Thank you for joining this session

Pharmacology

This module module five the assessment ofdrug effects has five sessions: biomarkers of drug effects pharmacodynamic and pharmacokineticmodeling of data disease progression models role of pharmacodynamics in drug developmentand Immunotherapeutics

Well if the definition of clinical pharmacologyis the science of drug action in humans and their optimal clinical use in patients thenthat begs the big question how can we measure drug effects in humans?

Well that large question can be broke downinto two main subcomponents

The first is how can we measure the effectsof humans on drugs?

When a drug is administered to a patientwhat does the human body actually do to the drug?

The second is how can we measure the effectsof drugs on humans?

What are the clinical effects and how canwe infer those from certain other indirect measurements?

To illustrate the importance of the measurementof the effect of drugs I thought Id talk about how common drugs are

There are nearly 000 about a third ofwhich have been approved

Most of those drugs are small molecule drugslike acetaminophen or ibuprofen about 0000

There are almost 00 biotechnology relateddrugs or protein related drugs

And there are over 9000 targets for thosedrugs that have been approved

And thats an average of two and a half drugtargets per drug

And it ranges up to as many as 0

About two out of every three people in theUnited States have used a prescription drug within the past months

And drugs account for about nine percent ofthe overall health spending

So its important that we be able to measurethe effects of drugs accurately

The first topic relates to biomarkers in health

When we administer a drug to a patient weneed to be able to measure something accurately and objectively and reliably

And that is called a biomarker

And ideally a biomarker should be reflectiveof the actual biology going on in the human or the disease itself

Examples of biomarkers include: sweat chloridewhich can be used in the diagnosis of cystic fibrosis; blood glucose which can be usedfor diagnosis and monitoring of patients with diabetes; blood pressure again diagnosisand monitoring in patients who have hypertension; and the CEA which can be used in the diagnosisof patients with colon cancer and fibrinogen which can be used to determine the prognosisof patients with COPD

Pharmacokinetics is defined as the study ofthe time course of drugs in the body

And the main components are referred to asADME and that includes absorption distribution metabolism and excretion

Clinical pharmacokinetics is the applicationof pharmacokinetic principles to the use of drugs in patients

Pharmacokinetics requites the ability to accuratelyand precisely measure the concentration of drugs in either blood tissues or any otherbodily fluid

Commonly pharmacokinetics are influencedby the root of administration

If the drug is given by intravenous routeit has a quick effect

If its given by oral or topical administrationit may have a delayed onset of effect

And its important to be able to characterizethe quantity of the drug in the system at varying times

Measurements can be made after administeringeither a single dose of the drugs or multiple

doses of a drug throughout a range of dosesincluding low medium and high

This is an example of an arbitrary drug

On the Yaxis you have drug concentrationand the Xaxis time

And you can see the line shows the drug beingabsorbed into the body being distributed and eventually eliminated by the drug by metabolismor excretion

And that drug has an area under the plasmaconcentration curve that is reflective of the overall effect of the drug

Pharmacodynamics then is the relationshipbetween drug concentration at the site of action and the resulting effect

It includes the time course and the intensityof the therapeutic effect or the adverse effect

And we can address the potency of a givendrug within a class of similar drugs

Commonly pharmacodynamics is exhibited bya typical Sshaped curve

At low concentrations measured on the Xaxis we can have a given effect

And thats measured on the Yaxis

At very low concentrations you can see thatthere is no appreciable effect

And then as the concentration increases thateffect increases dramatically until a plateau is hit

And one of the common parameters that we useis the effective concentration in 0 percent of the individuals or 0 percent of theeffect and the EC0

What is the role of pharmacodynamics in drugdevelopment?

Drug development is a natural extension ofpharmacodynamics

The first step is proof of mechanism whichis the effects of a drug on a given drug target

And the second step is the proof of conceptwhich is the consequences of the drug in the body

All phases of drug development use pharmacodynamicsfrom the preclinical to the clinical and

the postmarketing effects of the drug

Disease progression models have been dramaticallyimproving over the last one to two decades

And these models involve math to quantitativelydetermine the change in a diseases status over time

We can compare the natural progression ofthe disease with a treatment effect and we commonly use biomarkers and we link them withpharmacokinetic and pharmacodynamic data

Pharmacodynamics can be used to improve drugdevelopment productivity

And finally we can use disease progressionmodels in the application of costeffectiveness and genomewide analyses

Here is an example of a hypothetical drugfor disease modeling

The yaxis has the disease severity and thexaxis has time

And the solid line depicts the increase inseverity of the disease over time

The dotted line as to do with a drug effectthat might temporarily reduce symptoms and you can see the symptoms improve when thedrug is given and then revert back to baseline when the drug is taken away

A second option for a drug effect on diseaseseverity is where a drug modifies a given severity of the disease and you can see thatby the dashed line having a decreased slope compared to the natural course of disease

Immunotherapeutics also called biologic responsemodifiers or biologics have a dramatically increased role in healthcare in the past recentyears

They can be used to treat disease by alteringthe immune system

And theres two effects that can occur

One is by activating the immune system orenhancing or amplifying it when were trying to get rid of something bad like cancer cell

And the other effect is suppressing or reducingor blocking the immune system when it is in overdrive function

And that would be an inflammatory conditionlike rheumatoid arthritis or inflammatory bowel disease or psoriasis

The advantage of immunotherapies is that theyhave the potential for greater effectiveness or decreased side effects because they aretarget to a narrow therapeutic role

We can combine the immunotherapies with traditionaltreatments and again have improved effectiveness or decreased toxicity

The downside is that these drugs may be associatedwith their own unique adverse effects

Heres an example of a monoclonal antibody

The top portion of the antibody is the variableor Fab region

And that is what binds to the antigen

The fixed portion or Fc region of the antibodydoes not change

These monoclonal antibodies may inhibit inflammatoryreactions like cytokine release interleukin release and they may inhibit cellular functionas well and activation like Tcells macrophages fibroblasts and osteoclasts

Common examples of immunotherapeutic drugsinclude CAR T cell therapy for cancer cancer vaccines which can prevent cancers or treatthem after they occur viruses that can be used to treat cancers and antitumor necrosisfactors drugs used in inflammatory conditions and finally the checkpoint inhibitors whichhave dramatically increased over the last few years

So in summary it is imperative that we accuratelymeasure drug effects

And we can measure drug effects either directlyor indirectly

Assessing drug effects plays an essentialrole throughout the drug development process

Thank you for attending this session