Hello Im Dr Anne Zajicek from the NIH

So the topics I am going to cover today verybriefly are the definitions of pharmacokinetics pharmacodynamics clearance volume of distributionhalflife firstorder and zeroorder pharmacokinetics peaks and troughs and the utility of alteringthe dosage interval

We will also speak briefly on the concentrationeffectrelationship and a commonsense approach to pharmacokinetics

Okay so lets define our terms

What do pharmacokinetics and pharmacodynamicsmean?

Pharmaco comes from the Greek pharmakon meaningpoison or remedy

Pharmacokinetics is what the body does tothe drug and is a mathematical description of absorption distribution metabolism andelimination

Pharmacodynamics on the other hand is whatthe drug does to the body

So movement of drug

So what we are talking about overall isthe drug site of administration

On the left in the blue is oral or poadministration which undergoes absorption

In some cases firstpass metabolism clearancethrough the liver distribution through the body clearance again through renal and hepaticmechanisms and elimination

Drug can also be administered intravascularlywhere it undergoes distribution then clearance through renal and hepatic mechanisms andelimination from the body

What is absorption?

Absorption is the movement of drug from thesite of administration to the site of action in the vascular space

What routes of administration provide drugfrom the small intestine to the portal vein and then to the liver for firstpass metabolism?

Those routes of administration are oral deeprectal administration hepatic arterial and

portal venous

And one example would be propranolol

And one thing to note is for drugs that undergoextensive firstpass metabolism is theres a large discrepancy between the oral doseand the IV dose

What routes of administration avoid the portalcirculation and firstpass metabolism?

And these include intravenous intravascularsubcutaneous sublingual transdermal and inhalation pathways

What is distribution?

Distribution is the movement of drug fromthe site of administration or absorption to the rest of the body

The volume of distribution is a proportionalityrelating the amount of drug in body to the concentration

And is not related to a physiologic volume

The range can be somewhere between 0 and liters per kilogram

Drugs that have a small volume of distributiongenerally are bound to carrier proteins in blood and are more water soluble

The clinical relevance for this is for adrug which is greater than 90 percent bound to proteins in the blood decreased binding

In other words changes in binding from 90percent to 0 percent cause large increases in the percent unbound drug and greater clinicaleffects

Since the assumption is that the free drugor the unbound drug is the active drug

Drugs with a large volume of distributionare generally tissue bound lipidsoluble

And the clinical relevance here is that itis very difficult to remove these drugs by dialysis

What is drug clearance?

The volume of blood cleared of drug per unittime

Generally liters per hour is the drug clearance

Drug removal from the body is by the kidneysor renal elimination liver or hepatic and metabolic elimination and also through breastmilkvia lactation

What is the halflife?

The halflife is the time to clear half ofthe total body load of the drug or the time for the concentration of the drug to dropby onehalf

So for example on the left side I havea listing of times when blood was drawn and the drug concentration

So at hour two the concentration was 0

At four the concentration was 0

At hour six five

And at eight hours the concentration wastwo and a half

Its clear that it has taken two hours foreach of those concentrations to drop by half

So in other words the halflife is two hours

You can plot these concentrations on a semilogplot with time on the Xaxis and log concentration on the Yaxis and that would form a straightline the slope of the decline which as a point of trivia is the elimination rate constant

The other value of knowing the halflife isthe time it takes to reach steady state

And in this plot you are seeing drug beingadministered by the jagged lines and the gradual increase in drug concentration

And you can see at the bottom of Figure stating that the steady state is reached by hours or five times the hour halflife

So in other words time to achieve steadystate five halflives

I wanted to mention the concept of firstorderversus zeroorder pharmacokinetics

Firstorder kinetics drugs which exhibitfirstorder kinetics have a constant percentage of drug eliminated per unit time

In other words if the drug concentrationis 00 at one halflife it drops to 0 percent

and then percent and so on

And the important thing about this is theresa proportionality between the dose and the concentration

So as you double the dose you double theplasma concentrations

And this is in contrast to zeroorder pharmacokineticswhere a constant amount of drug is eliminated per unit time

So if you start with 00 milligrams thenthe concentration will drop to 90 0 0

and so on

And the problem here is that when you doublethe dose there is an unpredictable increase in concentration

And three examples of drugs or substanceschemicals that exhibit zeroorder kinetics

are ethanol phenytoin and aspirin

And in this case there is no relevant halflife

Okay I wanted to talk about some concentrationtime curves just so you know what they look like

This is for intravenous

Here were seeing a plot of concentrationagainst time

At the bottom you see the time of the infusion

The Tmax which by definition is the concentrationat the end of the infusion

And that concentration going up is the distributionphase

The highest concentration is called the Cmax

The decline is the elimination phase

And the AUC is the area under the concentrationtime curve

Here is a picture of the concentration timecurve for an oral dosage form

This is again a plot of concentration againsttime

And what youre seeing here is that the timeof administration is at time zero

As the concentrations go up absorption isoccurring primarily and also distribution

As the concentrations decline that is thedistribution and the clearance phase

And again were looking at the Cmax beingthe highest concentration

And the area under the time curve as beingan estimate of drug exposure

Now these are some shapes of concentrationtime curves just to see differences when you see differences in clearance or differencesin absorption

On the left you see the IVtime curve wheretheres the rapid increase in concentrations during the time of the infusion and then thedropoff during the elimination phase

And on the right are pictures of concentrationtime curves when the drug is given orally

And the two parameters that people are generallyinterested in including the Food and Drug Administration when they make determinationsabout bioavailability or bioequivalence are the Cmax and the AUC

So you can see the first curve here is aCmax area under the curve for one oral dosage form

In the second panel you can see the Cmaxand the AUC

The AUC looks fairly similar to the firstone but you can see that the Cmax is moved to the right showing delayed oral absorption

So in the third panel you see a Cmax whichis shifted to the left a small AUC which can indicate either poor absorption or rapidclearance

The next set of curves will describe the concentrationresponse relationship

And here Ive plotted on the Xaxis thelog ibuprofen concentration

And on the Yaxis the percent of maximumreduction in headache which would be the response

And you can see is the area under the curvethe concentrations increase and then dropoff

You can see a slight delay but a relationshipbetween the concentrations of ibuprofen and

pain relief

Another way of looking at this would be toplot the pain score against time

And again you see the ibuprofen area underthe curve

And then the decline in headache pain

I think this is a nice way to look at concentrationeffect relationships

So Id like to talk about one equation

And this equation is that the steady stateconcentration of drug is equal to the fraction

of drug absorbed times the dose divided byclearance times the dosage interval

And this all makes a lot of sense

So the fraction absorbed can range from zeroto one

And if the fraction absorbed drug changesthat will affect the steady state concentration

For example if you have a drug for examplethe tetracyclines bind to calcium

So if a patient is taking a tetracyclineand then this is administered with yogurt

or a calciumcontaining antacid that willchelate the tetracycline and decrease the

fraction of drug absorbed

You will have a lower concentration

If the dose of drug is increased or decreasedthere will be a proportional change in steady

state drug concentration

If the clearance is altered

For example if you have a drug that is liableto be induced by a compound and that compound

thats the drug inducer iscoadministered with the drug of interest

and the clearance increases then the concentrationof drug will decrease

And as the dosage interval is spaced out fromevery four hours to every eight hours and

so on the drug concentrations will also beaffected by that change in dosage interval

Okay Id like to talk briefly about therapeuticdrug monitoring

Therapeutic drug monitoring is used when thedrug concentration is closely related to effect

So here is a case

MG is an yearold 0pound female admittedtwo days ago with urosepsis

Labs include a white count of 000 with0 percent bands

BUN and creatinine of 0 and respectively

And a urine gram stain showing gramnegativerods

Okay so what you can see here is that sheis elderly

She is thin

She is probably frail probably does not havea lot of muscle mass but her creatinine is

And that would be fine if she were a 0yearoldbody builder

But she is a frail yearold 0poundfemale

So its likely that she has some renal dysfunction

She is started on gentamycin 0 milligramsIV q hours

Peak and trough concentrations are drawn todayon day two

The halfhour peak is 0 micrograms per milliliter

Target concentration being somewhere betweenfour and 0

And the trough concentration three microgramsper milliliter

The target being less than two microgramsper milliliter

And my question to you is should you Adecrease the dose; B increase the dosage interval in other words give it less frequently;or C hold the next dose for four hours and restart with the same dose at an increaseddosage interval or less frequently?

Okay so just to define our terms the peakis the highest concentration after the short infusion and its proportional to the dose

The trough is the lowest concentration orthe concentration before the next dose

And its related to the clearance and thedosage interval but not the dose

This is a key piece of information

This is commonly misunderstood

So lets plot whats going on here

So our Xaxis has the time and the Yaxishas the concentrations

And you can see the first curve everythinglooks fine

The concentrations are within bounds

The peak is between you know its less than0 probably around eightish

And the trough is probably around one

But what you can see is that the drug is startingto accumulate because the trough is not going to down to zero

And so the peak concentration is equal tothe peak from the dose plus the trough from the previous dose

And so whats happening is that at the timethat your concentrations are being drawn on that second day

The peak is now higher than 0 and the troughis now higher than two

Okay so this is your thought process

A high aminoglycoside peak is associated withototoxicity or hearing damage

A high trough concentration is associatedwith nephrotoxicity or kidney damage

The peak as it stands right now is on thehigh end of the desired range and the trough is too high

And our current order again is your basicstarting dose of gentamicin 0 milligrams every eight hours

Okay so this is a drawing of the gentamicinPK sampling

And I find this to be very helpful to plotout exactly whats going on so that you can get a better understanding of what the peaksare what the troughs are and what the time interval is

So this is my schematic of what is goingon

So lets say that the drug is infused at:00 am

Its usually infused for about 0 minutes

So from :00 am to :0 am the infusionis going on

Blood is drawn at 0 minutes after the infusionwhich Im going to round off to about 9:00 am

And there as we know the peak was 0 microgramsper milliliter

And then the trough is drawn before the nextdose which is at 00 hours or :00 pm

and its three micrograms per milliliters

So the time difference between 9:00 amwhen the peak was drawn and the trough drawn at 00 hours is seven hours

Okay so 9:00 am the concentration is 0and :00 pm the concentration is three

So the concentration would have dropped from0 to five and five to two and a half about three in seven hours

So that means that two halflives is sevenhours

So one halflife is three and a half hours

So that tells you that if you hold the nextdose for four more hours the trough will

drop from three micrograms per milliliterto micrograms per millimeter

And this will also decrease the peak by thesame amount

So the new peak will be 0 minus or micrograms per milliliter

And this is a plot of what the concentrationsare going to look like and this is really nice now

Because again after those first three dosesyou can see that the peak is coming up the trough concentrations are coming up

But if you let the concentrations drop offby somewhere around a halflife or three and a half or four hours and you change the dosageinterval but not the dose

The dosage interval to every hours

The concentrations will drop off

The peak will drop and the trough will bedown in the range that youre looking for

So our answer to the question should youdecrease the dose increase the dosage interval

or C the most correct answer hold the nextdose for four hours and restart the same dose

at a less frequent dosage interval or an increaseddosage interval to every hours

So in summary pharmacokinetic principlesdo not need to be complicated

And dose and dosage intervals can be changedto maximize efficacy and reduce toxicity

Thank you very much for your attention