Welcome to the introductory lecture for modulethree of the principles of clinical pharmacology

My name is Lisa Cordes and Im an oncologyclinical pharmacy specialist at the National Institute of Health and today well focusour presentation on drug metabolism and drug transports

The primary objective of the lecture todayis to go over the basic principles and provide you with an overview or even perhaps a reviewof the basic concepts of drug metabolism and drug transport

The faculty and the subsequent lectures ofthis module will then go into these topics into greater detail

So lets start with drug metabolism and welldo an introduction and discuss the clinical relevance

Well focus on phase one and phase two metabolismand then give cytochrome p0 as our example

For drug transporters again well talk aboutan introduction and discuss clinical relevance

Well talk about the ABC and SLC superfamiliesand go into Pglycoprotein for our example

And as youve learned from the previous lecturesin this course drug metabolism is one of the steps in the pharmacokinetic process

So what exactly is metabolism?

Metabolism is the biotransformation or howthe body changes a substance into a new entity or chemical which is known as a metabolite

And this is important because most drugs areadministered in their lipophilic form and the lipophilic characteristics are importantto allow the molecule to pass through plasma membranes and reached their site of action

However these same lipophilic characteristicsactually hinder the elimination of the drug from the body

So we need metabolism in order to transferthe molecule into a more polar or hydrophilic

compound in order to allow for elimination

And this primarily occurs in the hepatic enzymesbut it does also occur in the small intestine for orally administered products

So knowledge of drug metabolism is vitalfor both people who develop pharmaceuticals and for those caring for our patients andwe need to know how exactly a drug is broken down after we administer it

So here are a couple of examples

Most drugs are administered as an active compound

That is then metabolized or broken down intoan inactive compound which is then eliminated from the body

However some drugs are administered as inactivecompounds

Those are then transferred into active compoundsand this is known as a prodrug

We do occasionally have some compounds thatare administered in the active or inactive form and these are actually broken down intotoxic metabolites and its important that were aware of these so that we can quicklyeliminate them so that they dont cause unexpected adverse events

So these compounds can be broken down throughphase one metabolism or through phase two metabolism but in most scenarios they occurredfrom phase one metabolism and then thats followed by phase two metabolism

So well look at this table here and wellstart with phase one metabolism

So as you can see here we have phase onemetabolism is known as functionalization

And this is where a functional group suchas OH or NH is either added to or unmasked from a parent drug the drug thats administeredand this is primarily done through an oxidation reaction in the endoplasmic reticulum of thecell

As a result of this process we typicallyjust see a small change in the hydrophilicity

Subsequently we see phase two metabolismand this is known as conjugation and this

is when a covalent link is formed betweenthat functional group that we just talked about in phase one metabolism and an endogenoussubstrate

And this is primarily done through glucuronideconjugation

And metabolites formed in these syntheticreactions are more polar thus allowing for better elimination

In other words we see a major increase inthe hydrophilicity of these drugs through phase two metabolism

First pass metabolism is unique to orallyadministered products and its where the concentration of an oral product is greatlyreduced before it ever reaches systemic circulation

And as you can see in this image the smallintestine and the hepatocytes of the liver are the primary site of an activation duringfirst pass metabolism

And well go through this image step by stepso you can get a good understanding of this process

So here we have the drug

In this case its a tablet thats administeredin its oral form

As you can see here its going through theGI system into the stomach where it reaches the small intestine and this is the placewhere most oral medications are absorbed

So you can see here well jump over intoa more detailed view of the small intestine

So we have the drug here in the lumen andthats going to get into the enterocyte of the small intestine where its going to runinto something called CYPA cytochrome p0

A and this is an enzyme thats involvedwith drug metabolism and well go into it more on the next page

But this just represents any enzyme that canbe in involved in drug metabolism

So once the drug is in the enterocyte ofthe small intestine the CYPA enzyme actually breaks it down and in this case mostly intoinactive components 0 percent and only 0 percent of the drug product is left in itsactive form

Well then jump over to the main picture hereand it is going to then get into the liver

And heres a more detailed version of thatprocess

So currently its in the sinusoid againin that 0 percent active form where its

going to get into the hepatocyte of the liver

And once again its going to run into CYPAwhere its going to undergo further metabolism

And its going to break down further intoinactive metabolites and then only percent

of the drug product in this case is stillin its active form

That percent of the active form will thengo on for systemic circulation

And in this case this product is known tohave high first pass metabolism

And the extent of the first pass metabolismdepends on a number of physiological factors

and these include enzyme activities we justdescribed and also GI motility

And you might come across this clinicallywhen you have a drug thats administered orally

and the dose is much higher of that oral formcompared to when its administered in the

IV formulation

So as I just described cytochrome p0 isinvolved with drug metabolism

So what exactly is the cytochrome p0 system?

So this is a microsomal superfamily of enzymesthat catalyzes the oxidation of drugs

And so we know since were seeing oxidationin this step that its involved with phase

one metabolism as we described earlier

I do want to take just a moment to describethe nomenclature of cytochrome p0

So cyto comes from the fact that its boundto membranes within a cell; chrome P means

that it contains a heme pigment; and the 0comes from the fact that it absorbs light

at a wavelength of 0 nanometers when itsexposed to carbon monoxide

Heres an example of CYPA

So each enzyme encoded by cytochrome p0gene is named CYP as you can see here

In this case the group is number three thesubgroup is A and finally at the end we have

the gene in this case four

Now its thought that the cytochrome p0is the most clinically important of the phase one metabolizing processes and it soughtthat humans have approximately 0 cytochrome p0 genes accounting for about threefourthsof enzymes involved in drug metabolism

And we believe that the most clinically significantof these enzymes are cytochrome p0A and CYPDSo since discovering cytochrome p0 back

in the 90s weve learned that many variablesimpact how a drug is metabolized and one of these are genetic factors

So a specific gene encodes a specific enzymethats involved in metabolism

So well go through an example here on thisslide

So lets say we give a normal metabolizera substance that is a cytochrome p0 D substrate

We would anticipate the standard metabolismthe expected toxicities and the anticipated efficacy

So really nothing out of the ordinary thanwhats published in the literature

However if we give a patient whos thoughtto be a poor metabolizer that same drug at that same dose we might actually see decreasedmetabolism and that patient might have more toxicities than we would expect

On the other side of the spectrum we haveultrarapid metabolizers

So these patients are thought to metabolizethe drugs too quickly and that could actually lead to decreased efficacy and possibly therapeuticfailure of that substance

So drug interactions also play a big rolein drug metabolism

We have our CYP substrates that we just talkedabout and we also have our CYP inhibitors and our CYP inducers

And this classification system helps aid inpredicting the impact of a CYP inhibitor or inducer on AUC or area under the curve ofthe substrate

So take for example a strong CYP inhibitor

Strong CYP inhibitors have shown to increasethe AUC of their sensitive substrates by approximately fivefold

CYP inducers are thought to strong CYPinducers are thought to decrease the AUC of the sensitive index substrates by greaterthan or equal to 0 percent and so typically strong inducers and strong inhibitors arethought to be clinically significant

There are other coexisting conditions suchas chronic liver failure and advanced heart failure that also play a role in drug metabolism

So as you can imagine if we take a patientthats in front of us and think about all these different factors that play a role indrug metabolism we might actually be able to modify that dose based on these patientspecific factors so that we can prevent a toxicity or we can prevent therapeutic failure

So lets transition gears a little bit intothe basics of drug transport

So what exactly are membrane transporters?

So these are proteins involved with the transportof their substrates across all membranes

And this results in either the transfer ofdrug molecules into the cell which is known as influx or drug molecules out of the cellwhich is known as efflux

And remember that bio membranes are predominantlylipophilic in nature

So lipophilic compounds can generally passthrough that cell membrane through passive diffusion

However transporters are actually neededfor hydrophilic substances to cross those membranes

So why is this important clinically?

In the early 000s it was actually broughtto light that transporters were evolved in drugdrug interactions

Its also important because it is thoughtto have an impact on drug efficacy

So this we can see with cancer cells andwith bacteria cells

So cancer cells and bacteria are very smart

They actually overexpress efflux transporters

So if a drug gets into a bacteria or a cancercell for example and the primary objective would be to cause a ptosis or kill that cell

However that cell is smart and actually hasthese efflux transporters over express and there are a lot of them that actually effluxthat drug product out of that cell and dont allow that cell dont allow that treatmentto do its job

So transporters are overexpressed or expressedin various types of cell membranes but the ones on plasma membranes are really the oneswe think about that are being important for pharmacology

And theyre divided into major two majorsubfamilies; and that is the ATP binding cassette ABC as we see here and the cellular carrieror SLC as we see here

Now ABC transporters are active transportersand they require energy to move against the concentration gradient and theyre responsiblefor efflux

So thats demonstrated here with our ABCtransporter which is an efflux transporter

On the other hand SLC transporters for themost part theyre involved with the uptake of small molecules into the cell

This diagram as a whole shows the transepithelialand transendothelial flux of drugs and we can see that primarily occurs in the smallintestine in the liver in the kidney and in the blood brain barrier

We do also see this see transporters inthe testes and in the placenta and interestingly its thought that efflux transporters werethought to be an evolutionary adaptation against potentially toxic substances allowing themto protect vital organs

Well go through one example of Pglycoprotein

Pglycoprotein is an ABC transporter so itsinvolved with the efflux of substances out

of the cell and its also known as ABCD

And heres an example

So Pglycoprotein is expressed on the enterocytesin the small intestine and typically it reduces the oral bioavailability of drugs that arentsubstrates

So here we have our Pgp substrate thatsin the cell the enterocyte of the small intestine and the Pgp transporter is effluxing thatsubstrate out of that cell and then its going to get sent for elimination

If however we give a Pgp inhibitor concurrentlywith a Pgp substrate we see that the Pgp inhibitor blocks that transporter efflux outof the cell

That results in an increase of the Pgp substratewithin the cell and that means more of that Pgp substrate is available to go onto systemiccirculation

Opposite of that we actually have Pgp inducerswhich caused more of that Pgp substrate to be out of that cell and that will decreasethe Pgp substrate in the cell again decreasing the concentration of the substrate thatsavailable for systemic circulation

Wrap up this lecture as you have seen drugmetabolism and transport are complex processes and I hope Ive been able to provide you witha basic introduction to these concepts

Please continue to watch the subsequent lecturesin this module for a more indepth look

Thanks for watching