our next speaker today is dr amit pai
clinical pharmacy and deputy director of
the pharmacokinetic core laboratory at
the university of michigan
dr pies research focus is on optimizing
drug dose selection in special
populations such as obesity
he earned his doctorate of pharmacy
degree from the university of texas
health science center and completed a
pharmacy practice residency at bassett
healthcare followed by infectious
disease and pharmacokinetic fellowship
at the university of illinois at chicago
we know you will enjoy todays lecture
hello my name is amit pai im an
associate professor of clinical pharmacy
at the university of michigan and the
deputy director of the pharmacokinetics
corps its my pleasure today to present
on the pharmacokinetics of obesity
this slide contains my disclosures
what id like to cover today is
reviewing the definition and
epidemiology of obesity explain the

effects of body size on drug exposure

with the focus on antimicrobials

demonstrate the similarity and

differences in body size scalers for

drug dosing and explain the rationale

for alternate approaches to dose

selection in obesity adult patients

this graphic gives a

global distribution and prevalence of

obesity in adult females and males

across across the world and different

parts of the world

as you can see from this graph obesity

has more than doubled since 90

from

almost

less than 0 percent

to

over percent in the united states and

similar trends are seen in the

developing countries represented by the

bric nations brazil

russia india and china

based on current definitions in 0

over 00 million adults were classified

as obese

and this is really important because the

consequences of overweight and obesity

kill more individuals in the world today

for the first time in history than

underweight

individuals than the effects in

underweight individuals

this is the prevalence of obesity across

the united states by county

and clearly theres diversity

in the prevalence of obesity in the

united states with the lowest rate seen

in route county and the highest in green

county

which again this area here represents

the southeast part of the united states

its also associated with a high

prevalence of diabetes

and we think about obesity an important

point is the definition and prevalence

of obesity and when you think of obesity

this definition

the original definition was derived by

adolf catalay in

he

came up with

the body mass index definition which is

basically the weight of an individual

divided by height

in meters squared

and the purpose that adolf kitale

sought was basically to find a

correlation between body size parameters

and different events such as probability

of criminal behavior and so when you

think of this metric it was really not

designed

for a pharmacological purpose or for

other classification purposes

and not until 9 uh was this index uh

transformed into what we call today as

the body mass index a term defined by dr

ansel keyes

who did a lot of the uh initial work on

the effects of starvation

in uh in humans

based on this definition that was

adopted by the national institutes of

health in 9

body mass index is categorized into

three major categories for obesity and

those are obese class

between 0 and

99 kilogram per meter squared to

obese class

which is

greater than or equal to 0 kilogram per

meter squared

and so again this classification

is broken down into units of five

in a way for simplicity

but these may not necessarily correlate

with

predictors of prognostic variables such

as incidence of diabetes so if you look

at specific populations

asian versus caucasian

the risk for diabetes actually increases

when the body mass index is greater than

kilogram per meter squared

irrespective of that

current definitions are based on an

obese

categorization of 0 kilogram per meter

squared or greater

based on that definition

one out of three adults in the united

states meet that definition and one in

six children meet that definition

now when you think about body mass index

its clearly not a perfect index because

it doesnt represent

the uh

the true body weight uh composition when

you think of extremes of individuals in

height and so heres a graphical

representation of two individuals from

the movie twins

uh demonstrating uh arnold

schwarzenegger with a body mass index of

kilogram per meter squared and danny

devito with the kilogram per meter

squared

who clearly have very very different uh

body composition but have very similar

bmis

and this is important because bmi again

was adopted in 9 but several of our

pharmacologic studies were based on

another metric known as the ideal body

weight

this is based on height and gender

its a very simple rule and im going to

go over that specific equation and

explain the origins of that equation

that equation has been used in several

pharmacokinetic studies

and in general terms individuals who are

0 to 0 percent above ideal body weight

are categorized as being obese

despite these definitions of obesity

there really hasnt been much progress

in modifications of product labels to

provide specific dosage recommendations

for obese individuals

this is important because this drives a

lot of dosage selection and our current

paradigms and product labels are based

on three scenarios one is dosing

individuals based on their body surface

area this is a common practice in

oncology

weightbased dosing a common practice in

antimicrobial chemotherapy

and when its weightbased dosed this is

often based on

total body weight dosing

or in some

in some labels as lean body weight

dosing

but the predominant approach to dosing

drugs is using the fixed dosing strategy

this is using a dose for example 00

milligrams irrespective of body size

but this always raises the question that

if you use a fixed dose across a

population of adults is using the same

dose sufficient

for a versus 0 kilogram individual

for example

this dosing controversy has also been

seen in oncology despite body mass index

dosing

a study by griggs and colleagues showed

that percent of women with a body

mass index over kilograms per meter

squared received lower

standard first cycle doses

obesity patients are also seen to have

lower risks of grade and toxicities

despite using

higher higher doses

and this in part may be related to

underdosing these individuals

a survey by fields and colleagues

showed that 0 percent of oncologists

dose capped at two meters squared again

the idea here is

individuals felt that they were

overdosing individuals when they used

total body weight to compute body

surface area and have

in the past arbitrarily dose capped at

two meters two meters squared

and this is important because this can

lead to underdosing

individuals especially those individuals

who are at

greater risk for cancers that are

associated with obesity such as breast

cancer and colon cancer

because of this discrepancy

efforts by

griggs and colleagues and several

investigators around the united states

has led to issuance of guidance by the

american society of clinical oncology

against capping these doses and actually

using total body weight to compute body

surface area

and what i will do today is explain the

mathematical rationale for why that is

the right approach of computing body

surface

area this has also been seen with

anticoagulants looking at the crusade

trial which did include about one out of

five individuals over 00 kilograms

0 percent of patients

over 0 kilograms uh received below the

standard dose and

those individuals that that were likely

to re receive the standard dose actually

were at a higher risk for bleeding

and so this is an example of a drug that

has been historically dosed on body

weight and a scenario where using body

weight may lead to overdosing the drug

and lead to events such as bleeding

other groups have shown that

individualized dosing using lean body

weight equation which ill also review

is actually less likely to re uh to

cause this problem

of bleeding and bruising in obese

patients and so may serve as a better

metric

of dosing patients on an oxyparent

so the question at hand is really do

bigger adults need bigger doses

and so conceptually overdosing is likely

when you use weightbased doses because

using the same milligram per kilogram

dose across a body

distribution can lead to computation of

much higher doses

the opposite is true with fixed dosing

using the same dose across a population

can have the opposite effect of leading

to lower exposures in larger individuals

and so its really balancing these two

dosing paradigms

that we have to consider really on a

drug by drug basis

so lets think of that dose selection

that

from a pharmacokinetic perspective and

when you think of it from a

pharmacokinetic perspective

a key concept is that of by equivalence

that is

trying to ensure that individuals across

the population have the same expo or

have similar exposures

and that exposure

can be quantified by the area under the

curve

that is assuming having a similar auc

across

across a population or having similar

peak concentrations of the cmax

concentration

and so when this is administered when

the drug is administered orally

we also think of other parameters such

as time to peak concentrations of the

tmax or in some multiple dose studies

we may also consider the minimum

concentration or trough concentration

as a metric to assess by equivalence

now i think its really important to

separate the concepts of dose and

exposure because theyre certainly

related

but can vary across a population so if

we give a

a one gram dose

to three individuals for example those

three individuals can have very

different concentration time profiles

and so when we simulate that across a

population we may get a distribution

represented here

in this histogram

as a distribution of aucs for that

population and thats that happens

because

we may have a lot of interindividual

variability in the volume of

distribution that impacts the the peak

concentration

and interindividual variability in the

clearance of a drug that can impact the

auc or air into the curve

so when we think of these

pharmacokinetic parameters the volume of

distribution

is often a term thats thats easily

confused is not a physiological space

but rather a proportionality constant

that represents the apparent size of a

compartment that the drug will fill

when you review the literature

for a specific drug what you may see is

a lot of different v terms and so this

really depends on the method the

mathematical approach that was used to

compute the volume of distribution so if

you use a noncompartmental method

you may see the value reported as vd or

vdss

if you use a two compartment approach

you may see the value reported as vc and

vp which represent the central and

peripheral compartment

and if you have uh larger compartments

describing this you may see this

numbered as v v and v and and so on

and so forth

these volumes essentially are used to

help fit the shape of the concentration

curve and again they do not represent an

actual physical space

theyre helpful

because they can help compute the c max

or the peak concentration and here

represented by this equation is a very

simple way of thinking of this which is

if a dose was administered as a bolus

that dose divided by the central

compartment value gives you some

estimate of what that peak concentration

would be

the clearance is

then just the mathematical

representation of

a

volume thats being cleared of drug in

unit time

and that parameter is useful because it

can help compute the auc or air into the

curve represent it again very simply as

the dose divided by clearance

our objective most often when were

thinking about buy equivalence is to

achieve isometric aecs across a

population

and to do that what we really need to do

is ensure that clearance scales with

body size so if youre going to dose a

drug based on body size we want to

ensure that that scalar is really

representative of clearance

another perspective when were thinking

about optimal dose selection is

the pharmacokinetic pharmacodynamic or

pkpd perspective

and whats done here is essentially

looking at the concentration time curve

and breaking it up into different

parameters so often whats done is to

look at the peak concentration of the c

max

the area under the curve or the auc

and the trough concentration which is

the the c min

these values can then be uh scaled to a

potency measure in this case looking at

antimicrobials we rely on something

known as the mic or minimum inhibitory

concentrations

and we can then index

the pharmacokinetic

term with a

a potency measure

such as cmax or mic ac over mic or the

time above that mic

once we have those parameters we can

then look and see which of those

parameters best correlates with the

effect of the drug the safety of the

drug or some other measure doesnt not

have to be affected it could also be

emergence of resistance for example

once we do that the parameters that best

predict effect help us classify that

drug as either being concentration

dependent

or time dependent and that helps us

decide whether we should dose a drug

once a day or multiple times a day

when we use that principle we can

in essence bucket drugs

into different uh

compar into different

categories

and so when we see drugs

that are correlated by their cmaxed mic

and ac and mic we tend to refer to those

drugs as being concentration dependent

when we see drugs that are

really predicted by the time above mic

we refer to those drugs as being time

dependent

and when we look at antibiotics

specifically what we see is the auc to

mic really categorizes most of the drugs

and the reason for this is auc is really

a mathematical representation of

concentration and time

and because it has both of those

parameters

this parameter often correlates with

effect

beyond just looking at pkpd we can also

look at how drugs are currently dosed

and when we look at antimicrobials again

they fit the pattern that we would

expect that is most of them are dosed on

a fixed basis that is using the same

dose across a population

a few of them like the aminoglycosides

and polymixins and other drugs similar

are that are dosed on body weight

usually on a milligram per kilogram

basis

and then some drugs actually have

recommendations for both a fixed dosing

strategy and a weightbased strategy

and so lets review

again why this may or may not be

appropriate

again going back to the pharmacokinetic

term of volume of distribution what you

have here is two individuals

who are represented roughly twice twice

in body weight

having very different body compositions

but what volume of distribution really

represents again is nothing physiologic

it simply represents a proportionality

constant

the value is then indexed to body weight

and so is often reported as liter per

kilogram

that parameter helps us define what the

peak concentration is

and also as that value gets larger it

impacts the terminal halflife of the

drug but again

this term does not represent

biodistribution

but just represents a physical space

which is again very simply represented

here

and does not reflect the physiologic

space

now lets simulate what would happen uh

in an indiv to individuals based on

their body weight if volume increased

with weight but the clearance of the

drug did not increase with weight so

what you have here in blue is an

individual thats

0 kilograms versus 0 kilograms so

roughly twice the body weight

what you see in these profiles is

because the volume of distribution is

smaller in the smaller individual you

see higher concentrations

the effect of this is going to be

lower concentrations of the drug early

on

but because the clearance is not

changing the area under the curve

actually will be identical

for these two simulations what you again

will see is a lower c max

but youll also see over time a higher c

min

so when youre thinking about a drug

where the volume increases with body

weight clearance does not

this may be beneficial for drugs that

are time dependent because what youll

essentially have is increasing time

above a threshold concentration

where this may be risky is if that time

above a threshold is associated with

toxicity or some sort of adverse event

now the solution if the effect is

needed to be early on for example if

youre using a drug for surgical

prophylaxis

this can be overcome by using a higher

initial dose

to achieve the same concentration

profile

later in the regimen

when we think about clearance

this again is the is taking that volume

and and computing how much of that

volume is is clearing drug over time so

its represented by liter per hour

what we know is this parameter really

does not increase in proportion to body

size

so what you saw is a reduction

that is not proportionate to body size

but often represents about a 0 percent

increase

as body weight increa doubles for

example

the terminal halflife is

inversely proportional to this parameter

and so this parameter also affects the

halflife of the drug

heres another simulation using the same

principles again 0 kilogram versus a

0 kilogram individual

because the clearance increases but the

volume does not increase

what essentially happens is you will see

a lower auc

you will see a slightly lower c max over

time because the semen and trough

concentration is also decreasing but the

principal change is a reduction in the

auc

and so in this scenario

what you will see is the potential for

failure

if lower aacs are associated with a

lower effect and thats often a case

thats seen

youll also see propensity for emergence

of resistance if the dose is not

modified with increasing body size

so the solution in this scenario is the

need for a higher dose and really the

need for a higher maintenance dose

so when you think about all these

different

scenarios that have been presented so

far what are the actual physiologic

changes that weve seen

one of the things one of the studies

thats really done this well is a study

done by jeffrey young and colleagues at

the national

toxicology center

that have looked at autopsy data and

over 00 individuals to sort of quantify

what happens to

[Music]

tissue

as body weight increases and have

created mathematical models to explain

this

what you see in this graphical

representation is

an expectation that when individuals are

over 00 kilograms what you really see a

gain in is a gain at adipose mass

relative to muscle mass

when you think of

the specific organs what you see is most

organs will increase in size such as the

heart lung kidneys and liver

but theyll usually reach a max of no

more than a twofold change in size

and perhaps a a threefold change when

youre thinking of muscle mass

but again these organs responsible for

clearance of drugs do not increase by

more than twofold in size across a

across on almost fivefold

distribution of body weight

now this is important

because again when were scaling this

information we really need to consider

how does

the change in body weight impact the uh

the change in drug clearance when youre

thinking about distribution and

metabolism in general there are not a

lot of

great studies that have done this its

not really well characterized but we can

have general trends when were thinking

about drug distribution that can be

based on the physiochemical properties

of the drug

typically what we see is were dealing

with drugs that are more acidic

we tend to see

smaller volumes of distributions

compared to drugs that are more basic

that can be sequestered within tissue

and tend to have larger volumes of

distribution

when were looking at metabolism

specifically

looking at the cytochrome p0 system

[Music]

what has been evaluated

has been specific probes of cytochrome

p0 a c9 9 and sipd

and these studies that have looked at

specific probes of those pathways have

seen limited effects of increasing body

size and

metabolism

an area where there has been a to

fold increase in clearance

has been through the cytochrome

pe isoenzyme system thats really

not responsible for the metabolism of a

lot of drugs

this isoenzyme system is responsible for

the

metabolism of more lipophilic compounds

that are typically less than 00 daltons

in weight and so this can impact

some anesthetics it can impact a key

probe substrate known as cloroxoxyzane

chloroxoxazone sorry

and

the metabolic profile of acetaminophen

into its more toxic metabolites

again this pathway

does not influence the metabolism of

most drugs

so when we think about

sip metabolism in general we do not

anticipate

an increase in the metabolism as

individuals increase in body body size

now when were accounting for uh these

parameters uh clearly weight that weve

spent quite a bit of time so far

discussing

is really a parameter that tends to

correlate with the volume of

distribution

when we look at clearance there are

several factors that that are usually

accounted for in population pk studies

that look at race

height weight age sex

serum creatinine

there are also several intrinsic

variables that i wont have an

opportunity to cover today but discuss

that that include pharmacogenetic

variation

there could also be extrinsic variables

such as the impact of smoking

or dietary changes that can impact

clearance

but typically these are the parameters

that are looked at and often these

parameters are consolidated

into a variable such as kidney function

that incorporates

some of these parameters into a

composite parameter that correlates with

clearance

again we tend to treat in population pk

analyses these these terms to be

independent

but they can be interrelated for example

height

clearly correlates with sex and so that

may not necessarily be an independent

parameter

when incorporated into these models

what i did earlier is show changes in

body size

how those body size changes relate to

tissue changes and organ weights

but how do those actually relate to

function and so this is a

one of the few studies

thats done this really well and this is

a study done by arvie shagnac and

colleagues who

have looked at

healthy obese individuals these are

again defining healthy obese individuals

is quite complicated these are

individuals who did not have

hypertension and diabetes but were very

large on body weight

and so looking at these individuals

similar

age

they

they looked at a at glomerular

filtration rates

and when you look at these again

although individuals were almost twice

in body size what you see is only a

percent increase

in the glomerular filtration rate

and this is again consistent with

several animal model experiments that

have also shown similar trends for

increases in gfr relative to to body

size

another study by friedman and colleagues

has looked at the population

pharmacokinetics of via hexahole which

is another marker that can be used to

compute glomerular filtration

and if you do a simulation using that

population model what you also see is if

you look at the change in body weight

between 0 and 00 kilograms you would

not anticipate the glomerular filtration

rate to increase by more than 0 percent

and so there are several data sets that

essentially show

that we do not expect body

weight to increase

mechanisms that would be associated with

drug clearance by more than

0 to 0 percent on average

now uh in the clinical practice we often

cannot measure uh the creatine clearance

or or

or estimate the glomerular filtration

rate and so we often rely on equations

and so what id like to point out here

is that there are really two broad ways

of doing this one is using the egfr or

estimated gfr equations

and this method currently incorporates

serum creatinine age

and race

but does not incorporate body weight

instead that parameter

is sometimes modified in individuals by

converting this term

uh from a scalar thats thats a

benchmark to body surface area to a

nonnormalized term

this equation also has been calibrated

using the isotopic dilution mass

spectrometry traceable creatinine which

is currently the standard to ensure that

creatinine measurements across

institutions are similar

the more classical equation that is

actually incorporated in clinical trials

uh over the last 0 years has been the

cockroft and galt equation

this equation that was introduced in

9

is a simple equation and is often stud

uh taught in many

schools and incorporates the use of age

weight

serum creatinine this study

actually did not include any females in

its design

and so this was

an assumption that was placed into the

equation with the expectation that women

on average have 0 to 0 percent

less

lean body weight and so a term of a 0

lower

um

weight was used in females as an

expression again this model uh was never

really validated in females but has has

been used over time and shown to be

useful for several drugs

another equation thats emerged

is the chronic kidney disease and

epidemiology equation

this equation was developed primarily to

resolve the issue of the former equation

known as the modified diet and renal

disease equation or mdrd equation that

was really restricted to individuals who

have gfr estimates less than 0 ml

for meters squared

so what this equation accomplishes is it

permits the calculation of gfr across

the gfr distribution so values below 0

and above 0 ml per meter squared

as seen by this equation again

it is uh uh more much more complicated

because it includes several equations

that account for sex and and race of

individuals

uh but clearly and there has been

controversy on the use of a race as a

factor in this equation

especially in multiethnic societies

this equation has not necessarily worked

out

in those populations

now

this brings us back to again use of this

term because

clearance often correlates with several

kidney function markers but we often

dose the drug on

on body weight

for certain drugs and if were going to

dose the drug and body weight

a scenario thats expected is that the

clearance of the drug should increase in

a linear and proportionate weight

instead what we see is that relationship

is really nonlinear

and the reason why this error may occur

is early phase clinical trials tend to

include individuals within a relatively

narrow

bandwidth of body weight and so if you

include individuals that are for example

between 0 and 0 kilograms you may

consider those individuals to have a

linear change in clearance

but when you include a larger body

weight distribution in your

pharmacokinetic studies youre more

likely to see this curvature and

nonlinearity

now this phenomenon is not an old

phenomenon this phenomenon has been

evaluated in several disciplines

and so the principles that are used in

pharmacology really relate to principles

that were generated in the early

understandings of

resting metabolism

and so what we have here are two major

paradigms that develop that have

developed over time

and so this is what i often refer to as

the battle of the maxis this is max

rubners work

from the early 0s

to almost 0 years later by work by max

klieber

max rupners work was

a pivotal understanding of the

relationship

of heat production relative to body

surface area

and so his work

included experiments

that obviously would not be conducted

today but involved the use of animals

that were placed in chambers and allowed

to starve over time

what was seen in dogs

is heat production

declined as a function of their body

weight scaled

to 0

max reubners work really looked at

scaling uh resting metabolism across

species uh

and then so in those experiments was was

shown is a

when you plot log heat production

relative to log body weight production a

log body weight im sorry

what you see is a relationship that that

has a slope parameter of 0

and his original work actually

was around 0 but again for

simplification most of the literature

reports it as 0

now this is relevant uh when were

thinking about alimetry because were

thinking about relationships between

body size

shape and physiology

and so

often we think of

disparate comparisons as apples and

oranges

in this scenario im giving the example

of an apple versus a romanesco

and this is relevant because

when were thinking about computation of

surface area

we have to think of the world as either

being smooth surfaces

or

the true

phenomena which is more rough surfaces

so when you think of smooth surfaces if

were going to compute the surface area

of this apple we would have to think of

this apple in three dimensions

and the area would simply be the volume

of this cube

to the power or 0

whats been shown

uh more eloquently now by west uh and

colleagues

is that our computation of surface uh

and and uh really

physiology are these relationships are

really driven by fractal geometry

and the area is better represented by

the volume of

of tissue or or

other

spaces

to the threequarters power or basically

0

and so the work by rubner and

by clieber basically exist within these

two expected paradigms

in science

now this is again relevant because our

approaches to computation of body

surface area that

are used for drug dosing

also rely on euclidean geometry and so

what i have here are basically graphics

from about 00 years ago

that used

a simple computation of body surface

area

by

by

one example here which is this is an

image

from the work of dubois and dubois so

dubois and dubois and colleagues

essentially took

a small number of individuals and paper

mached them

and after paper machining them they

removed the paper mache placed them on

the ground and took photographs of that

paper mache

after taking those photographs they then

computed the surface area and derived an

equation

so again that process would have

required a computation based on smooth

surfaces

and the dubois dubai equation is

represented here

by by this equation

which is basically body weight to an

exponent and height to an exponent

and other individuals over time have

have thought this equation to not be

representative

because again it was based on

nine individuals and then include and

then basically included an additional

individuals in their in their model

so gihan and george tried to expand on

this model

by studying larger a larger sample of

individuals but really came up with

similar exponents

and im going to explain why thats the

case

haycock and colleagues tried to expand

this to include pediatric populations

and then we have mo stellar

who wrote a simple letter to the editor

in england journal medicine that

simplified a lot of these equations and

this is the equation again because of

its simplicity is included in a lot of

textbooks and simply includes

the weight times height of individual

divided by 00 and is essentially the

square root

of that now im going to show you that

all these equations have similar

answers because they all rely on

euclidean geometry so with euclidean

geometry what you have is weight is a

function of volume

times density and height as you can

imagine is just a

single dimension

so if you take the exponent over weight

which is a threedimensional term

and add it to height which is a

onedimensional term what you will see

with all equations that have been

constructed to date is all those values

add up to two and the reason they add up

to two again is its based on euclidean

geometry that has

integer based

dimensions

and thats essentially what you see with

body surface area which is meter meter

square or

which is a meter squared term

and so these body surface equations

essentially uh

several of them have been developed over

time

but really are very similar because

theyre scaling the information

the same way

the dubai and dubai equation will lead

to computation of slightly lower values

and the reason that occurs is because

the weight term has an exponent of 0

so it has a smaller term overweight and

will lead to computation of a smaller

surface area but again the scaling is

essentially the same

so this has dosing implications because

if the dose increases with weight or

body surface area but clearance does not

increase with that parameter then what

you would expect to see is at higher auc

in larger individuals

so

is it really acceptable when we think

about this when were thinking about a

milligram per kilogram dose so if you

think about a drug and the drugs product

label is reported as six milligram per

kilogram

if you use that same milligram per

kilogram in a 0 kilogram individual

youre going to collect youre going to

calculate a dose of 0 milligrams if

you use the same in 0 kilogram person

you would calculate a dose of a thousand

milligrams

on average you would calculate a dose of

00 milligrams so the question often is

is that okay again this is a common

thing that we do

uh in in practice

we address this issue often

in obesity by using another weight

parameter and so now lets discuss what

those other weight parameters might be

one of those is lean body weight which

we often think of as a good metric

of muscle mass

now

measuring lean body weight is not as

simple

as we would think one when you think

about measurement

even

acquiring total body weight in a very

large or morbidly obese individual is

not simple

its not simple because a very large

individual may not be ambulatory and so

its difficult to actually get a body

weight you may also not have

the right scales in your institution to

to compute body weight for very large

individuals computation of height also

may be compromised if this is not done

correctly

measurement can also include use of

other modalities such as bioma

bioelectric impedance analysis

you can have underwater underwater

weighing

you can have dexa

which is an xraybased method or you

can have a more

recent method you which relies on air

displacement bledsmography

which again

these

systems

can be used in healthy individuals but

often not a system that can be used in

acutely ill individuals

of this we often rely on estimation and

that estimation happens with several

equations such as the ideal body weight

all the way to the predicted normal

weight and im going to review some of

those equations with you

when you think about these descriptors

total body weight uh is often sometimes

referred to as actual body weight so

theres different terms used in

literature and this is measured and as i

mentioned not always easy to do

we have the ideal body weight equation

and this is an equation that was uh

developed

over time

and

referenced for the first time in 9 by

ben divine without an actual source

and as a resident this was one of the

first

questions i had to tackle

through a literature search was finding

the origin of the ideal body weight

equation and what i discovered was it

was simply a

rule of thumb a farmers rule of thumb

that was based on

our

our

principle of fives because again what

you see in the literature is this love

for the number five

because we have five fingers

we believe

that five kilograms for every inch over

five feet would represent an ideal

individual and so this term again thats

been used in pharmacology was based on a

very simple rule that men started 0

pounds and gained

five

and gained five pounds for every inch

and and women also gained the same

weight

for every inch which again is not a

reasonable

a reasonable hypothesis

because the ideal body weight term did

not work for several drugs a

modification was done and that

modification was called the adjusted

body weight this was tested primarily

with the aminoglycosides and a

correction factor was found

now that correction factor in the

literature actually ranges between 0

and 09 but on average is between 0

and 0 and so what you see in a lot of

textbooks is the average of these

averages which is 0

and so the adjusted body weight is

simply saying

0

of the difference between total and

ideal body weight plus ideal body weight

is what we would term the adjusted body

weight and then use that weight to

compute the dose of the drug

again

whether or not these are are truly

accurate ways of representing body

weight whats been shown is that they

help

dosing of certain drugs

we also have other weight descriptors

that have been defined using more

scientific methods

such as bioelectrical impedance and also

based on on animal data

and the best representation of that is

the most recent equation known as the

lean body weight 00 or the gen

generation equation

this was based on 00 individuals in uh

in australia

where they relied on body mass

body electrical uh

impedance analysis to compete lean body

weight and this equation has been used

in the literature in more recent times

and computes

lean body weight as a function of total

body weight and body mass index with

slightly different parameters based on

males and females

but again all of these equations are

essentially transforming

height and weight

into different metrics and so thats an

important

thing to remember that all were

essentially doing is taking height and

weight and transforming them

mathematically uh into into another term

so

i want to highlight again whats been

done in the literature just to show that

there is some harmonization in the

principles that ive laid out in this

lecture

one of the approaches thats often used

in in pharmacy

is using a combination of total body

weight ideal body weight and adjusted

body weight

now you can imagine if youre using

total body weight to dose a drug

as a person increases in body weight you

would get a proportionate increase in

the dose of the drug

and clearly thats not

necessarily a good idea especially in

the extremes of weight

if you were to use that weight

distribution

actually if you were to use the height

distribution because again ideal body

weight is based simply on height

you would get a distribution of weights

computed in this manner

if you then used

adjusted body weight you would get

another distribution of weight

and then if you used

a combination based on this metric of

thats often used in literature you

would get this distribution of dosing

weights across a population

and then if you model that data what you

essentially show

is using those distribution of weights

essentially gives you a dosing weight

function thats three times total body

weight to the 0 power

so in essence what you see in the

literature are really divergent methods

of actually dosing drugs but in reality

in mathematical reality these are really

congruent approaches of of scaling doses

and really the objective again whether

you use body surface area or use an

alternate body size descriptor is youre

essentially preventing someone from

getting twice the dose

as would a normal weight individual

so again this brings

you know the question of who is right

should we be scaling to this power or

that power

and the reality is that there really

the answer exists somewhere in between

that

when you look at

this study by mclean colleagues what

theyve demonstrated is its really drug

dependent

and so on average what you find is

several drugs will scale based on body

surface area but some drugs

where the exponent is closer to zero

would imply that a fixed dosing strategy

would be better and other drugs

using

actual body weight or total body weight

may actually be beneficial for the

dosing of the drug but on average you

would expect most drugs

to be dosed on a parameter such as body

surface area

this is relevant

because when we think about drug

development current paradigms include

more physiologic based pharmacokinetic

modeling systems

and often whats seen in the literature

is reporting of values

based on a kilogram basis

and that kilogram basis is often used to

scale information

and so its important to ensure that the

the methods that are being used to scale

information in obese individuals are

scaling them

using some sort of factor

and not in a linear way so essentially

what needs to be done is ensuring that

when this physiologic based models are

used to derive estimates and obese

individuals that theyre being scaled

appropriately

based on information thats actually

derived from the drug

in question

so now that ive gone through a lot of

theory what id like to do is actually

go over some key examples to illustrate

how this impacts drug dosing

when you think about the source of these

different weight descriptors the

aminoglycosides serve as the key example

these are drugs that have a volume of

distribution between 0 and 0 liter

per kilogram

what weve recognized over the last 0

years

with these class of drugs where they

were first classified as antibiotics

are that theres a higher risk for

toxicity when youre dosing them on

total body weight

and that you can adjust the doses of

these drugs based on kidney function and

in this case we actually also have

therapeutic drug monitoring available

that can allow you to modify

the maintenance dose

there are several alternate body size

descriptors that have been used

these drugs are relatively small in size

they have low plasma protein binding

we also know that the clearance of this

drug correlates very well with the

glomerular filtration rate

the dosing of this drug is based on body

weight and when you look at the

literature theres a range of doses

between one and seven milligram per

kilogram based on the indication of the

drug

and again in most institutions the

dosing is individualized based on

therapeutic direct

monitoring this is a study that i

conducted

over a decade ago looking at almost

000 individuals who are dosed on

gentamicin and tobramycin across a very

wide

body weight distribution of 0 to almost

0 kilograms

what we showed

in this data set is that if you were to

rely on total body weight to scale the

volume of distribution of the drug

what happens is you get an unsteady

estimate of the volume of distribution

that is the volume of distribution

parameter goes down as the body weight

goes up

if you were to use ideal body weight you

see the opposite phenomenon and again

this is because ideal body weight is a

function of of height and not weight

instead if you were to use the equation

that i mentioned

the lean body weight 00 equation what

you get is

similar estimates

of

lean body weight of volume distribution

across the body distribute body

distribution

so the implications of that is

if you were to define a dose based on

lean body weight youre more likely to

have a predictable cmax concentration

for this drug

that is considered to be a concentration

dependent or cmax or ac

aec driven drug and ill show you how

this actually also can affect the aec of

the drug

this finding also matches what was seen

in animal models so work done by salazar

and colleagues showed a value that was

also similar in the in in rats

when they scale the information to fat

free mass or lean mass

now

with aminoglycosides when you think

about the pharmacodynamics theyre

driven both by the peak to mic and also

by the aec mic

and so the area under the curve is also

important and so thats driven by the

clearance of the drug

and so what we did is we also evaluated

all the different equations that could

exist

to compute the

the clearance of the drug and see what

the correlations are and when you look

at that what we found is that the krakow

the

chronic kidney disease and epidemiology

equation actually gave us the best

correlation

but its really important to show that

even for a drug class like the immune

glycosides that are considered to be

well correlated to clearance that an

equation like the ckdb equation

only explains

0 percent

of the interindividual variability

in the clearance of the aminoglycosides

and so this is again the rationale for

using therapeutic drug monitoring to

modify the dose of this drug

so

when you think about initial dose

selection of amino glycosides were

perhaps gearing it to a cmax to mic

target or an acdmic target but if youre

thinking about it from an ac to mic

target

we would consider

the milligram per kilogram dose of this

drug

and we may consider different approaches

so when youre thinking about this drug

use of tobramycin and cystic fibrosis

patients

whats published in the literature is

use of a higher milligram per kilogram

dose or 0 milligram per kilogram

and the reason this makes sense is

cystic fibrosis individuals tend to be

leaner

and because theyre lower in body weight

the expectation is the need for a higher

milligram per kilogram dose

in contrast if youre going to think

about dosing this drug across a weight

distribution

what could be considered is

if youre using

a higher if you have individuals across

a higher weight distribution what may be

necessary is using a lower milligram per

kilogram

term

and so this again fits within the

paradigm because

the paradigm is based on five to seven

milligram per kilogram

but you may make the decision to use a

lower milligram per kilogram in a larger

individual

and then the third alternative is

is saying this may be a confusing

algorithm so instead

if you could use a fixed milligram per

kilogram across a population and then

use

lean body weight you would then compute

again very similar doses

but have a simpler metric

to dose across a weight distribution

another approach could be

consideration of of kidney function as

the dosing strategy and this is

if you believe the ac to mic to be the

driver of the relationship

in this scenario

weve published equations

that demonstrate how this could be done

and essentially you would use the

creatinine clearance estimate using a

krakroff galt equation

to compute an amino glycoside clearance

to compute an initial dose based on this

target value

this article

for reference

also relays how the information can then

if therapeutic drug monitoring is

applied

equations are provided that can be used

to compute the auc of the drug to modify

the dosing of the drug

another drug where this is seen to be

quite relevant is with the dosing of

vancomycin

this dosing historically

has been thought to be reasonable

based on

actual or total body weight because the

the volume of distribution of this drug

is thought to be very similar to total

body water

estimates

in most individuals

now there could be multiple approaches

that are used so one approach

thats used in in current guidelines is

to dose the drug based on total body

weight

and so when you look at that

using total body weight

you uh where if you were to use

milligram per kilogram you will clearly

compute a much higher dose in a larger

individual

and so for most clinicians this may lead

to consideration of too high of a dose

the alternate uh in other guidelines

when youre looking at the methicillin

resistant staph aureus guidelines the

recommendation is to use no more than

000 milligrams as the dose

and so in this scenario in a larger

individual you may end up using a

milligram per kilogram dose

and so for some clinicians that may be

too low of a dose

so what would be the alternative one of

the alternatives would be to use the

same milligram per kilogram dosage

but then use an a different body weight

descriptor and so as the individual gets

larger instead of using

total body weight use the adjusted body

weight function and you would compute

much lower doses

a simpler alternative could be to scale

the doses and so since most individuals

have calculators have square root

function what im showing here

is if you take the weight of the

individual divided by the average weight

and take the square root of it you would

basically be able to replicate the

dosing of this drug across a population

that would match up

to

adjusted body weight dosing

when youre thinking about vancomycin

again this is a drug that also undergoes

therapeutic drug monitoring

what has happened over time

is guidelines that have suggested that

only trough concentrations are necessary

but a point that needs to be highlighted

is that trough concentrations do

correlate with the auc of this drug but

only predict

about 0 percent of the interindividual

variability and so the trough

concentration is a simple metric its

easy because a single concentration can

be measured but it may not represent the

true auc in a specific individual

what weve shown

in a series of studies is is the

importance of getting a peak

concentration measurement in obese

individuals

and this is really important because

uh bayesian approaches that can be used

to compute the auc of of a drug like

vancomycin

in a population

really

needs an accurate estimate of the volume

of distribution

and so you can imagine if you are

missing a peak

concentration measurement you dont

actually know which concentration time

profile truly represents the individual

and so you can have different scenarios

represented here with the true scenario

represented by the

actual concentration measurement

and a two compartment model

and so again

when we think about achieving the right

dose in an obese individual

a common

issue is not being able to approximate

what the true volume of distribution is

for the specific drug and so in this

scenario what we we demonstrate is the

importance of a peak concentration

measurement

more recently weve published a study

looking at the pharmacokinetics of

vancomycin

and looking at alternate metrics as i

mentioned with the several equations

what weve relied on for over a hundred

years is using height and weight

to compute alternate body size

descriptors

stuart wong and colleagues at the

university of michigan have led a group

known as the morphomics group

these individuals have developed

mathematical algorithms that can take

existing

computer tomography data and convert

them to different body size metrics

so this graphical representation is

taking existing data

from individuals or in the hospital who

have may have had a ct scan done for

some medical reason

and then taking that data to compute

parameters such as body depth

fascial area

total psoas area

and and several other parameters

represented in this slide

what we then did is uh look

retrospectively at the pharmacokinetic

profile of vancomycin and assess the

correlation of these pharmacokinetic

parameters

to these newer body composition metrics

what we were able to clearly demonstrate

is that the volume of distribution of

vancomycin was poorly predicted by body

weight

and was really better predicted by t

to t

base which is representing again the

vertebral columns t to t torso torso

area was a better correlate

but again

looking at this youd see a very poor

correlation

but in relative terms a better

correlation to body weight

were also able to demonstrate that

using total source area

that which would be a metric

representative of muscle mass that this

metric was a better predictor of

clearance than relying simply on body

weight

and so again this

more recent study is clearly not ready

for a prime time use but just represents

a movement away from our simple measures

of height and weight to define drug

dosing

for other drugs that are just dosed on a

fixed dosing basis drugs like

ceftaroline that that whose

pharmacodynamics are based on time above

mic which youll see for several drugs

and shown earlier

is reductions in the peak concentration

but really a convergence in the profile

and so this study

by justin colleagues out of keith

rodfelds group at the university of

illinois at chicago

have clearly shown that for certain

drugs like beta lactams you may need

higher doses with the first dose

but really because of this convergence

in the profile maintenance doses

probably do not need to be adjusted for

for most beta lactams

for another drug like the like

levofloxacin a drug thats concentration

dependent

whats shown in the label is use of a

higher milligram

dose that allowed

really shortening of the dosage regimen

from 0 days

to a to a shorter regimen

in patients with with pneumonia

for this drug the aec mic is predictive

of the response and the observed auc of

this drug is between 0 and 0

milligram per hour leader

this drug also has a really good

correlation to kidney function

and because the clearance of this drug

has a good correlation in theory the

dosing of this drug could be improved

by computing the clearance of the drug

relative to creating clearance

now in the united states

we do not offer therapeutic drug

monitoring for drugs like levofloxacin

but this study

conducted in collaboration with dr

federico pia at the university of udenai

in italy were able to show is

therapeutic drug monitoring can be used

to improve the dosing of drugs

in individuals across a much larger body

weight distribution of 9 to 0

kilograms

what were able to show is those

individuals

may need doses higher than 0

milligrams to achieve isometric

exposures

to those that are that are that are

smaller in size

but again the critical piece here is

that therapeutic drug monitoring was

available to ensure that we didnt

overdose individuals

and so this recommendation of using

higher doses is truly off label

and cannot be recommended in clinical

practice in the united states

but for institutions that do have

therapeutic drug monitoring it does

create a mechanism to consider uses of

higher doses of drugs to achieve

the exposures necessary to improve

outcome of a drug like levofloxacin

additional examples for other drugs that

are nonantimicrobials include work by

dr catherine neebs group at the

university of leiden

this group has done several studies

looking at specific probes of sip

metabolism and theyve done a really

nice study more recently with midazolam

looking at a population of individuals

whove undergone bariatric surgery

and so this is an important study

because this study allows

an evaluation of individuals as their

own controls

so this would represent this figure here

represents individuals who are

larger who are obese who undergo

bariatric surgery and over a oneyear

span

lose

quite a bit of weight

and because they lose weight and you can

measure pharmacokinetics before

and after weight loss you can look at

changes in drug clearance and what

theyve shown with midazolam

which is a probe of sip a

is that the systemic clearance increased

with this drug with weight loss

but theres really no alterations in

oral bioavailability and so this

expectation

is different again because we would

think

in terms of do we need to increase the

dose for body size in this scenario

the idea is we perhaps may need to lower

certain doses of certain drugs if this

if this is really true

in obese individuals

for other drugs like acetaminophen this

is actually metabolized by multiple

pathways

and so its not really a good probe for

sipe but this is an important study

because this study shows

a shift in the metabolic profile in

morbidly bees individuals

represented by the

blue

box plot versus the green blox plot of

nonobese individuals

what you see is an increase in the

cysteine and although not statistically

significant increase in the

mercapta pure rate metabolite of

acetaminophen

metabolites that would be associated

with the

hepatotoxicity potential of this drug

and so in this scenario even though

clearance may increase with the drug

like acetaminophen

recommendations cannot be made to

increase the dosage of a drug like

casino menophane

because this may lead to increase

in toxic metabolites of the drug and so

studies like this are really important

to uh because they can give us good

insights

on whether doses should be improved

changed in certain populations but

really if metabolites are also changing

in those in obese individuals

another important compound thats been

evaluated is propofol

and so this study again by neban

colleagues

looked at the glucoronidation profile of

propofol

and really were able to show that the

clearance of a compound like propofol

which is a very low molecular weight

small compound

best scales allometrically and this is

going to be again a phenomenon thats

seen with several drugs again is that

for most of these drugs we would expect

that the clearance of the drug to scale

to an exponent of 0 or 0

and that is essentially what was seen in

this study implying

that perhaps a

body surface area or a metric like that

may be reasonable to the dosing of

propofol

now this has been actually investigated

in much more detail by eleveld and

colleagues who have taken

data sets across different weight

distributions

and across different populations of

adults children and elderly and have

come up with a much more complex and

comprehensive model

that not just

deals with the issue of obesity but

really deals with the overall

profile

and this is

a process thats being heralded through

the open tci initiative and is an

important one to help improve the dosing

of compounds like propofol

that is you that are used in anesthesia

so

what ive presented today is a lot of

different paradigms that are currently

used to define the dosing of

drugs and obesity but its important to

consider that if we have some drugs

where we shouldnt be dosing them on

body weight

rather where we should be dosing them on

a fixed basis how do we change that

dosing paradigm

and what and if were going to do that

how do we pay attention to improving the

dosing of a drug once a drug is marketed

so id like to present

in the last few slides here is the data

with daptomycin so this is a study that

i performed about a decade ago at the

university of new mexico where we looked

at morbidly obese versus normal weight

individuals

and

dosed adaptomycin

based on body weight

and what we saw is very small change in

the volume of distribution of this drug

even though that the weight of

individual was almost twice as high in

the morbidity obese versus the normal

weight individuals the volume of

distribution did not increase

proportionately to body weight we also

used body bioelectrical impedance

analysis to compute the fatfree mass of

these individuals

and when we do that we actually were

able to normalize the volume of

distribution implying that total body

weight is not the right metric for this

drug

when we looked at clearance of this drug

were also able to show that the

clearance of this drug does not

increase proportionately to body weight

and again this parameter was scaled

better with fat free weight

and in this scenario we also looked at

measurement of clearance because these

individuals were matched on their sodium

ithalmate glomerular filtration rate so

this is a wellperformed study and we

were able to show again that neither of

these parameters really scaled scaled to

body weight

this is important because this drug is

currently dosed on body weight

on a four milligram per kilogram and six

milligram per kilogram basis with

specific guidance to not modify the dose

for obesity

there are also recent guidance that

suggests that the dose of this drug

should be increased to to 0 milligram

per kilogram which would imply much

higher exposures in

obese individuals

more recently we published a study in

collaboration with

marco falcone and calgary colleagues at

the university of rome

and this study was based in individuals

in that were critically ill

and in these 0 individuals what were

able to show again

is that body weight does not correlate

with the clearance of this drug

rather there were certain individuals

who had augmented clearance of this drug

and in fact what we were able to show is

individuals who

had

bacteremias who were sicker individuals

tended to have higher clearance and that

clearance was not related to to body

weight

again we were able to discover that

through therapeutic drug monitoring

which is widely not available for this

drug

now the our findings are consistent with

the original findings from over a decade

ago so if you look where to look at the

original population pk model for a drug

like daptomycin what you would see is

the clearance of this drug was actually

related to body temperature which is

in most cases when youre looking at

this youd say that this is an odd term

to incorporate into a population model

but what it really represents is this

idea of illness

if someone is has a severe infection

theyre more likely to be febrile and if

theyre likely to be

febrile their temperature will be higher

and so you would compute a higher

clearance

they also incorporated

renal clearance in the term but when you

looked at the function most of that

clearance is not really driven by by

kidney function

theres just a value of 00

which is the same value that we saw in

our healthy volunteers

now if you look at this again tabulated

and using a referent population what you

would expect is even if the kidney

function increased

and body temperature increased your

maximal expectation for clearance across

that population would be no more than a

0 percent higher clearance which would

imply that the dosing of the drug or the

absolute dose of the drug does not need

to be increased by more than twofold

so again if youre going to dose a 0

kilogram person versus 0 kilogram

person you would dose that individual

the 0 kilogram person three times more

if you used total body weight

and clearly the mathematical

expectations are that that would be too

high

this has also been shown in febrile

neutropenic patients when youre

thinking about the effects of of

severity of illness and clearance

now this is problematic because how do

we solve this issue once a drug is on

the market so the product label

currently recommends that the drug be

dosed on total body weight

and so some

investigators have suggested in larger

individuals

in larger individuals to switch scalars

so instead of using total body weight

because you would accidentally perhaps

calculate too high of a dose

consider switching to lean body weight

and why this is an issue is if you were

to look at the distribution of lean body

weight across a population

this is a representation of the lean

body weight in males and this is the

representation in females

if you were to use these distributions

you would get this phenomenon

you would dose individuals between 0

and kilograms on total body weight

and so what would happen is you would

compute a dose between 00 and

milligrams and then by switching scalars

what youd essentially do is drop the

dose

for individuals that are larger

so the effect of switching scalars for

some drugs is you would end up giving

larger individuals

much smaller doses than they need

and so

our group has proposed consideration of

fixed dosing strategy for this drug to

essentially give similar doses across

across a population but that

recommendation also needs to be

validated through a prospective study

so to summarize

the key points that ive laid out today

obesity is associated with changes in

volume of distribution

that may require the use of higher

initial doses relative to to maintenance

doses

our expectation is obesity has limited

changes in drug clearance and that for

the majority of drugs those changes are

likely explained by alimetry

we also expect that total body weight

may be reasonable for an initial dose

but its really unlikely to be a useful

metric for maintenance for defining the

maintenance dose

and

the loading dose of a drug

could be used to

to aid the dosing of drugs that are time

dependent

pharmacokinetics but we should really

move towards consideration of body size

stratified or composition stratified

dosing regimens for computation of the

maintenance dose of a drug

with that id like to thank you for your

attention id also like to thank dr

william figg and dr lisa cordes the

national institutes of health for this

opportunity to present in the principles

of clinical pharmacology

if you have any questions please direct

them to the coordinators of this course