Bruce Waldrop:Hello and welcome to Module of the NIH

My name is Bruce Waldrop

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So Module is going to be looking at thepharmacokinetics and drug therapy in special populations

The purpose of this lecture is just to giveyou a brief overview of the different topics that we will be covering in Module and orientyou to some of the terminology and concepts that we will be covering later on

Now special populations refers to patientpopulations which have important differences in pharmacokinetics or pharmacodynamic responsescompared to the general population

Well be looking at six of those special populationsin this module which are shown here

And again over the next few minutes werejust going to hit some major points for each of these six areas just so that youre readyand prepared to go into more detail later

The first we will look at is renal replacementtherapy

Now theres various types of renal replacementtherapy

Two of these are shown here

But the main function of renal replacementtherapy is to replace the nonendocrine functions of the kidney basically to serve as a filterto remove waste products solutes and so on

Now sometimes that also includes drug andwell get to that in just a second

On the left we have continuous venovenoushemofiltration

In this process we take the patients bloodpass it through a filter using pressure and by convective flow solute is removed

And then the blood is returned to the patient

On the right we have essentially the sameprocess but this time we add dialysis

So in addition to the convective flow wealso have diffusion of solute so a little

bit different but the same principles apply

Now when we look at drug removal and renalreplacement therapy theres a few things

we have to consider

First what are the properties of the filter?

Is it a highpermeability filter?

Does it have a large pore size or is it atlow permeability?

Whats the surface area of the filter andwhats the thickness of the filter?

Additionally lets look at the propertiesof the drug

Is this a highmolecularweight drug?

Is it too large to pass through the poresof the filter?

Is it or is it low molecular weight?

Is the drug hydrophilic or is it lipophilic?

Drugs with very large VDs that extensivelybind to tissue will have very little of the

drug in the plasma so those drugs will notbe very effectively removed by renal replacement

therapy

Also if the drug has a high degree of proteinbinding its not going to be able to pass

through the filter

So drugs that have very low fraction unboundthose drugs will not be good candidates for

removal by renal replacement therapy

And finally the transmembrane pressure gradientas well as the dialysis flow rate can dictate

how well solute and therefore drug can beremoved by these processes

Well also be spending a lot of time on hepaticdrug metabolism and factors that affect hepatic

drug metabolism

So as you know the liver serves very importantrole in physiology including drug metabolism

and elimination

Some other things that are listed there includecarbohydrate fat and cholesterol metabolism

the synthesis of protein importantly plasmaproteins that drugs bind to such as plasma

albumin

Clotting factors are also synthesized in theliver

And then the liver serves as a storage sidefor fatsoluble vitamins as well as glycogen

and other substances

Now when we look at drug clearance by theliver we have to consider how much blood

flow is going to the liver and what is theextraction ratio of that particular drug in

the liver

So the clearance is determined by hepaticblood flow or Q times the extraction ratio

Well get more into detail on the next slideon that

Now theres two main types of metabolism thatoccur in the liver

Phase I metabolism involves CYP0mediatedmetabolism such as hydroxylation or dealkylation

reactions

Phase II metabolism involves conjugation reactionssuch as glucuronidation or sulfation

Phase II involves the addition of a usuallypolar molecule to the drug molecule to make

it more water soluble

Phase I and Phase II may occur independentlyor sequentially through the liver

Now going back to extraction ratio we canhave a highE drug which has an extraction

ratio of 0 percent or higher or a lowEdrug which is 0 percent or lower

So highE drugs the only thing that limitsthe ability of the liver to clear those drugs

is how much blood flow you are sending tothe liver so those will be flowlimited drugs

On the other hand lowE drugs changing bloodflow does not really alter the clearance that

much

Its really determined by the fraction thatis free or the fraction unbound as well

as the intrinsic clearance properties of theliver

Now the enzymes in the liver thats handlingthe metabolism can be inhibited by other drugs or induced by some drugs

So that could definitely change the intrinsicability of the liver to clear drug

Also we know that polymorphisms exist in P0enzymes that would change the ability of the enzyme to function and therefore metabolizedrug

So we can have a poormetabolizer phenotypeintermediate extensive or ultrarapid for example for cytochrome P0 D

And we know that Q as we saw previouslyis an important factor for determining hepatic clearance

So changes in hepatic blood flow such aswe might see in chronic liver failure or in heart failure would certainly impact theability of the liver to clear drug

Another topic that we will be covering inthis module is drug therapy in pregnant and nursing women

So we know that theres some physiologicchanges in pregnancy that affect important pharmacokinetic parameters in the mother

So for example during pregnancy the motherhas an increase in glomerular filtration rate that would change the renal clearance of drug

Theres also changes in hepatic drug metabolismand also theres an increase in total body water which would play a role especiallyfor drugs that have a volume and distribution in total body water

Now once that drug is ingested by the motherwe have to be concerned with fetal drug exposure

And that is determined or influenced by severalfactors listed here

First what are the physicochemical propertiesof the drug?

Is the drug lipophilic or hydrophilic?

Is it ionized at physiologic pH?

Whats the molecular weight of the drug?

How easily does it cross the placenta?

Also theres some transporters on the placentathat can determine how easily a drug can move across the placenta from the maternal circulationto the fetal circulation

And then finally lets consider the developmentalstage of the fetus

If the drug does enter into the fetal circulationis the fetus able to metabolize that drug?

So these are all considerations regardingfetal drug exposure

Now we also know that following birth wehave to be concerned with drug getting into breastmilk and then subsequently ingestedby a nursing infant

So drug partitioning into breastmilk is dependentupon several factors many of which weve already covered previously

So those include lipid solubility of thedrug the plasma protein binding of the drug its ionization as well as its molecular weight

Once the drug does get into breastmilk wehave to consider how much gets into breastmilk how much is actually dosed to the baby duringfeeding if the drug is absorbed is the is the infant able to metabolize or eliminatethe drug and finally what is the timing of the feeding relative to when the mothertook the drug

So these are all factors that we have tobe worried about when we look at drug exposure to a nursing infant

In this module were going to look at developmentaland pediatric pharmacology as well as geriatric pharmacology which we will get to next

But we know that infants and children arenot just miniature versions of adults

They have important differences in physiologythat affect drug therapy

So for example total body water is muchdifferent in a preterm infant or a fullterm infant compared to an adult

So as you can see here a premature infanthas 0 percent of total body weight is actually

body water

For a full term its 0 percent

For an adult its about 0 percent

For a geriatric patient we see that itsabout percent

So understanding and appreciating the bodywater content of an infant versus an adult is very important when we look at dosing ofa drug

We also know that during fetal developmentas well as after birth theres some major changes in the expression of drugmetabolizingenzymes

So having a knowledge of which enzymes arepresent and when during development is very important when we look at this patient population

Another pharmacokinetic change that we seeor a physiologic change that we can see during development that would affect drug therapyis the amount of gastric acid thats produced in an infant following birth versus a fewweeks out

So this might affect drug dissolution andultimately drug absorption

And then finally renal function is generallyvery low when a baby is first born

However it increases over the next week orso

So drugs that are eliminated by the kidneydefinitely would have to be altered

The dosing of those would have to be alteredin a pediatric patient

Now just as we saw some physiologic changesin the early stages of life that would affect drug therapy we have the same considerationsin a geriatric population

So as we age we know that renal functiondeclines

So for drugs that are eliminated by the kidneythat would definitely require a dose adjustment

Theres also a reduction in cardiac output

That means that blood flow is going to bereduced to eliminating organs such as the liver and the kidney

We saw previously that body fat increasesas we age

So in an elderly patient for drugs thatare distributed into body fat the volume

of distribution will go up compared to anadult patient

And then finally CYP0 A activity hasbeen shown to decrease in the elderly population

Fifty percent of drugs are metabolized byA so this is definitely an important consideration

when we look at this patient population

And not only do we have pharmacokinetic changesthat occur we have pharmacodynamic changes

that occur

So as an example we know that elderly patientshave an increased sensitivity to muscarinic

receptor antagonists or anticholinergic drugs

They also have decreased sensitivity to betaadrenergicdrugs such as beta agonists or beta antagonists

Many of you are familiar with the Beers Criteria

This is a publication that is periodicallyupdated that lists potentially inappropriate

medications in this patient population

So theres many drugs not just the onesthat are listed here many drugs that may

be affected in this patient population

Now finally within the elderly populationtheyre just going to be on more medication

So theres an increased risk for drug interactionsso that would be drugdrug interactions drugfood

or drugdisease interactions

So as you can see here that patients whoare 0 years or over in age over a third

of them are on five or more medications

Now the last topic we will cover in the introductionhere is pharmacokinetics and obesity

So we know that we are in an obesity epidemicin the United States

Every state in the United States had at least0 percent of adults with obesity

Seven states had over a third of adults withobesity

Now obesity is classified by body mass index

We use that in dosing and we will be coveringthat in more detail later on in the module

So just as an overview theres some importantfactors that we need to consider in obesity

some important pharmacokinetic changes

So one of those changes is the percent bodyfat in an obese patient

So not only are they larger they have ahigher degree of body fat

Thats going to affect the volume of distributionof lipophilic drugs

Now we can make adjustments on drug dosingbased upon the patients total body weight or actual body weight their ideal body weightor some type of weight to adjust for body weight

And we need to consider these factors whenwere dosing the drug because without picking the appropriate weight to dose the patientyou may potentially underdose or overdose the obese patient

Not only is volume a distribution changealso clearance is altered

So generally clearance increases but itsnot in a linear relationship

It does not scale to body weight

Also P0 activity may actually increase ordecrease in these patients

So theres evidence that have shown thatA activity decreases in the obese patient population whereas E activity may actuallyincrease in this population

Thank you for your time

I hope this introductory lecture gave youa good overview and hit the main points of whats going to come ahead for Module thepharmacokinetics and drug therapy in special populations module for the NIH Principlesof Clinical Pharmacy course

Thank you