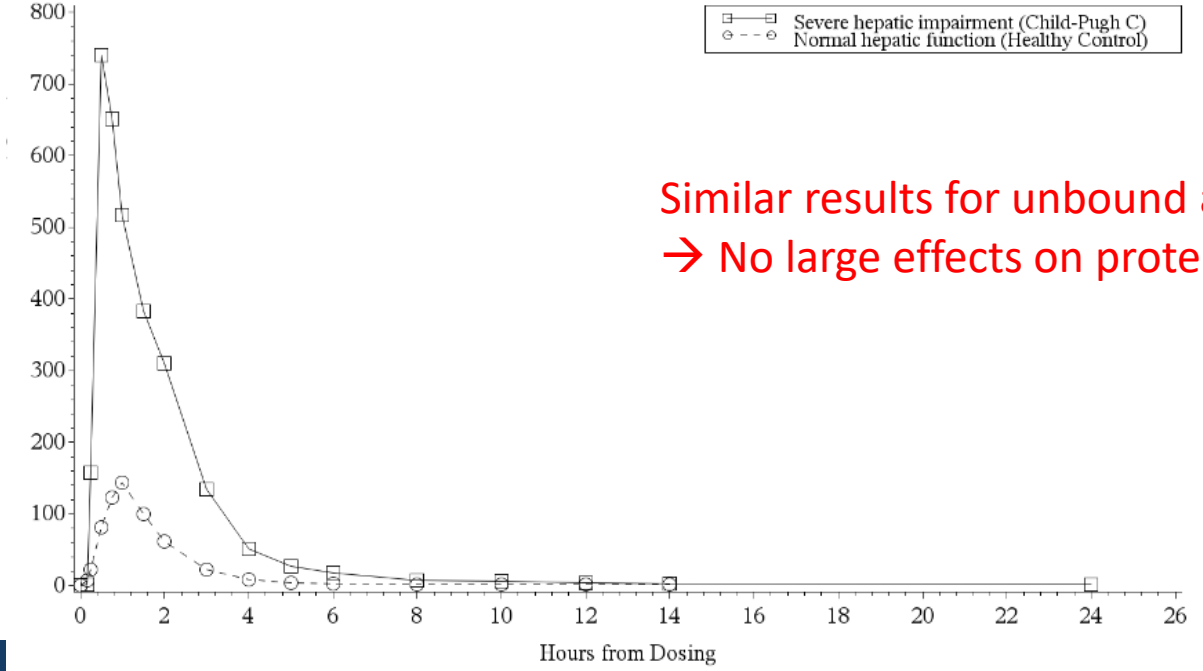
Appendix 16.2.4.2 Child-Pugh Classification

Group	Site	Subject Number	Child Pugh Scoring#						
			Ascites	Bilirubin	Albumin	PT/INR Score	Encephalopathy	Total Score	Classification
A	31-Preston	31-001	1	1	1	1	2	6	MILD
		31-004	1	1	1	1	2	6	MILD
	32-Marbury	32-001	1	1	1	1	1	5	MILD
		32-003	1	1	1	1	1	5	MILD
	33-Smith	33-001	1	1	1	1	1	5	MILD
		33-003	1	1	1	1	1	5	MILD
B	31-Preston	31-003	2	1	1	1	2	7	MODERATE
		31-006	2	1	1	1	2	7	MODERATE
	32-Marbury	32-005	3	1	1	1	2	8	MODERATE
		32-006	3	1	1	1	3	9	MODERATE
	33-Smith	33-004	3	1	2	1	2	9	MODERATE
		33-006	2	1	2	1	2	8	MODERATE

Another study in severe HI – this time subjects with higher risk were included

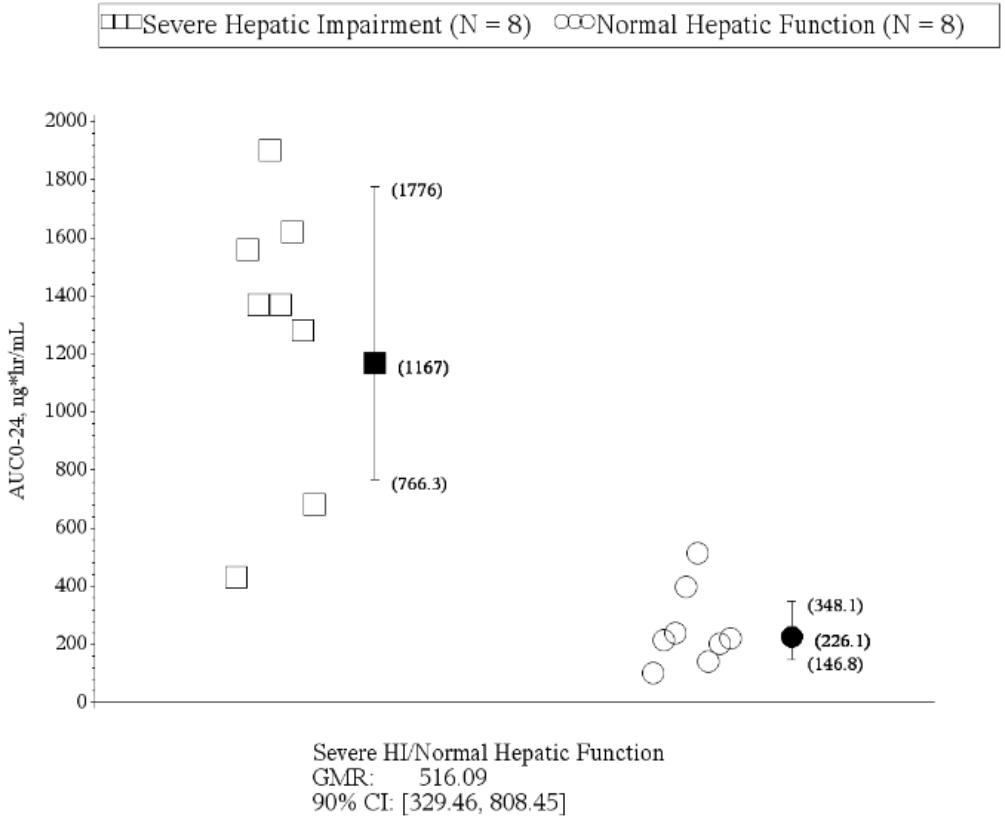
Group	Subject Number	Visit	Date	Ascites	Bilirubin	Albumin	PT/INR Score	Encephalopathy	Total Score	Classification
Severe HI	31-00001	Screen	08JAN2019	3	2	2	1	3	11	SEVERE
	31-00002	Screen	08JAN2019	3	3	2	1	3	12	SEVERE
	31-00005	Screen	25FEB2019	3	1	3	1	3	11	SEVERE
	32-00001	Screen	12NOV2018	3	3	2	1	2	11	SEVERE
	32-00003	Screen	17DEC2018	3	3	3	3	3	15	SEVERE
	32-00004	Screen	31DEC2018	3	2	2	1	3	11	SEVERE
	33-00001	Screen	16NOV2018	3	2	2	1	2	10	SEVERE
	33-00004	Screen	05DEC2018	3	1	3	1	2	10	SEVERE

A 5-fold increase in drug X exposure compared with control group

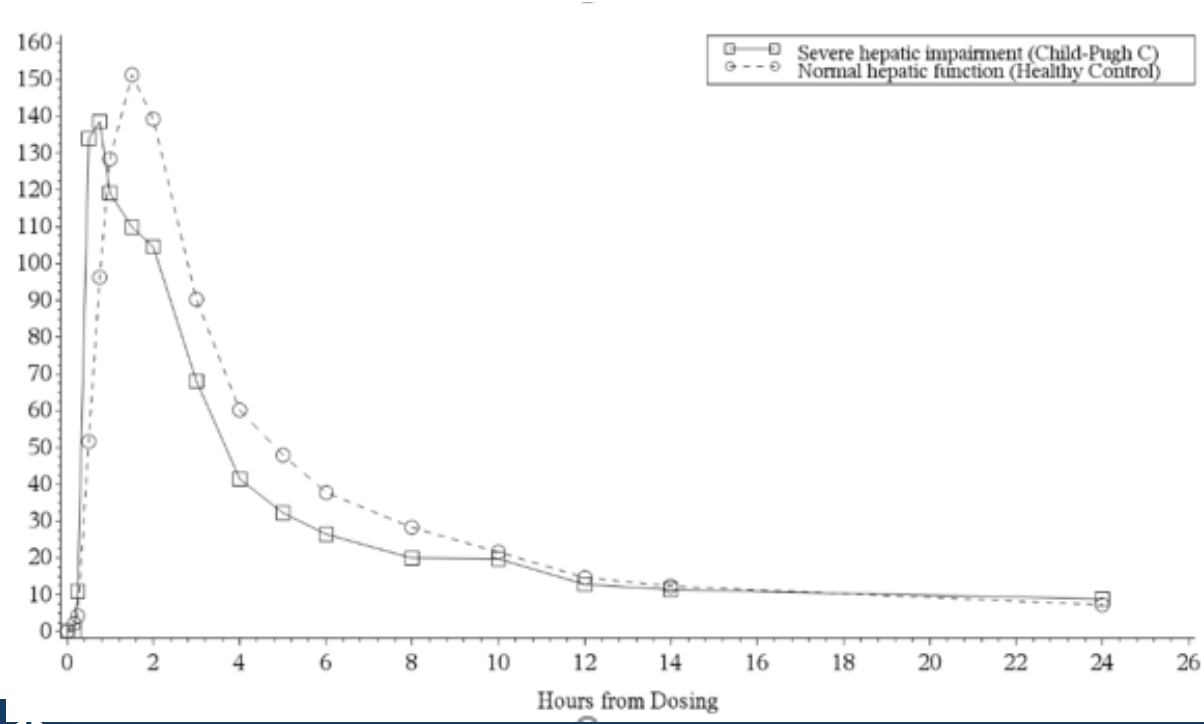


Similar results for unbound and total concentrations
→ No large effects on protein binding

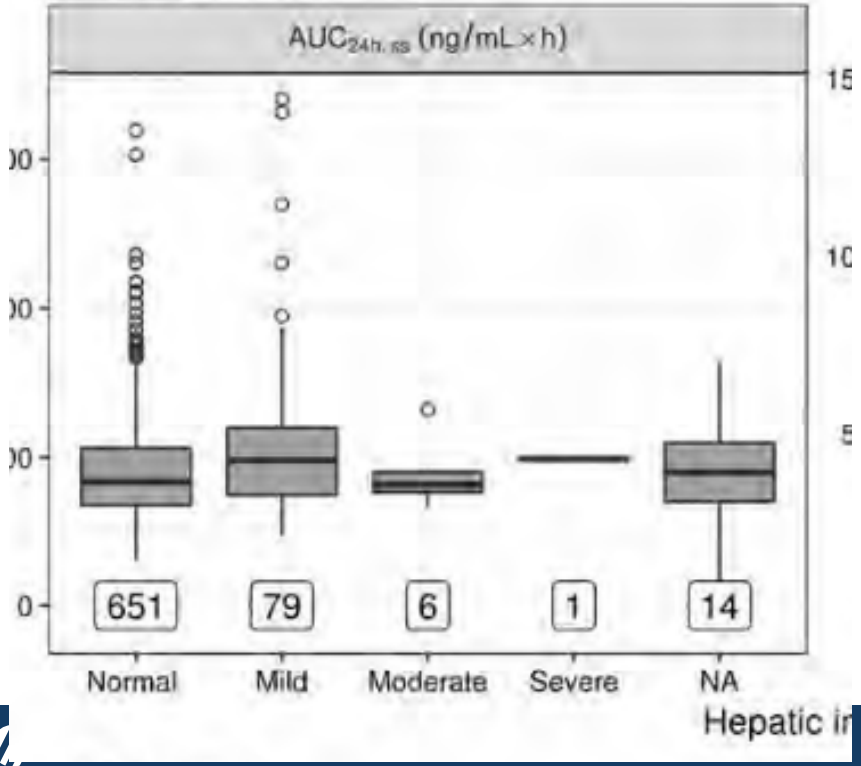
Variability in exposure is large in the HI group



PK of metabolite does not differ substantially between severe HI and normal liver function. The metabolite is both formed and eliminated through CYP3A4.



Data from phase 3 were also analysed with popPK, patients were classified with NCI-criteria



- Very few patients with moderate or severe HI in the studies, not conclusive.
- Phase 3 data from patients with mild HI confirms that a more limited hepatic impairment does not affect PK

Resulting SmPC recommendations

No dose adjustment is recommended in patients with mild or moderate hepatic impairment …..

…..However, patients with moderate hepatic impairment should be closely monitored for signs of toxicity. It is not recommended to use drug X in patients with severe hepatic impairment (Child-Pugh C or total bilirubin >3 times ULN and any AST) (see section 5.2).

Recommendations

- Based on the PK data and knowledge about PK/PD for efficacy and safety, the company should propose recommendations for patients with HI.

- Recommendations for HI should always be available in the SmPC section 4.2. Further information can be found in 4.3 contraindication, 4.4 warnings and 5.2 pharmacokinetics.

- *No dose adjustment needed*
- *Additional monitoring or precautions*
- *Dose adjustment (exposure normalisation)*
- *Not recommended*
- *Contraindication*

What if no data is available?

- For hepatically eliminated drugs, normally use in (at least severe) hepatic impairment is *not recommended* unless the drug has a very wide therapeutic marigin.
- For renally eliminated drugs or for proteins, it can be mentioned that *no effect of HI is expected*.

- For old drugs, there may be a lack of PK data but there may instead be clinical experience in patients with HI.

An overview of the clinical implications of hepatic impairment on some common pharmaceutical groups/products

- Disclaimer: This is a practical overview from a clinical, hepatologic perspective and not always in line with the wording in the SmPC or the regulatory guidance.

Drugs to patient with hepatic impairment

Analgetics	
-paracetamol	May be used in stable cirrhotic patients but in reduced dose in more severe disease. A common dose used is 2 g/d. Avoid in decompensation.
-NSAID	Do not use in severe liver impairment. Increased risk for bleeding from esophageal varices, reduced efficacy of diuretics
-opioids	Increased bioavailibility but can be used but in low doses and longer interval between doses. Higher risk for encephalopathy. Some data indicate that fentanyl have lower risk for accumulation. Aviod pethidine.
Codeine /tramadol	Avoid use reduced transformation of codeine to morphine. Risk for constipation and encephalopathy. Tramadol -reduced transformation and no studies on analgesic effect.

Drugs to patient with hepatic impairment

Psychotropic drugs	
-benzodiazepines	Reduced dosing. Higher CNS sensitivity. Use primarily oxazepam or lorazepam-less risk för accumaulation compared to other benzodiazepines
-klometiazol (Heminevrin)	10 times increased bioavailability
-SSRI	Reduced clearance – careful dosing (CYP2C19)

Drugs to patient with hepatic impairment

Vasoactive drugs	
Betablocker	High first pass metabolism leads to major increase in bio-availability. Very low doses of propranolol is given for prophylaxis of bleeding from esophageal varices.
Calcium channel blockers	High bioavailability- avoid. Cirrhotic patients in general has no need of antihypertensive drugs
Ergotamine	High first pass metabolism- if needed lower dose to approximately 10% of normal dose
ACE inhibitors	Avoid use if possible. Blood pressure in cirrhotic patients is dependent of angiotensin II. If blocked it may lead to severe hypotension

Drugs to patient with hepatic impairment

Antibiotics	
metronidazole	Reduced clearance. Higher risk of neurological side effect. Maximum dose 250 mg/d when used for prophylaxis of hepatic encephalopathy. Avoid long term use.
Rifampicine	Reduced dosage in hyperbilirubinemia. In severe liver disease maximum dosage 6-8mg/kg 2 times weekly.(Björnson)
trimethoprim and sulfamethoxazole.	Can be used short term in hepatic impairment if kidney function is normal
aminoglycosides	Higher risk for hepatic associated kidney injury

Drugs to patient with hepatic impairment

Antibiotics (cont.)	
β-lactam antibiotics	Risk for leukopenia in patients with hepatic impairment.
amoxicilline	Can be used low or no hepatic metabolism. Eliminated by the kidneys
cefotaxime	Low hepatic metabolism-often used in bacterial complications of cirrhosis (SBP)
Quinolones	Considered safe for use in patients with hepatic impairment. (SBP)

SBP= spontaneous bacterial peritonitis

Drugs to patient with hepatic impairment

Other	
Acid reduction	PPI can be used (SBP?). Avoid H2 blockers-decreased elimination
Hormones	HRT-studies on PBC patients does have not shown higher risk for increased cholestasis. Oral contraceptives- High first passage-however low dosed in milder form of hepatic disease seems safe.
Diuretics	Spironolactone and furosemide can be used and is regularly used in treatment of ascites. Dose adjustment primality based on kidney function.

Drugs to patient with hepatic impairment

Anticoagulants	
Altered hemostasis	Higher risk both for bleeding and thombosis
portal venous thrombosis (PVT)	Common complication. Some data indicate lower risk of bleeding from esophageal varices when treating PVT
LMWH	Appears safe for treatment of portal venous thrombosis
Warfarin	Can be used in stable cirrhosis when INR is assessable
DOAC	Used sometimes off-label in clinical practice in cirrhotic patients. (compensated CP A,(B))

Coagulation in Cirrhosis AGA guidelines Gastroenterology 2019;157:34–43

Conclusive remarks

- In patients with mild liver disease and no signs of cirrhosis there is no general need to reduce the dosage of a drug.
- In patients with severe liver disease many drugs must be given in a lower dose and some medications should be avoided.
- Child-Pugh assessment still in use
- SmPC 4.2 and 5.2 but also 4.3 and 4.4
- Lack of published high quality data in patients with sever hepatic impairment
- References

References

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