im excited to introduce todays lecture

professor in multiple departments at

virginia commonwealth university school

of pharmacy he is also the vice chair of

the department of pharmaceutics and the

director of the pharmacokinetic and

pharmacodynamic laboratory at the school

of pharmacy in addition he is a fellow

in the center for study of complex

sciences at vcu

in 9 jurgen received his md and phd

from sarland university in germany

from 9 to 9 he was the director of

clinical research and development at the

institute for clinical pharmacology in

gunstro germany then completed

postdoctoral fellowship training at the

university of florida

in 9 jurgen joined the faculty of vcu

school of pharmacy he has published

extensively and presented extensively in

the area of quantitative pharmacology

im confident you will enjoy todays

lecture

hello my name is jurgen vanets im a

clinical pharmacologist and a professor

at virginia commonwealth university

school of pharmacy and its my privilege

and honor to contribute to the nih

principles in clinical pharmacology

lecture series

ill be your entertainer for today and

the topic du jour is going to be drugs

and the liver so what im going to try

to do with the next 0 minutes or so is

review basic concepts as they relate to

what the drug can do to the liver and

what the liver can do to the drug

so if you look at the objectives that i

have i want to start off by talking

about what we call liver function tests

how we can assess

the liver functioning

or how we cannot assess it and then talk

about drug induced liver injury in other

words what drugs do to the liver

the second part of my lecture is going

to deal with the opposite so here were

going to look at what happens if the

liver doesnt function properly

relative to the kinetics of drugs and

how can we account for that clinically

and then im going to use in my last

item im going to use acetaminophen

as an example of a drug that is

toxic and as far as liver is concerned

and how we can deal with it

you can see in my outline i have

supplement

supplementing reading supplemental

reading material and attachments

that you can download as part of the

lecture itself that go into more depth

than im able to do in my

lecture

so lets start off by looking at liver

function assessment

obviously in order to understand liver

function assessments we need to know

what the main functions of the liver and

ive listed them here the one that is

most important to us in

the world of pkpd is drug metabolism so

were talking about detoxifying

metabolism meaning formation of

metabolites catabolism breaking down

of endogenous and exogenous

things like drugs

but hybrid also includes protein

synthesis

and thats particularly important as it

relates to plasma albumin

because that can contribute to binding

of drugs in the blood and coagulation

factors

and lastly of less importance to us in

clinical pharmacology is that it serves

as a storage organ of endogenous

substances like glycogen or iron

so the first

notion that i want you to disabuse of is

that the socalled lfts or liver

function tests

are liver function tests

they really are not so lets look at

what we mean by lfts

most people would refer to what i call

serum transaminases

as lfts so those are enzyme activities

that we can measure in plasma

but they tell us something about hepatic

cellular injury meaning damage to the

liver itself not necessarily its

functioning

the particular enzymes that are involved

the first one is ast or the

oldfashioned name is sgot

thats an enzyme that is present in the

mitochondria that gets leaked into the

plasma

anytime liver

cells hepatocytes get damaged

the second one is the elt or formerly

called sgpt thats an enzyme again but

thats present in the cytosol

that gets leaked into plasma

when hepatocytes die

of node specifically to the alt is the

fact that this is an enzyme that is not

only present in liver cells but also

muscle cells and as i point out here in

red blood cells

so anytime you have damage outside the

liver those enzymes would be released as

well

in addition to that the alt also depends

on the

bass

body mass index

a third one that is less commonly used

because of its unspecificity is the

gamma gt

it is highly variable

there is some association with

elevations of that particular enzyme and

chronic alcohol use

so the transaminases they measure

hepatocellular damage

not liver functioning per se

now in this table i am listing

a few

conditions that are

causing elevated ast

or alt sometimes called transaminitis

to distinguish that from

bona fide

liver damage so you can see alcoholic

liver damage cirrhosis would lead to

astlt elevations something that

were going to be talking about is here

medications

drug induced liver injury but you can

see

hepatitis

of various origins can do the same thing

so sometimes that makes it difficult to

distinguish between

drug interviews toxicity and underlying

pathophysiological conditions you can

see here the toxic hepatitis for

mushroom poisoning and so on so you can

see theres a whole laundry list of

conditions besides drugs which is what

im talking about today that can cause

elevations of transaminases meaning they

can cause hepatocellular damage

a much better marker

or at least of part of what the liver

does liver function is

bilirubin and alp

so they are not measuring the damage to

a particular

part of the level hepatocytes but

theyre looking at intra and

posthepatic cholestasis

so is there any damage to the ability of

the liver to synthesize or release

bile acids into the gallbladder

the alp alkaline phosphatase measures

the potency of that

pathway that the bile actually can flow

freely to the gallbladder

the unfortunate or the disadvantage of

the elp its not only

a measure of biliary excretion but its

also affected by bone homeostasis stasis

so you have to rule out any conditions

that relate to bone

damage

bitter ruben is probably the most

commonly used

marker of bitter excretion so let me

just walk you through

what it is and then we look at the

scheme below so bitter rubin is a

degradation product as a result of

breaking down hemoglobin

uh that happens in the spleen it then

gets highly bound to plasma proteins

because it is very lipophilic

and gets transported as whats called

indirect bilirubin meaning plasma

proteinbound bilirubin to the liver

it gets taken up into the liver and

conjugated

by a ugt iso enzyme called

ugta that forms the clichornite

metabolites or what we call

in clinical chemistry direct bilirubin

that bilirubin then is excreted in the

bile

as well as

spilling over into the bloodstream and

some of this conjugated bilirubin gets

excreted in the urine or can get

excreted in the urine under normal

conditions its almost exclusively

excreted in the bile

it is almost the almost exclusively

showing up in the feces and ultimately

what you end up with are degradation

products of this bilirubin

degradation products due to the

bacterial flora and the colon that form

sterobilin which is a

dye that basically constitutes the color

of the feces

so what youre typically measuring when

you look at a metabolic panel for

example would be the total bilirubin in

plasma which would be the sum of the

indirect the unconjugated plasma protein

bound bilirubin and the direct or the

conjugated bitter ruben

so now let me just skip those uh

syndromes and lets look at this little

scheme

so you can see that the hemoglobin

breakdown

in the spleen leads to unconjugated

ability that gets bound to albumin

gets transported to the liver

gets taken up into the liver into the

hepatocyte

once its taken up into the hepatic site

we have this metabolic

conversion occur where its being

chloranidated by ugt

the conjugated bilirubin

gets excreted into the bile to

ultimately show up in feces

or it can be secreted especially at

higher concentrations can be secreted

into

plasma and then because of its polarity

can get really eliminated

now you can see there are a couple of

transporters and enzymes involved so ugt

is

ugta is the enzyme that metabolizes

unconjugated to conjugated bilirubin and

as i pointed out here

there are various inborn errors of

metabolisms that can lead to

hyperbilirubinemia

the most common one in about five to ten

percent of the population at large is

called gilbert syndrome

so here there is a genetic deficiency in

the activity of that enzyme

that is usually asymptomatic

can sometimes lead to transcend

scale

hectares a much more severe syndrome is

whats called the curriculum or jaw

syndrome so here theres a complete

absence of ugta

and you have persistent

hyperbarimia

but we can also have

problems genetic problems with those

transporters you can see there are mrp

mrp and mrp mrp or multidrug

resistant protein is the major efflux

transporter that kicks out the bilirubin

from the hepatocyte in the

bile

and dubin johnson syndrome

is

characterized by the virtual absence of

that particular transporter so again you

have a high levels of

bilirubin because everything is backing

up

the second cartoon that i have here

shows you again

the various transporters so on the uh

cannalicular side so this is the side of

the hepatocyte that faces the bile duct

we have the mrps

on the

capillary or the sinusoidal side so this

is where the hepatocyte faces the

bloodstream we have efflux transporters

mrp so they kick out the conjugated

bilirubin

and the bilirubin into the the

bloodstream but we also have uptake

transporters so this is where the

oatpb

comes into play so drug transporters and

drug metabolizing enzymes are involved

in the disposition hepatic disposition

of bitterrubin

the reason why i point that out

when we look at bilirubin as a marker of

hepato hepatic

injury you should be aware that those

enzymes and those transporters that are

involved in its hepatic disposition can

be affected meaning inhibited primarily

by other drugs

leading to hyperbilirubine anemia

without being a sign of hepatic toxicity

the last set of markers that we want to

look at so now were looking at a

different function that the liver has

and that is protein synthesis

so here we would be looking at serum

albumin levels they reflect

uh hepatic synthesis

they are maintaining or albumin is

intended to maintain oncotic pressure

but it also plays a role in binding

drugs so when we get into the second

part of my presentation we talk about

this

by the same token i mentioned early on

coagulation factors

especially the vitamin k dependent ones

factor

9 and 0

are

hap or those

clotting factors are

synthesized

in the liver and any especially severe

liver damage would affect the ability of

the liver to synthesize those clotting

factors

so in addition to those lab values that

we talked about what other signs and

symptoms do we have especially in

chronic chronic hepatic

failure uh the pain and tenderness in

the right upper quadrant of the abdomen

thats where the

liver is located would be a potential

uh probably the most pathognomic one is

the second one that ive listed here and

that is dark urine and discolored stool

and if you remember the uh

breakdown products in feces of

bilirubin they give

the dark color to the stool so if

bilirubin doesnt get excreted in the

feces

the stool is light

on the other hand

what happens then is that the bilirubin

conjugate gets rerouted from the bile

into the urine

and once it is in the urine it can

actually especially when you let the

urine stand forward it can lead to a

darkening of the urine so if your

patient tells you that they have

observed that they have dark urine and

light stool the first thing to think of

is

changes in bitter excretion related to

liver damage

another one that again your patient will

be able to report would be jaundice so

this is a yellowing of the skin

and the sclera the eye

leading to parietas severe itching all

this is a result of deposition of

bilirubin in

the tissues

ascites so this is the accumulation of

fluid in the

abdominal cavity are primarily the

results of low albumin levels

which means there is a lower

osmolarity or oncotic pressure

it also is

caused by portal hypertension

so this would be

another sign and symptom

looking at the

potential changes in vasculature

esophageal varices and

hemorrhoids can result as a function of

portal hypertension

where the portal vein is seeking to

circumvent the liver because the liver

provides too much

vascular resistance and then tries to

find uh

[Music]

tries to circumvent it by

going through the esophagus or the

hemorrhoids

related to the decreased

vitamin k dependent clotting factor

synthesis

pleading

nose or gum pleading and then what

usually is

terminal condition

gi hemorrhage

would be signs and symptoms related to

the coagulation effects

and then something were going to

discuss again

once the liver

is functioning is impaired

metabolites endogenous metabolites

accumulate and

something called hepatic encephalopathy

is caused which is characterized by

confusion and altered level of

consciousness

which is typically part of the end stage

in liver impairment

okay so moving on from

how the liver functions how we can

measure measure it now lets see what

happens

when drugs cause liver toxicity or the

technical term is drug intrused liver

injury or hepatotoxicity

and on this table

i have listed or copied a list

that compiles

various drugs and you can see the main

distinction is

whether they cause hepatocellular damage

so that would be the transaminitis

elevated alt asd

or whether they call cholestasis

so here the bilirubin and or the

alkaline phosphatase would be

elevated

and ive highlighted a few drugs of

interest acetaminophen is an example

that were going to go through in more

detail later on that causes doserelated

hepatocellular

hepatocellular damage

okay and well talk about the particular

mechanisms

statins can also cause in

relatively rare cases can cause

hepatocellular damage

on the other hand you can see steroids

both antibiotic steroids and all

contraceptives are associated with

static uh

hepatic injury

so were using now those markers that we

talked about to kind of categorize

which of those

two extremes

a drug would fall into and you can see

theres a lot of

drugs there in the mixed category they

both elevate the alkaline phosphatase

and they elevate the transaminases

now how would you approach

the question with a

particular liver injury

that you have observed whether its

related to a drug or something else

and here the basic idea is that the drug

induced liver injury is a diagnosis by

excluding everything else so you have to

exclude every

pathophysiology other than the drug

being the most likely cause

and you can see here if you look at this

decision tree if you like there are

imaging

[Music]

studies that you can do

to look for example whether you have

patent uh bile

ducts in other words you dont have

cortisos because you have a gallbladder

stone or something like that

you want to rule out a very common cause

of

especially elevated transaminases and

thats viral hepatitis

there are autoimmune diseases

probably the most common cause of

hepatic impairment is chronic alcohol

use

and you can see that does affect the

transaminases

preferably the ast so the ast is

elevated

about two to one relative to the alt

there are other rarer genetic and

metabolic diseases

obviously secondary uh changes in the

liver as a result of reduced cardiac

output only after you rule all of this

out

then you might consider possible

drugrelated hepatotoxicity

so what are the criteria then that you

would use to assess the causality

whether the drug is actually the cause

of a

liver impairment the obvious one is the

exposure to the drug must precede the

onset of liver injury

however in practice

the time between the onset of liver

injury and the drug exposure can highly

vary

it can be in the

order of months

so your patient might be taking a drug

for months

before you see any signs of liver injury

so this is not necessarily a very

helpful but its a required criteria

before i talked about number two that

all other potential causes of

liver impairment

need to be

ruled out including other drugs other

than the one that you suspect

probably the most powerful ways of

assessing causality are called d

challenge and rechallenge dchallenge

basically very simple you stop giving

the suspected drug or the drug that you

suspect of liver injury and the liver

injury dissipates

again as pointed out there are caveats

to that if the liver injury

might actually worsen at least initially

after you discontinue giving the

suspected drugs

okay in addition to that the

uh

falling transaminase levels might

actually be related to

more severe liver impairment because

more

liver cells die rather than a recovery

the last one the one that is not used in

clinic in

a clinical situation a whole lot is a

challenge where you withhold giving the

suspected drug and then you give it

again and you want to basically prove

that by giving the drug again youre

worsening or you can

get the

liver injury signs to reoccur

now this has been formalized into a

causality assessment to the rule came

russell uh ooklaf

just want to review that briefly uh one

of the references that ive included

actually has the entire

um uh scoring scheme but i want you to

get a sense for whats being considered

in order to uh assess

a level of suspicion so the time to

onset

whether its suggested compatible and

you can see the large ranges that you

have and i should point out

the first column thats the

hepatocellular type

the hepatocellular damage transaminitis

the second is the codostatic type

either way you can see there is a large

uh period of onset

that would be compatible or suggested of

druginduced liver injury

then the course so here youre looking

at what happens

in terms of changing the alt or changing

the alkaline phosphatase over time

other risk factors you can see whats

listed here particularly is pregnancy

age

uh other

drugs

that are known to cause liver injury

other

hepatotoxins

or whether you have a weed positively

challenged okay

and then there are a whole bunch of

other

conditions that weve already talked

about that you would like to rule out

and if you rule them out that would

contribute quite a bit to your suspicion

if you dont well that means there

always is a chance that they might cause

your liver injury

information about the drug of interest

and

the read challenge as i said in clinic

thats rarely done but if it is done you

can see that contributes a lot to the

overall score so by adding up the

various cores you can get a total score

and that total score expresses the

probability or the level of suspicion

that the drug has actually caused the

liver injury

the second part

of my uh lecture today is going to look

at the reverse so we looked at first

what drugs can do the liver now we want

to look at what the liver can do to

drugs

so we want to figure out those

adjustments in patients with chronic

hepatic impairment and i want to give

you some background on

the role of liver and

the drug drug

kinetics or the add me before we go into

specific

impairment effects

so here we have a hepatocyte and i want

you to realize that the drug has to get

from the bloodstream

the sinusoidal side into the uh

hepatocyte which may involve drug

transport or it may be passively

transported

there is metabolic metabolism that

occurs inside the hepatocyte

and theres

and or there is billiard excretion into

the canaliculi

okay you can see some of the drugs and

all the metabolites can also be influxed

back into blood just like we illustrated

for bilirubin

from a big picture point of view we can

look at the liver as a clearing organ

where drug comes in via the portal vein

and the hepatic artery

and the the blood drains into the

hepatic vein

and we can identify or we can estimate

whats called the extraction ratio

which basically looks at the arterial

venous difference

relative to the ethereal inflow

so if you have

a tier concentrations of the drug and

venous concentrations being equal

the extraction ratio is zero nothing

gets removed

if the arterial concentration is some

value and the venous concentration is

zero

this ratio becomes one that means a

hundred percent gets removed

so this extraction ratio tells us

something about the innate ability of

the organ in this case the liver to

remove a drug but we have to consider

that the

organ the liver is also perfused so the

entire organ clearance is the product of

the extraction ratio and liver blood

flow so if we apply that then to the

liver there are three factors

that impact the liver clearance

the first one as i alluded to before is

liver blood flow

the interesting thing here is not only

does that change the delivery of the

drug to the liver but it also changes

the extraction ratio

so increasing speeding up the liver

blood flow reduces the hepatic

extraction ratio as the transit time of

the drug is shortened and the hepatic

uptake and subsequent metabolism

mobility excretion is reduced

the reason why thats important in

hepatic cirrhosis we have things like

intrahepatic shunting

so chronic hepatic impairment is known

to affect liver blood flow number one

number two plasma protein binding drugs

that are highly plasma protein bound are

unable to dissociate and get taken up

into the hepatocyte so theyre

protecting if you like the drug from

hepatic uptake and subsequent bitter

excretion and or metabolism

the reason why thats important in

chronic liver disease well chronic liver

impairment can actually affect plasma

protein binding and are alluded to the

fact that a lot of drugs can bind to

albumin and albumin synthesis is reduced

in

chronic hepatic impairment

the last and sometimes

the most important factor uh in

determining the liver clearance is the

intrinsic clearance so this is the

intrinsic ability of the liver to get

rid of the drug regardless of any liver

blood flow or supply issues

its basically determined by the

metabolic capacity or the capacity to

eliminate viability excretion

so what can happen in chronic hepatic

impairment is that this intrinsic

clearance this metabolic or a biliary

capacity is reduced

depending on the particular pathway

depending on the particular transporters

now in order for us to kind of draw some

general conclusions we

usually categorize drugs into high and

low hepatic extraction ratio drugs as

ive outlined here

so a high hepatic extraction ratio is a

drug that has an extraction ratio of 0

percent

which means during one pass across the

liver 0 percent gets taken out and only

0 shows up on the venous side

those are drugs where the rate limiting

step is the delivery

to the liver so liver blood flow is

weight limiting their intrinsic

clearance

and plasma protein binding corrected in

transit clearance i should say is so

high its an excess of liver blood flow

that liver blood flow becomes weird

limiting

that also means they have high hepatic

first pass effect if you remember the

liver is

anatomically positioned between the the

gut and the rest of the body so any drug

that gets absorbed from the gut has to

cross the liver unchanged in order to be

absorbed

but high extraction ratio drugs actually

remove during that first pass 0 or more

so they have high first pass extraction

which as a result leads to low or

bioavailability and i might add

high variability

low extraction ratio drugs are the exact

opposite so those are drugs where the

extraction ratio is less than 0 during

one pass across the liver

only about 0 or less get removed so 0

or more still show up on the venous side

the rate limiting step now is either

dissociation from plasma proteins so

theyre highly prosperous protein bound

they have to be able to issue dissociate

first before they can be removed or the

inability of the liver or the limited

ability of the liver to metabolize

or biliary excrete them so they have the

liver has

low efficiency to get rid of it

which also means as a result they have

low hepatic first pass effects

and everything else being

in terms of gastrointestinal absorption

being 00 they would have a high

bioavailability

now what are the mechanisms of hepatic

elimination ive already alluded to

metabolism so this is chemical

transformation

uh off the pan drug into metabolites

that can be inactive or active meaning

contribute to the biological activity or

not

with the intent of ultimately get

getting rid of them the liver is the

main metabolizing organ both in terms of

phase and phase metabolism

the

various pathways can can show genetic

polymorphisms

polymorphisms so patients could be what

we call poor metabolizers have lower

activity of particular enzymes

and we can have specific drug

interactions related to pathways or drug

transporters now as it relates to

hepatic impairment

chronic hepatic impairment cirrhosis etc

affects phase one metabolism

which are submediated oxidation

pathways

more or at the earlier stage while phase

two metabolism gluconadation sulfation

as we talked about for bilirubin are

actually preserved so depending on which

is the predominant pathway of the drug

liver impairment can have different

impacts

biliary excretion i showed you several

cartoons where the drug and or its

conjugated metabolites are excreted in

the bile typically involving drug

transporters

removing uh the drug uh or moving the

drug into the body doesnt technically

remove it from the body it still has a

chance to be reabsorbed from the gi

tract because thats where the bar

drains into and we can have endo hepatic

recycling

now in chronic hepatic impairment we can

see changes in drug transporters

involved in this biliary excretion that

are either down regulated or inhibited

and then would reduce

biliary excretion

this is a summary of what we expect to

happen

with and im only going to talk about

hepatic blood flow and intrinsic

clearance

so were looking at

hepatic a high extraction ratio drug to

the left

low extraction ratio to the right

for each of those two drugs were

looking at the area under the curve you

can think of that as systemic levels

we look at their halflife and this

would be the halflife and the area of

the iv administration

and were going to look at their all

bioavailability

okay so lets look at the hepatic blood

flow

changes the easiest to understand are

the low extraction ratio drugs

they are not affected at all by change

in liver blood flow

so if the only thing thats affected is

liver blood flow

the low extraction ratio drug wouldnt

show any change in their kinetic

properties on the other hand the high

extraction ratio drugs as you can see

hepatic blood flow

decrease which is what you would see

in cirrhosis would lead to increased

levels

prolonged halflife

and

increased bioavailability

due to reduced first pass effect

so this is basically two strikes you

have systemically reduced clearance and

you have increased bioavailability

on the other hand if you look at changes

in intrinsic clearance so this is where

the

liver impairment affects either

metabolic or biliary pathways so were

looking at a reduction

you can see that the low extraction

ratio truck is very sensitive so after

iv administration the low extraction

ratio drug would have

increased area

increased halflife but the

bioavailability thats already high

wouldnt change

okay so you would see those changes

meaning increased area prolonged

halflife after iv and after all

administration

on the other hand for a high extraction

ratio drug

systemically

intrinsic clearance is

high

relative to liver blood flow so you

wouldnt see any change so after iv you

wouldnt necessarily see a change

however if you give them by mouth you

would see

a change in bioavailability the

bioavailability would be increased

because you have a decreased

first pass effect so after all

administration high extraction ratio

drugs and low extraction ratio drugs

would be affected

both

all right so how do we then work our way

through the impact

of

chronic hepatic impairment on

pharmacokinetics and this is a scheme

that i took from one of the reference

that we talked about

so obviously the first thing you have to

somehow quantify

the degree of liver disease

and then you have to look at the various

kinetic and dynamic consequence the

first one that i just talked about

is there any change or would you expect

to be there any change in all

bioavailability

and as i just explained to you if your

drug is a high extraction ratio drug

this is very likely if the drug is a low

extraction ratio drug this is not very

likely

if the drug is highly blasto protein

bound then you have to ask whether

plasma protein binding is affected by

liver disease in other words is a drug

bound to albumin albumin levels are

reduced because of their impaired

synthesis is that the case or not

and as a result would you expect the

volume of distribution to be increased

if your drug is highly plasma protein

bound

you have less plasma protein binding

sites because you have less albumin you

would expect the drug to have a larger

volume of distribution and a longer

halflife

the most important part is here part

number five is the clearance

going to change well

that depends on how important the liver

clearance is to the overall clearance

and what particular pathways the liver

takes is it

oxidative metabolism conjugated

metabolism or biliary excretion

and lastly for certain drugs and were

going to look at examples in a minute

are there any effects on the

pharmacodynamics

so this is not related to the absorption

distribution metabolism excretion but is

there anything about liver disease that

would make the dynamic uh the

pharmacodynamics of the drug different

second question then is so once we

work our way through what is likely to

be affected

how do we quantify the degree of liver

impairment and the most common scheme

that is used in clinical pharmacology is

called child view scoring

now i should point out this is a scoring

system that was originally

developed to predict

the likelihood of liver transplant being

successful so were using that if you

like offlabel

as a global way of assessing

liver function

and its potential impact on

pharmacokinetics so you can think of

this as the equivalent of a creatinine

clearance that we use to

draw inferences about renal functioning

so you can see there are five variables

that go into the child pew

classification

three are laboratory ones the top three

and two are clinical

so you can see at the very top weve got

zero bilirubin

depending on the levels you assign

points the higher the level so less than

two

would be one point more than three would

be three points

the so this would be to look at what we

just discussed a bit area excretion ugt

metabolism serum albumin and prothombin

this the other two laboratory markers

are looking primarily at the

synthetic function of the liver again we

assign

points depending on the severity

on the reduction of albumin or the

prolongation of the

prothrombin time

the two clinical

markers that we use is the

encephalopathy that i mentioned before

so this is a clinical grading

and the ascites the intraabdominal

or the accumulation of fluid in the

intraabdominal cavity depending on how

much you have

you would assign scores

then you add up those points and you can

see the final gradation would be child

qa which we mild liver impairment sharp

ub would be moderate and child pu c

would be severe

underneath ive

exerted a

table

that tells for a few drugs what the

consequences are

so those are drugs were

according to the fda labor studies were

done to

investigate what happens to the drug

levels to drug exposures usually

as a result of

patients suffering from child pa child

pb

or child puc

and i should point out for the vast

majority of drugs they have never been

studied in child puc meaning in very

severe liver impairment so for most of

those drugs the only empiric information

that we have is child poo a and b

so you can see for example here

sildenafil

uh

there is a dose adjustment the reduction

in those uh recommended for child a and

b no cell benefit is a drug that is

highly metabolized so that would make

sense

no recommendation for the severe

liver impairment because no study was

done

if you look at that a little more

closely so i have a specific example

that i want to review with you and that

is river roxaram or sobelto one of the

novel

all anticoagulants

so let me just review some brief pk

information or pkpd information and then

we see how that impacts on

liver impairment

so you can see it has a very good all

bioavailability

may be limited at higher doses by gi

solubility but it is a low hepatic

extraction ratio drug

okay so you already know that

means

the first pass should not be affected by

liver disease

it has a relatively small volume

distribution primarily because its

highly plasma protein bound so the

plasma protein binding could be affected

by liver disease

if you look at the relative distribution

of the total clearance you can see

about onethird is

via the kidney so that shouldnt be

affected at least not in the

unless its a terminal hepatic disease

that shouldnt be affected by hepatic

disease

and then twothirds is affected by

or is caused by a hepatic clearance

and you can see that

the metabolic metabolic routes involve

cytochrome p0s

you can also see that the metabolites

are not active so we only have to worry

about the pain we dont have to worry

about metabolites and we can see that

the target biophase its a factor 0a

inhibit inhibitor is in the blood so

when we look at blood levels they are

directly associated with the target and

theres a linear relationship

so what does the label tell us about

seralta

you can see the label tells us a

single dose study was done where 0

milligrams which is on the low end

depending on the indication

was studied in healthy volunteers and

studies and various degrees of hepatic

impairment

only child pure a and b so no child you

see as is typical the case

and they observed so if you look at the

table now they observed that in child

pua

the area under the curve

is

basically insignificantly elevated

relative to health healthy volunteers

because this drug can be easily measured

in terms of its dynamics they also

measure the inhibition of factor 0a and

you can see again theres an

insignificant change

and the p

prothombian prolongation again

significant change

so child qa patients are basically not

different from healthy volunteers

if you move to the more severe stage the

child pb you can now see that

plasma levels went up both in terms of

the area and the peak levels

factor 0 inhibition went up and pt

prolongation went up

so we have increased exposures that

translate into into increased

pharmacological response now keep in

mind the pharmacological response

relates to clotting factors so part of

those pharmacodynamic changes are not

just driven by the

increased drug levels but also by the

reduced

synthesis

of clotting factors

now to put that on perspective i put

this little diagram

here at the very bottom where youre

looking at the change the fold change in

exposure thats right here on the yaxis

so one means there is no change relative

to healthy volunteers

and then we look at various conditions

so we already looked at the liver

so a child pua theres maybe a 0 change

very little change on the other hand

child pb theres a

0 percent change in

exposure on the other hand if you look

at renal impairment so this would be

mild moderately and

severely impaired

renal function

renal function is much less important as

you would have expected because thats a

relatively

small about onethird pathway of

elimination compared to the liver

if you look at specific drug

interactions you can see

that the majority or the largest drug

interaction is for drugs that inhibit

pgp and va

very potently and you can see that the

levels increased

about two and a half fold

which tells you basically that uh

child pube child pew baby patients

have the same increase in drug level the

same reduction in hepatic clearance

as in presence of inhibitors of

cytokine pa and or pgp

okay and this is something that is

clinically meaningful and needs to be

considered

all right let me wrap up

by uh using acetaminophen tylenol

as an example of a drug that is well

known to cause hepatic toxicity

and is

available over the counter

and i should add one of the reasons why

i included it here is also either the

most common or the second most common

cause of

requiring liver transplant so

inadvertent or intentional

acetaminophen overdose is a major public

health

issue but i also want to talk about the

mechanism because it is a prime example

of a doserelated hepatotoxic drugs

a drug

so acetaminophen is a small molecule

drug its a neutral molecule

so if you look at the all

bioavailability you can see its quite

high so it has

low first pass effect so it would be a

low hepatic extraction ratio drug in my

terminology

it has high solubility and permeability

in the gut

and its all absorption depends on

gastric emptying so its rapidly

absorbed unless for example you take it

with a meal where the absorption gets

slowed down

distribution wise it has a relatively

small volume distribution about 0

liters per kilogram it is virtually not

plasma protein bond at all or very

little so plasma protein bond binding is

not something that we need to consider

this is where the important piece of

information comes in so its total

clearance

is about mils per minute per

kilogram

relative to liver blood flow of 0 mils

per minute per kilogram which makes it

as i say before a low extraction ratio

drought

this liver clearance is the only

way

that

acetaminophen can leave the body it is

not subject to renal excretion its so

small and relatively lipophilic and

relatively hydrophilic enough

to be reabsorbed in the tubulin so it

does not really show up unchanged in

urine

okay so the main pathways are

phase one and phase two routes of

metabolism and then the metabolites

which are polar or most of them are

polar are eliminated in the urine

so if you look at that under the

microscope because this is important

relative to the

liver toxicity which is what i want to

focus on

so here we have the parent molecule

it is primarily metabolized to its

glucuronide

okay so ugtmediated gluconation and

sulfation are the main

pathways of elimination

and virtually none shows up unchanged in

europe however theres also a relatively

minor pathway

that is

related to cytochrome p0 e a fairly

uncommon

isosyn

okay and that forms a

reactive intermediate metabolite nab qi

okay so this is an oxidative metabolite

that has the ability to react with

tissue proteins now this reaction

happens in the liver so it reacts with

liver proteins and it forms those

macromolecules that basically to cell

death or hepatocellular damage

now

in order for that not to happen the body

has a system in place to

[Music]

neutralize those reactive metabolites

and that is the glutathione system so

you can see at low doses of uh

acetaminophen

this metabolite get gets formed but then

it gets swept up and neutralized by

glutathione conjugation

and this is the gluta glutathione

conjugation product that gets then

further

eliminated in the urine

so even though

we have this metabolite formed at all

doses at low doses

the body has the ability to neutralize

and eliminate the metabolite

if not meaning at high doses once you

start

saturating the glutathione

neutralization pathway

then you have this hepatotoxic effect

that i mentioned before

now where does glutathione come from

where glutathione is a tripeptide you

can see it starts off by the

reaction of acetyl uh or

acetyl cysteine form cysteine system and

glutamate

form a dipeptide that then forms the

reduced glutathione

and that is whats required to

neutralize the um

toxic metabolite

so what does the uh

prescribing information what does the

label tell us about the

toxicity that an overthecounter

product has

you can see in adults it tells us this

product contains acetaminophen severe

liver damage may occur if you take

more than 000 milligrams so this is

clearly dose related and the risk goes

up exponentially if you exceed total

daily doses of grams and above

if you take other drugs that add to your

total your daily total

and if you

continue to drink alcohol now thats an

interesting interaction between alcohol

and acetaminophen so let me go back

because theres something else that is

unique about

cytochrome e thats the

metabolic enzyme that forms this

reactive intermediate

this enzyme can be inhibited by alcohol

so in presence of acute alcohol

you would actually

inhibit and protect

the liver from formation of this toxic

metabolite however chronic alcohol use

which is what the labor refers to

induces this enzyme so patients that are

chronic consumers of alcohol they

actually have higher levels of this

enzyme which in turn means they form

more of this toxic metabolite

okay so thats where the third bullet

item comes in and you can see uh

something that is uh even more

concerning since uh cedar minofin is a

part of a lot of combination products

that are used in children

that we have equal or similar warnings

in children about not exceeding a total

daily dose of

four grams

okay now how do we assess lets assume

you have the misfortune of having to

deal with

a patient that is suspected of

acetaminophen overdose how do you deal

with that

well we obviously want to know what is

the likely dose that the patient has

ingested and are there any clinical

signs and symptoms that we talked about

before of hepatic failure

the most important step to take is to

measure levels of acetaminophen in

plasma and then we use the matthew

nomogram to decide what to do if

anything

and thats what youre looking at here

so here youre looking at on the xaxis

the time after the ingestion of

acetaminophen

and youre looking at the concentrations

of acetaminophen in plasma

okay and you have you can see the first

four hours

we dont have any information because

thats when the acetaminophen is being

absorbed so we dont really have any way

to decide whether to uh

treat a patient or not

however once we are beyond the four time

period then we have those three lines

the top line

means those are patients that are at

relatively

uh

they are at a high risk of developing uh

this hepatotoxicity

so theyre basically

good candidates to be treated

the blue line tells us they are at

probable risk

and the black line would tell us any

level that is to the left meaning lower

than the black line those patients are

not at risk of hepatic injury

you would also have to consider other

drugs that might affect the liver before

you decide what to proceed and you want

to assess

the lfts and as i mentioned before

based on the mechanism of toxicity

meaning you have a direct

interaction with proteins leading to

direct cell death

acetaminophen you have dose related

increases in ast and alt so this is a

very useful piece of information however

keep in mind there is a delay before

that occurs which is the reason why we

use the drug levels as our marker

if you decide to uh treat your patient

early on in this four hour window that i

mentioned before

you may consider giving charcoal

activated charcoal to reduce

all absorption but in most cases youre

going to basically have to think about

giving the specific antidote and the

specific antidote is an acetyl

cysteine or neck

and you can see

that is the

pre

cursor to the uh acetylcysteine

that ultimately goes into the

glutathione so what youre basically

providing the body youre providing the

body with a precursor to

glutathione and you can do that either

by all administration or by iv

and then you do clinical assessments to

decide

whether you should do additional

treatment or whether the condition is

worsening and you have to do other

vital support

okay so let me just summarize what i was

trying to convey to you uh we talked

about drugs and the liver being a two

bay street

that number one it is very difficult to

measure liver functioning

we typically use transaminases to

measure the or to assess the

hepatocellular damage were using

alkaline phosphatase and bilirubin to

tell us something about cholestasis

we then talked about uh how to rule out

other

causes of liver damage before we

conclude that a drug has

caused liver damage with the exception

of drugs like

a tylenol like acetaminophen where this

is well characterized and we can

actually measure drug levels instead

we also talked about the fact that the

liver can play a large role in handling

the drug

and for especially drugs that are

primarily handled by the liver where

metabolic clearance is the main pathway

that we have to consider the effects

that chronic hepatic impairment can have

on bioavailability and hepatic clearance

that we can make a distinction between

high and low extraction ratio drugs

that high extraction ratio drugs can be

hit both by a reduction hepatic

clearance but also an increase in

bioavailability

and lastly we are using the child use

coring system to quantitatively assess

the severity of

chronic liver disease

and nowadays pretty much any

drug labor that comes out has

information on what to do in terms of

dose adjustments or additional

monitoring in patients with

liver impairment

thank you for your attention i hope you

enjoyed listening to me and use this

material prospectively in your career

if you have any questions about this

course please contact the course

coordinator the project program

coordinator

thank you