Bill Zamboni:Hi my name is Bill Zamboni

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Today Ill be giving a lecture on the introductionto clinical pharmacology

The objectives of this presentation are todescribe how drugs are developed and where clinical pharmacology studies are performed;what involves pharmacokinetic studies which is part of the absorption distribution metabolismand elimination of drugs and how the exposures are associated with those the definitionof pharmacodynamic studies as related to explaining key terms such as doseresponse relationshipsincluding receptors and actions of drug targeting and predict how individual variability inthe pharmacokinetics effect of pharmacodynamics such as efficacy and toxicity

This slide depicts the process of drug discoveryand development and the different phases of drug development

Theres prediscovery which is identificationof molecules

Theres the early drug development in thispart

And then obviously theres preclinical drugdevelopment which involves pharmacology studies in animals

This will not be part of this lecture butjust understand that a lot of the studies that we perform in clinical pharmacologywhich are involved in patients as part of clinical trials are also performed in preclinicalstudies

So in most cases the clinical pharmacologystudies that were going to be discussing are performed in phase one and phase two studiesof drugs during development

Sometimes in phase three which are a muchlarger study and then also in postapproval studies which are called in many cases phasefour studies

Clinical pharmacology has two basic partspharmacokinetics and pharmacodynamics

Pharmacokinetics is what the body does tothe drug

So how the body handles the drug clearsit distributes it and other factors

And then pharmacodynamics is what the drugdoes to the body

What are the effects of the drug on the bodysuch as for efficacy targeting and also toxicity?

So pharmacokinetics we can explain the pharmacologyof the drug mathematically

Its basically the drugs journey throughthe body and how the drug is handled by the body

There are four different basic processes topharmacokinetics which is called ADME absorption distribution metabolism and elimination

When a drug is dosed either orally or IVit goes into the central compartment which is the absorption phase

It then goes into the peripheral compartmentwhich is a distribution phase

And then lastly the drug is eliminated whichis the elimination phase

So well talk about how these studies areperformed for various drugs in development

This slide depicts the concentration versustime curve which is involved in the pharmacokinetic studies

Time on the X axis concentration on the Yaxis

What were looking at is a term such as theminimum effective dose or exposure and the maximum tolerated dose

This would be the therapeutic range whichwell also talk about in a second

Theres important pharmacokinetic terms suchas the Cmax or maximum concentration

Theres Tmax which is the time of the maximumconcentration

And then area under the concentration timecurve which is the AUC and a measure of overall exposure

And so what we try to do in these studiesis to evaluate these different pharmacokinetic parameters and eventually see how they predictthe pharmacodynamic response

Drugs can be administered through variousroutes of administration

Theres parenteral administration such asIV IM or subcutaneous

Most drugs that use a parenteral administrationare IV

Theres oral administration with various formulationssuch as tablets capsules suspensions and liquids

Theres newer administrations such as sublingualtablets

And then theres also local administration

This is just a reference that can go throughdifferent information on routes of administration

Bioavailability is a very important pharmacokineticterm

Its the fraction or percentage of a drugthat reaches the systemic circulation

And what I mean by that is the blood exposure

So if you give a dose orally it goes inand it dissolves or breaks down into the gut

That is then absorbed into the blood and ismetabolized by the liver through firstpass effect

And then ultimately what gets to the bloodafter the liver is what is bioavailable

So the bioavailability here would be 0 percent

Obviously influenced by absorption and metabolismand bioavailability

Ultimately the fraction absorbed is calculatedas F which is the AUC of the desired dosage form for example the oral over the AUC achievedwith IV administration

So that would be the fraction absorbed throughvarious formulations or dosing besides IV

There are several factors affecting the distribution

Theres factors that affect absorption tissuepermeability blood flow binding to plasma proteins which well talk about in a secondand theres binding to additional cellular compartments which all determine where thedrug and how fast the drug distributes throughout the body

Again the distribution here related to thecapillary permeability

And also a specific site of exposure is inthe brain with the blood brain barrier

And so concentration time curves based ondistribution are different based on the different tissues

So the exposure in the plasma which is acompartment within the blood is represented by the black line

But how a drug distributes to a fat versuslean muscle versus what gets into the brain is highly variable and drug dependent

Protein binding is also a very importantkinetic term

Its related to the binding of the drug toplasma proteins such as albumin betaglobulin and alphaacid glycoprotein

Its important to remember that drugs thatare bound to these proteins have no effect

So the term for amount of drug bound is determinedby different concentrations

Theres the free drug concentration the proteinbound concentration and the affinity for binding sites

So percent of drug bound is the bound exposureover the bound exposure plus the free exposure times a hundred

But this fraction here which can be relativelysmall is the most important parameter

Because again that is the active of formof the drug

So what could change the percent drug thatis bound?

Renal failure inflammation malnutritionor fasting and also drug interactions where two drugs administered together would be bindingto the same particular protein or site

Now well move to elimination as a pharmacokineticmechanism

And therell be three different types of elimination

The first one well talk about is enzymaticmetabolism

The goal of this is to enhance the eliminationfrom the body

The enzymatic metabolism mostly occurs inthe liver by reactions that increase the water

solubility

The metabolites are then secreted back intothe blood or into the bowel where theyre eliminated from the body

There are different phases of enzymatic metabolism

Theres phase one which is making the drugmore hydrophilic such as SIP0 enzymes would be this case

And then theres phase two metabolism whichinvolves conjugating it to also make it more water soluble so that it is eliminated

A second type of elimination is renal elimination

And theres two different types of renal elimination

Theres filtration which goes through therenal glomerulus here and its elimination through the urine

There is also secretion where the drugs areactively secreted through the renal tubules of certain drugs

And again they go through elimination throughthe kidney and out in the urine

So again two types of renal elimination filtration and secretion

The last type of elimination like to discussis a relatively new or novel form of elimination

Its a cellular elimination via the mononuclearphagocyte system or MPS system

And this is for complex drugs such as nanoparticleconjugates and biologics

And by biologics I mean antibodies or antibodydrug conjugates

And so when an antibody or a nanoparticleis administered usually IV in most cases they reach the plasma

And then they are cleared via the kidneybut its not metabolism via the kidney

Its these active cells of monocytes and macrophagesor other phagocytic cell that are clear that phagocytose and uptake the particles to removethem from the blood

And this occurs in the liver and the spleenand also through circulating monocytes in

the blood

So this is a cellular active process by whichthese complex agents are removed from the circulation

An important pharmacokinetic parameter ishalflife

And by halflife what I mean is its definedas the time it takes for half the drug to be administered

So each drug has its own halflife that needsto be characterized

And so as youre giving repeated doses ofa drug either if its a IV infusion and then you stop the infusion

Then the drug clears

The wash out period here and the time it takesfor half the drug to be eliminated is what we would call the halflife

And then within five to seven intervals orfive to seven halflives is how long it takes the drug to be completely cleared from circulation

And also if youre giving repeated oral dosinghow long it would take to get to steady state

So again five to seven halflives is a veryimportant pharmacokinetic term

Pharmacodynamics now is the opposite

This is what the drug does to the body

Its related to the drugs destination orpurpose

Again this definition of what the drug doesto the body it involves efficacy and toxicity

Well talk about important terms such as therapeuticindex sites of action and an affinity for receptors

And so when you give a dose or a concentrationof a drug measured in pharmacokinetic studies the degree of response goes from zero up to00 percent

And you get this sigmoidal curve here

Once you reach a point where giving more ora higher concentration of drug you get no

more added effects

So this would be the maximum effect thatcan occur

And you never want to dose above that becauseyou dont get added response

You just get off target effects or toxicity

And so again theres different drugswill have different concentration versus response

relationships as related to which drug wouldbe more efficacious

Obviously if this drug only reaches a 0percent response versus this drug reaches

a hundred percent response the drug representedby the red would be more efficacious

Potency is a term a dynamic term relatedto the relative strength and response for

a given dose

The effect of concentration or dose neededto elicit half the maximum dose or response

either called the EC0 or ED0 are importantterms

And the potency is inversely related to theEC0 or ED0 which Ill show you here

So for example this would be the dose orexposure of a particular drug

This is an elevation or treatment of painfrom zero to a hundred percent

And as the potency curve moves to the leftthat means these drugs are more potent

And as the dose or exposure responsory curvemoves to the right these agents are less

potent

Therapeutic index is a very important pharmacodynamicterm

Therapeutic index is related to the toxicor lethal dose at 0 percent

An easier way to think about the therapeuticindex is to look at the range or distance

between what is required for efficacy or whatis required for toxicity

Again looking at the dose or exposure versusresponse relationship

The efficacy curve represented by the blue

The toxicity curve represented by the redline

The distance or interval or exposure rangebetween what causes efficacy and what causes

toxicity is called a therapeutic index

This agent here would have a wider therapeuticindex which is a good parameter or a good characteristic of the drug

This particular agent has a narrow therapeuticindex

So the which means the exposure that causes are associated with efficacy or causes toxicity is very close

This can be problematic for a particular drugdue to variability in kinetics and exposure from patient to patient and dynamic response

So in pharmacodynamics theres differentmolecular mechanisms of actions

Drugs must bind to a specific site to elicita response called the drug receptor site interaction

Theres many different targets for these receptorsand interactions lipids nucleic acids or proteins which are most receptors andmany of those have not been fully characterized or identified

So its a lock and key analogy

So basically you have a receptor

You need the drug either drug A or drug Bto bind to the receptor to achieve a response

If drug A binds it achieves a response oran action thats going on

And which one exactly happens is by affinity

And these have to do with chemical bonds andinteractions

The interactions are either reversible orirreversible

Irreversible but also called covalent binding

So multiple drugs bind to multiple differentreceptors to elicit a pharmacologic response

Theres different types of interactions oragents

Theres agonists and antagonists

These are therapeutic effects can be viathese different mechanisms

Drug interactions can also occur when an agonistand antagonist are dosed together

The affinity for a receptor actually endsup driving what their response will be

The amount of the attraction between the drugand receptor and how much drug is needed to bind to the receptor

So its related to the affinity and alsodrug exposures which then gets us back to pharmacokinetic studies and responses

So agonists bind to the receptor and causea measurable effect

Agonists are again driven by affinity andintrinsic activity

Theres partial agonists that have affinityand less intrinsic activity

And again if you look at the response versusthe curve here this would be an agonist

This would be a partial agonist representation

Here is depicted

Antagonist binds to a receptor but no measurablecellular or physiological change occurs

It blocks the usual receptor effect and itcan reduce the effect of an agonist

Again they do have affinity but no intrinsicactivity

The different antagonists can be competitiveor theyre binding to the same site as the agonist can be overcome with higher concentrationswhich is represented here

And then it can also be noncompetitive whereit binds to a different site besides the site where the agonist binds

And thats depicted by the cartoon now

So this slide depicts the summary of clinicalpharmacology which again involves pharmacokinetics and pharmacodynamics

Kinetics are what the body does to the drug

Pharmacodynamics are what the drug does tothe body

They are highly interactive

Obviously the kinetics affect the dynamicsbut in many cases when a system is affected

by a drug you can have a feedback loop thatmay change the kinetics

And so studies are ongoing for all drugsat different phases of development to understand how variability in pharmacokinetic parameters such as absorption distribution elimination and the overall exposures affect the pharmacodynamicresponse

Whether it makes the response steeper or lesssteep

And so these are important concepts thatneed to be performed for all drugs

Thank you very much