we are honored to have dr art atkinson

course

dr atkinson founded the nihs course on

principle of clinical pharmacology

almost 0 years ago

dr atkinson received his undergraduate

degree in chemistry from harvard college

in 99

in his medical degree from cornell

university in 9

following residency at mass general

hospital he was a clinical associate in

the laboratory of clinical investigation

here at the nihs niaid

he received his postdoctoral training in

clinical pharmacology at the university

of cincinnati

in 90 he moved to northwestern

university to start the clinical

pharmacology program there

while at northwestern he and his

colleagues set up the first us hospital

laboratory devoted to general

therapeutic drug monitoring

in 99 dr atkinson joined up john as a

vice president for clinical development

and medical affairs

following the up john pharmacy a merger

he joined the center for drug

development science at georgetown

university

in 99 he returned to the nih as a

senior advisor in clinical pharmacology

to the director

of the nihs clinical center dr atkinson

has received numerous honors and awards

over the years

i know youll enjoy todays presentation

thank you very much dr figg

my topic today will be the compartmental

analysis of drug distribution

and by that i mean the postabsorptive

transfer of drug from one location in

the body to another

there are a number of ways in which drug

distribution

is analyzed in pharmacokinetics

the first is a noncompartmental

analysis in which the theres

curves are fit to the data and this can

be used to calculate parameters like the

area under the curve the clearance the

distribution volume the c max and the t

max

what well focus on today is the the

second of these approaches the

compartmental analysis

where the parameters of a

pharmacokinetic model are actually fit

to the data and usually these are fairly

simple models with say one to three

compartments

as opposed to the increasingly popular

physiological models which are much more

extensive and actually represent a

chemical engineering approach

to the problem each organ is assigned

its own compartment and the model

parameters are are found from the

physiological literature

im an agnostic

about these modeling approaches and

believe that the choice of the model

should depend on what the intended

purpose of your analysis is

but today well focus primarily on

a

physiologic physiological basis of

multiuh compartment pharmacokinetic

models

and were indebted to a physiologist at

the university of sola

torsten trl

who many years ago

developed the first multicompartmental

model hes regarded therefore as the

father of both compartmental modeling

and physiologically based

pharmacokinetics

and this is a picture of one of his

models and what you can see here is a

central compartment which represents

intravascular space theres distribution

into tissues here elimination by various

organs essentially he was working with a

twocompartmental model

now

what do these compartments mean

if we look at a classic drug like

digoxin you can see here that the

distribution volume of liters

doesnt really correspond to what we can

recognize as a physiological compartment

but well go into that in a few minutes

and start with the conventional view of

these physiological compartments that

consist of first the intravascular space

the interstitial fluid space and the

intracellular fluid space

well most drugs dont have distribution

volumes that correspond exactly to those

compartments but there are some

compounds

that do have a correspondence and a

classic marker for

the

extracellular fluid space is inulin

and

proteins and other macromolecules also

distribute in the extracellular fluid

spaces do

the neuromuscular blocking drugs and

initially the aminoglycoside antibiotics

there are a number of markers for total

body water urea

the caffeine that you have in your

coffee or coke

ethyl alcohol and some people have used

antipyrene as a marker even though it

does exhibit some protein binding

so how do we rationalize most of the

distribution volume estimates that we

find

theyre really two factors that i think

are most important to consider the first

is binding to plasma proteins

and well take theophyll and thyroxine

and theophylline as uh as examples

and then theres the

tissue binding or partitioning of a vast

array of other compounds

so the first thing i would like to

disabuse you of is the concept

that plasma proteins are only

distributed in the intravascular space

in fact these binding proteins

distribute

throughout extracellular fluid space

so essentially we have two main

compartments to think about

extracellular fluid space

and

intracellular water when we think of

distribution volumes

and one can mathematically analyze

the end predict the effects of protein

binding

on distribution volume with this fairly

simple

equation

what you see here for thyroxine

which has a protein binding of

999 percent because its total

distribution volume corresponds with the

expected value for extracellular fluid

space

on the other hand theophylline is a drug

chemically very similar to caffeine if

it didnt bind to plasma proteins its

distribution volume like caffeine would

be total body water

but because of the protein binding this

distribution volume is less and here we

can see

that its somewhat less than 0 protein

bound and so its distribution volume is

uh

less than

one would expect for total body water

now this kind of approach allows us to

understand some of the effects of

physiological change on drug

distribution lets take the example of

the pregnant woman

in the third trimester

not only is the protein binding of

theophylline decreased but the fluids s

space estimates for extracellular fluid

and total body water are increased and

so you can see if we take all these

factors into consideration

we come up with estimated estimates for

distribution volume that agree

quite uh

simply uh quite closely rather to

to what we can measure experimentally

now what about drugs that distribute

extensively into tissues and here we

have to add another factor

phi to our equation and i will call this

the ratio of tissue to plasma drug

concentration

and generally speaking this factor

is

correlated with the octanol water

partition coefficient for the various

compounding question and this is a a

rough graph

that shows

this relationship

lets get back to the example of digoxin

we

know that the fraction free is 0 and

we can calculate back calculate from the

observed distribution volume that has to

have very high partitioning into tissues

a factor of fee of 0 and heres

experimental data the binding also

includes binding to sodium potassium

atpase actually every tissue in the body

here

has much higher concentrations of

digoxin

than does

the concentration in blood

so how do we analyze

experimental data using compartmental

models

well the

first question is how many compartments

in the model a lot of people agonize

about it but my approach is rather

simple

the number of exponential phases in the

plasma level versus time curve

will determine the number of

compartments

and so here we have a bi exponential

equation that means were going to wind

up with a two compartment model

there are four parameters in this

equation two

coefficients and two exponents

four parameters there means that we can

identify four model parameters and here

ive highlighted

two

rake distribution rate constants and

elimination rate constant and the

central compartment

but we could also

calculate the the two distribution

volumes through the two compartments uh

and two clearances

and

the uh total distribution volume in the

compartmental system is simply the sum

of the two compartment volumes

and this now

to add to the confusion gives you a

third way

of calculating distribution volume weve

already

learned earlier in the course about vdx

strap and vd area this is the third way

of calculating distribution volumes

and that

obviously adds to the confusion

now

the

primary parameters of the system are not

the rate constants theyre the

distribution and the elimination

parameters are the clearances and here

we have for our model elimination

clearance is simply as you know the

product of the elimination rate constant

and the central compartment volume

there is a clearance also that describes

the rate of drug distribution

and that is calculated in an analogous

way to the elimination

clearance and like the elimination

clearance its a volume independent

parameter that characterizes the rate of

analyte transfer between compartments of

the kinetic model this parameter has

been

really

pretty much ignored

in pharmacokinetic studies

well try to

explain a little bit more about it as we

go on

lets go back though to our conventional

view of physiologic spaces

and

what ive shown you here is a three

compartment model a catenary model

comes from the latin for chain you can

see the three compartments are linked

together in this horizontal way and

these first two compartments

intravascular space and interstitial

fluid space are combined to form what we

call the extracellular fluid space

traditionally we think of extracellular

fluid spaces as being having two

compartments

and that understanding is based on this

type of study heres a study done by

mario gagdino

way back in 99 before he had computers

to help him

you can see his experimental lines

and his

uh his theoretical lines and his

experimental data points after both a

prolonged infusion and after bolus

injections of

inulin

and what i want to call your attention

to

is this region of his curves you can see

here after the bolus injection the data

points are below his theoretical line

after the prolonged infusion the data

points are above

and this uh

suggests that hes missed the

compartment

and so

what these days

when we think of

inulin distribution we really have to

think of a three compartment model with

a more rapidly equilibrating compartment

and a slow

equilibrating interstitial fluid

compartment in other words interstitial

fluid is kinetically

heterogeneous

and the basis of this lies in the

anatomy of capillary beds

the splenic bed has very large

holes in it

and so

solutes can pass into the splankinic

tissues much more rapidly than in the

somatic

compartment

where we have

uh continuous capillaries and heres a

scanning electron like micro typograph

of hepatic sinusoids

these are called

fenestry

im a sailor so they look more like

portholes to me

but theyre big holes and you get big

molecules going through these holes very

rapidly

on the other hand heres a high power

electron micrograph of the

interendothelial cell capillary

junction

and you can see how much narrower this

is certainly in this blow up and that

retards the passage of

hydrophilic solutes

through these capillaries

theres a brilliant study done many

years ago by

bob sherwin and his colleagues

at both yale and nih in fact and they

studied the kinetics of of insulin a

molecule about the same size as inulin

but obviously one that has a

pharmacologic effect

and the pharmacologic effect of insulin

that were interested in is its ability

to lower blood sugar by increasing

skeletal muscle uptake of glucose

this study was done not only as a

kinetic study but as a study performed

with a eu glycemic glucose clamp in

other words the investigators infused

intravenous glucose

so as to maintain constant blood sugars

even though insulin was acting to

increase glucose uptake by skeletal

muscle and heres the slow

equilibrating compartment

in their three compartment model

and you can see it parallels skeletal

muscle uptake of glucose if you will

so this is

one

very rare example where the

pharmacodynamic

compartment actually is a

pharmacokinetic compartment and so for

that reason its of

a particular interest

urea also can be described with the

three compartment model and the central

compartment again if the urea is given

rapidly intravenously

is intravascular space

so

lets look now at a revised model of

physiologic spaces

we have kinetic heterogeneity for the

extracellular fluid space

and that also affects

urea distribution into total body water

in both cases

the trans capillary exchange

is the rate limiting step

and uh thats the process uh that we

would like to analyze in terms of

understanding uh what makes up the trans

capillary

the the intercompartmental clearance of

these compounds

there are actually three parameters

that need to be considered capillary

blood flow which will designate by q

the capillary

permeability coefficient

which well call p

and the capillary surface area

and this gentleman eugene renkin who is

former chairman of physiology at uc

davis was the first to apply

this equation to the transcapillary

clearance of solutes

its a rather simple equation and it can

be adapted to study the

intercompartmental clearance of

inulin and urea

the challenge as you can see is we have

experimentally one term a clearance term

and wed like to calculate two terms

a permeability coefficient a surface

area product and a a flow term

in order to do that

we have to study urea and inulin

simultaneously

in both cases transcapillary exchange

is the

the basis for the intercompartmental

clearance

and we need three equations

so the first two equations are

rearranged versions of the renkin

equation

and the last equation simply assumes

that the the trans capillary exchange of

inulin urea will be

the ratio of those permeability

coefficients the surface area products

will be the same as the ratio of their

free water diffusion coefficients which

you measure in vitro

and if we do that

and simultaneously measure cardiac

output

we now can compare our flow estimates

for the two compartments in our model

with independently measured cardiac

output and you can see here

the correspondence is fairly close

so

obviously most pharmacokinetic studies

are not performed with this level of

detail

but in certain circumstances

it can be illustrative to have this

amount of detail in our analysis

in the subsequent lecture well talk

about how we can use these models to

understand

physiologic changes that occur

during hemodialysis

that have obviously have an impact on

hemodialysis pharmacokinetics

and they also have a bearing

on

analyzing why

patients with reduced cardiac output

might not absorb drugs as well as

patients whose cardiac status is better

now youll have a subsequent lecture on

drug absorption and all these various

factors will be considered but the one

factor thats hardest for us to get our

hands around in the in clinical studies

at least is the importance of splenic

blood flow

well remember our model

the fast equilibrating compartment

is the distribution of drug in many of

our models two splenic tissues and here

were looking at a drug an acetyl

propane amide where again the central

compartment is intravascular space we

have fast and slow peripheral

compartments and you can see that if the

fast intercompartmental clearance is

less than

theres a reduction in bioavailability

now

obviously what were really trying to

get our hands on

is splenic blood flow

and we can use in this case a fast

intercompartmental clearance perhaps is

a surrogate for that

well what are the mechanisms

for trans capillary exchange of a

variety of compounds

weve talked

so far about polar uncharged compounds

inulin and urea

here weve said the transfer should be

proportional to the free water diffusion

coefficient

but there are many small molecules some

of them polar that that have a slower

transfer rate than we would predict from

their free water diffusion coefficient

some of these are highly charged and

others have

properties that that cause them probably

to interact with those pores in

capillary walls that weve been talking

about

certainly the quaternion compounds

have a major interaction

in other cases the transfer rate is much

faster than wed predict

for example the uh

studies with the antiarrhythmic drug

ibutilide the intercompartment of

clearance to the peripheral compartments

from the intravascular space

is

some of those

clearances adds up to what wed expect

for cardiac output

and the lipidsoluble compounds

of a variety

of compounds act that way

the the other reproxy thing is that

theophylline

actually

goes faster across capillaries than we

would predict from its free water

diffusion coefficient

and this is a very unusual study in

which theophile and pharmacokinetics

were studied in dogs

simultaneously with urea and inulin and

we measured the cardiac output as well

and what you can see here for

theophylline is that

the intercompartmental clearances for

theophylline

are very close

to blood flow calculated from the urea

and inulin kinetics

and why should this be

well

theophylline obviously is bigger

than urea

it has a

corrected stokes einstein radius thats

bigger it should go more slowly the free

water diffusion coefficient is less and

yet it crosses capillary walls faster

than urea

so the assumption is there is a

facilitated transport

carrier has yet to be identified

that is responsible for this rapid

transfer

now lets continue this

line of thought by considering some of

the clinical implications of drug

distribution kinetics

first of all

there are some drugs that are given

rapidly by intravenous injection are

quite toxic

theophylline again is the case in point

in the late 0s it was found to be a

valuable drug in treating patients

asthmatic patients with status

asthmaticus

but several years later

it was noted to have both

fatal arrhythmic

toxic effects and central nervous system

cardiorespiratory toxicity

its interesting its been a

puzzle to me why why people wait for

three cases before they write a paper

but that seems to be the magic rule

even in 9

it was known that the injection of this

drug intravenously oh even over a three

to five minute period

resulted in 0 percent

of drug related cardiac arrests

in the los angeles county

shaw cord

so people correctly surmised fairly

early on that speed of injection was

important in this toxicity

and i will

say that the reason speed of injection

is important is that speed of

distribution of this drug is extremely

rapid

and of course the current recommendation

is to slow it up and give the theophany

over a 0 to 0 minute period

well conversely distribution can delay

the onset of drug action of a number of

compounds weve seen previously

how

the delayed distribution of insulin the

skeletal muscle delays its onset of

pharmacologic action and lets go back

to to digoxin again you can see that the

pillars are slow buildup of digoxin

concentrations in the heart

and consequently a slow onset of the

therapeutic myocardial effects

on the other hand

the peripheral vascular system

reacts to

the high

intravascular concentrations that are

immediately obtained and that causes

vasoconstriction

and the the bottom line of this story is

if you have a patient with congestive

heart failure

and pulmonary edema

that if you begin therapy with a cardiac

glycoside

this delayed effect means that the

official the initial effect youll

observe is a reduction of cardiac output

and the patient will become worse

now another

consequence of this disparity is that

the digoxin if if ingested in a suicide

attempt say

can distribute very rapidly to the

central nervous uh medullary vomiting

center

and so the result of this action is that

that the patient will uh eliminate most

of the ingested dose before it has a

chance to kill them by working on their

heart

you can think of this as sort of a

a a

pro protective mechanism uh that has

been designed by

uh

the ultimate designer i guess to protect

us to some extent from eating poisonous

plants like foxglove

uh

well

distribution also

terminates

the action of many

drugs

given after a bolus dose

and perhaps the the one that

youve observed is the fact that if you

have somebody with a ventricular

arrhythmia

say vtac and you give them a bolus

injection of lidocaine

after eight to ten minutes the

arrhythmia comes back

and

thats not because the patient has

eliminated the lidocaine its because

the

the lidocaine has redistributed from

the

intravascular space to rapidly

equilibrating tissues

and

the metabolic elimination is a

relatively slower process

there are

certain special

cases that have been this designated

flipflop kinetics

and uh the poster child for this type of

a drug is is gentamicin all the

aminoglycosides so well demonstrate

this

and currently we give this drug in a

daily dose and you see the plasma

concentrations fall after each dose

and that

decrease in concentration actually

reflects the elimination of the drug

if you measure concentrations after the

drug dosing is stopped though you see a

prolonged distribution phase

so here we have drug

elimination phase preceding drug

distribution

phase thats the

very unusual the distribution phase

actually represents distribution of

gender mycin primarily from

extracellular fluid space to the kidneys

and

cobarn and shed tag and their colleagues

at

suny buffalo have shown that patients

who show nephrotoxicity actually are

accumulating more of the gender mycin in

their kidneys these are

these they can actually measure the

amount of genetomycin in the kidneys and

postmortem exams and account for almost

all

of the the gender mycin that is

distributed to the peripheral

compartment

ill finally talk about something that

ill call pseudo dose dependency

and uh something that causes

the

inaccurate estimate of pharmacokinetic

parameters

one of the most toxic noncancer drugs

that we use is dilantin or phenytoin

and you can see here that the plasma

levels increase much more rapidly than

the doses increased

and so this does not satisfy

a criteria that we call dose

proportionality and so let me give you

an example from the real world of drug

development

the uptrend company was developing a

drug with nasalite or xybox

and the phase one study

pharmacokinetic data showed that after a

milligram dose the auc was

micrograms power per milliliter

when the 00 milligram dose was given a

four time increase in dose

the auc increased times

and this data was presented to the

senior management at upcom

laboratories by the pharmacokinetics

group

and

theres incentive in the industry to

stop the development of a drug that

isnt going to work out as early as

possible

so the development of this antibiotic

was about to be stopped

when fortunately the pharmacokinetic

group showed their plasma level versus

time curves

what you see is after the milligram

dose

their assay wasnt sensitive enough to

transcribe the entire plasma level

versus time curve

so they only had this truncated curve

and so in fact that through the

estimates off the drug did show dose

proportionality but let me show you what

the pharmacokinetic estimates would have

been

had they just worked with these data

you can see here that with the

inadequate description

of the the plasma levels versus time

curve you had

an underestimation of distribution

volume

and an overestimation of clearance

now

the

the the current practical

significance of this is that were being

confronted with a whole bunch of

wonderful drugs that happen to be rather

large molecules

and what id like you to do

when you

examine pharmacokinetic data for these

drugs is to compare the distribution of

volume spaces with those of inulin

what you can see here is that generally

speaking the central compartment

intervascular space estimates are

generally pretty much in line with what

youd expect factor nine is a bit

unusual in many respects seems to bind

to something

and

but for most of these drugs the total

distribution volume

is much smaller

than the estimate of extracellular fluid

space

and that means not only that the

distribution volume

estimate is incorrect

and too low

but the clearance estimate in the

published papers is incorrect and too

high

so i want you to to try to remember that

is something perhaps youve learned from

this particular lecture

and i want to thank you for

uh for

for listening and i hope its been

enjoyable and instructive thank you