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 and 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 dr figg

im going to begin the

twopart presentation on

pharmacokinetics

in patients requiring renal replacement

therapy

by talking about

pharmacokinetics in patients who are

undergoing hemodialysis

well you may think its strange for a

pharmacologist to be interested in

hemodialysis

but as a matter of history

hemodialysis was first studied by john

jacob abel who actually was the first

pharmacologist in the united states

and

dr abel

published this paper way back in 9

and he was he called it vivid perfusion

and he

had to build his own apparatus he then

had to

to

make a leech extract to use as an

anticoagulant

and one of the studies he did was to

study the hemodialysis of the drug

salicylic acid

so you can see that a lot of what were

going to talk about has really its roots

in the founding of the founder of

american pharmacology

and although some investigators in in

germany did some studies on hemodialysis

in the 90s

it wasnt until

near the end of the second world war

that willem kolff actually applied it

to treat a woman

who was in renal failure and so that was

hes really credited with being the

first one to successfully use

hemodialysis

in

treating patients

the from the pharmacokineticist

standpoint

the artificial kidney is the ideal

eliminating organ

you can measure blood flow

you can measure drug concentrations

going into the dialyzer drug

concentrations leaving the dialyzer you

can actually

collect the dialysis bath fluid

and see how much drug youve actually

taken out

so previously weve talked about

youve talked heard about renal

clearance of drugs

and

the observations we can make are are

somewhat more limited we can measure the

eliminated drug obviously and the

concentration in blood going to the

kidney

yeah there are ways of measuring blood

flow but its hardly ever done and the

same goes for the nonrenal or hepatic

clearance of drugs where we

really have

only routine access to the the blood

concentrations themselves and obtain uh

hepatic clearance by subtraction from

renal clearance from total clearance

so here are all the sources in the north

schematic of a

patient on hemodialysis

there are convenient ports in the line

to sample blood going into the kidney

sample blood leaving the artificial

kidney you can measure blood flow here

and recover drug

now as you know

we the total elimination clearance

represents the sum

of renal clearance and nonrenal

clearance and when we study patients on

hemodialysis we have a third elimination

clearance to calculate

dr gerhard levy

has

said that for

hemodialysis clearance or extracorporeal

clearance to be considered effective

it has to be greater than 0 percent of

the sum

of renal and nonrenal clearances

the essential point that isnt often

considered is that these clearance

estimates

must be comparable and well talk about

that in just a minute

but first i want to discuss a number of

ways of thinking of hemodialysis

clearance

and weve previously

mentioned

professor eugene renkin in the context

of the equation that he used to analyze

transcapillary exchange

he also performed studies with the

artificial kidney using the very same

equation

and his equation

neglected certain things like

ultrafiltration and boundary effects

but it did

take into consideration characteristics

like the surface area the membrane the

thickness the porosity

drug binding to plasma proteins could be

considered

solute size and diffusivity

and so if we look for example at two

compounds procainamide and thats

acetylated metabolite napa we can see

that the ratio

of the dialyzer permeability

coefficients calculated from professor

renkens equation is very close to what

we can measure in terms of the ratio of

their free water diffusion coefficients

and

renkin

published this figure in which they

looked at the relationship between

dialysis clearance

and flow through the dialyzer

what you can see is urea

which has a very high permeability has a

clearance that that is

for a while at least quite close to to

uh blood flow uh measurements as we get

up to larger and larger compounds for

example phenol red once you get above

lets say 0

mils per minute for your your flow

you reach sort of a plateau

in the dialysis clearance that can be

obtained

so in a sense this elimination is

perfusion limited and urea is more flow

limited if you will in its clearance

now one of the problems we have in in

taking published literature data and

applying it to an actual patient is that

the study on which the literature is

based

may have been done with a different

dialyzer than were do

than our patient is using

and one way of of

theoretically

transforming the data between dial

dialyzers would be to do a preliminary

study and calculate the ratio of

permeability surface coefficients

for a

particular drug and the standard

compound

and then use the ratio to to estimate

what the dialyzer clearance would be for

another dialyzer but what needs to be

selected is the appropriate standard

compound maybe something like creatinine

uh would work for that

but uh

most of the kinetic studies that are

done do not use renkens equation there

are merely empirical analyses

and there are two major approaches the

first is what i will call the recovery

clearance

here were saying dialysis clearance is

equal to the product of the

dialysate bath concentration of drug

times dialysis bath volume times the

average concentration times the dialysis

divided by the dialysis time

but you can also use the area under the

the

the

curve of concentrations going to the

dialyzer during that same time period

this is the gold standard for

calculating dialysis clearance

unfortunately

whats most often used is the av

difference method which is based on the

fig equation

and here you have the av difference

divided by the arterial concentration

going to the dialyzer times flow these

terms in parentheses we call

the extraction coefficient theres also

an extraction coefficient in the renkin

equation if you will in both cases

clearance is flow times the extraction

ratio

now there are two myths id like to

disabuse you of in in the dialysis

literature one is that you need to use

blood concentrations when calculating

blood clearance

well the fact is that usually plasma

concentrations are

proportional to blood concentrations so

if youre calculating this ratio

it really doesnt matter what youre

using

the other thing that is much more

serious

is the socalled need to use plasma flow

when calculating plasma clearance

now

if we compare

the recovery and fix methods for

calculating both blood clearance

and plasma clearance you can see that

theres probably no problem when were

talking about blood concentrations here

but supposing now were basing our

clearance calculations on plasma

concentrations

and thats how we calculate

most of our pharmacokinetic clearances

with renal clearance hepatic clearance

theyre usually plasma clearances that

were calculating

and so if the plasma concentration is

less than the blood concentration that

means the plasma clearance is going to

be greater than the blood concentration

well

the only way we can get the equivalent

answer for plasma clearance from the av

difference method is to use a blood flow

that is a flow term thats greater than

blood flow

okay

and so

this is the major problem

with using the av difference method

in calculating dialysis clearance

because remember according to levy

you want to j to judge dialysis efficacy

on

the

the

percentage that that dialysis clearance

has compared to the uh renal and

nonrenal clearances so those clearances

have to be bona fide plasma clearances

and we can see here that

the correct clearance ill call the

correct flow ill call pharmacokinetic

flow in this case the measured flow is

9 mils per minute the pharmacokinetic

flow is substantially larger

and we can

estimate to some extent the correct

pharmacokinetic flow by taking into

account the partitioning of the drug

into red cells

because the drug in erythrocytes is by

and large accessible to the dialyzer

kidney

well

what about the actual conduct of

pharmacokinetic studies and this is a a

a topic of i will say increasing

uh concern and interest

chapter six in the principles of

clinical pharmacology book

does cover this more recently theres

another paper

and

i would most of all direct you to the

draft guidance that the fda is preparing

on the proper conduct of

studies in patients with impaired renal

function and the draft guidance for the

first time

as recommendations for the conduct of

these studies in dialysis patients and

by the way does emphasize the importance

of calculating recovery clearance

based on the actual

drug recovered

so all these

things recover drug

concentration leaving the dialyzer

concentration entering the dialyzer and

flow

are accessible to direct measurement

and in conducting a study of this you

first of all have to start with the pre

or post dialysis

kinetics

and then you modify in this case a

fairly simple three compartment model

by adding two more compartments

first of all you have to have a

compartment

that in which the drug is collected

and this is the direct way the recovery

method for calculating dialysis

clearance

the venous concentrations the

concentrations leaving the dialyzer are

calculating calculated from this ratio

its a proportionality

and that ratio really comes it looks

complicated but it comes from a

rearrangement of the thick equation

and here you see how that rearrangement

is accomplished

lets carry

this approach where were taking all

sources of data and building them into

the pharmacokinetic model something that

is very rarely done

and

when that is done

generally speaking youll find that

during dialysis

the arterial venous concentrations fall

more than expected from the amount of

drug that you recover

similarly

after dialysis this rebound in

concentrations

is less

than you would expect

now this is what our dialysis kinetic

model looks like

and

the only thing that can account for both

discrepancies

is a reduction

in slow

intercompartmental clearance

this is something thats hardly ever

i would say almost never been observed

because nobody has ever conducted

rigorous rigorous enough studies its

not a trivial change

on the average ive found with this

particular drug theres a reduction

in that slow intercompartmental

clearance

during hemodialysis

well well get back to analyzing the

reasons for that but lets

now move forward and say

of what clinical significance is this

change this reduction in slow

intercompartmental clearance

and

one of the obvious

implications is it enhances the efficacy

of dialysis in treating drug toxicity

and this is a an actual case report of a

year old woman who attempted suicide

by swallowing seven grams of

procainamide

and she became lethargic and confused

and hypotensive her kidneys stopped

working and she had a junctional

tachycardia with an intraventricular

conduction delay

hemodialysis was performed for four

hours

and by the end of the second hour her

blood pressure was maintained without

vasopressor therapy

and at the end of dialysis her she was

alert and oriented

even though

less than one gram of drug and

metabolite had been removed

so she swallowed seven grams weve taken

only one less than a gram away

and

and she seemed to be better

well

the procaine amide clearance was

increased by a factor of two napa almost

fourfold the metabolite

and

again the amount removed was little but

look at the

market drop in plasma concentrations

particularly of the parent drug

we look at the pharmacokinetic

parameters that were obtained in

studying the dialysis kinetics in this

woman we see that initially she did have

greatly prolonged half elimination

halflives of both propane amid and napa

that the elimination clearance was

greatly reduced the dialysis

significantly increased those clearances

but look the distribution volume

is much less

what is going on here

well

usually when we estimate distribution

volume we give a dose of drug and we

look at how much the concentration in

the

arises in the in the blood or plasma

in this case though

we used the amount of drug removed

and the change in concentration to

calculate that distribution volume

let me draw you schematic of what

we think is going on

the reduction in slow intercompartmental

clearance is essentially putting

a tourniquet

between skeletal muscle compartment out

here

and the intravascular space

okay so in fact were dialyzing a much

smaller distribution volume

than

we would if if this

intercompartmental clearance hadnt been

uh

reduced

and because the biophase where the

pharmacokinetic

effects where the pharmacologic effects

are seen

is in more rapid equilibrium with

intervascular space than say the

skeletal muscle compartment

we can have a marked clinical

improvement

even though weve

removed drug primarily only from

two of the three compartments

so yes the total extent of drug removal

is compromised by this change

but

it can accelerate

the

the

the the recovery of the patient

uh and

also

the reduction in intercompartmental

clearance persists for a while after

hemodialysis and that attenuates the

post dialysis rebound

well

what is actually going on

in terms of physiology to account for

this

and again

uh weve previously discussed in our

drug distribution lecture the renkin

equation

and so in terms of that equation we can

have a reduction in capillary blood flow

we can have a reduction in capillary

permeability coefficient surface area

product or both of them can be decreased

so in terms of our uh

capillary exchange model

uh thats what we think has to be going

on and again ill refresh your memory

here is our our three compartment model

of inulin distribution

and of urea distribution

we can use these marker compounds then

to try to investigate whats going on

and heres a study

in which the urea and inulin were given

simultaneously

and uh inulin is not dialyzable but urea

is this is the arterial and thats the

venous concentration and you can see

that the intercompartmental clearances

the above compounds decrease although

urea

dialysis intercompartmental clearance

falls much much more than the the uh

inulin does and that as weve emphasized

before is because urea

is more flow

dependent in its dialysis in its

intercompartmental clearance than inulin

so right away

theres a clue

that something has to be going on with

flow

in fact when we use the rankine

equations to see what exactly is going

on with flow

what you see here

is that

flow to the slow equilibrating

compartment has decreased by 90 percent

and that decrease persists even in the

post dialysis period

but there is relatively little change

in the permeability coefficient surface

area products for either inulin or urea

now

these are dogs that had that were

studied that had intact kidneys

so the arena angiotensin system is

intact

the challenge if you will physiological

challenge of hemodialysis

is that the body thinks its going into

shock

so it does activate the green and

angiotensin system you can see here

plasma levels of renin that increase

markedly during dialysis and remain

elevated for some time

now i will contrast

this situation

where the reninangiotensin system is

activated with what happens

in a study in which

arginine vasopressin

is activated

and

on the the yaxis here or the

permeability coefficient surface area

product changes

and you can see as the plasma level of

arginine vasopressin increases

the permeability coefficient surface

area product decreases

now this is markedly different from our

dog study

and and how is this accomplished

well first of all uh

one of my heroes august crowe

won the nobel prize and showed this

slide

a cross section of a

capillary

capillaries in the skeletal muscle of a

cat

and what the bottom line is that only

so many of these capillaries are open at

a given time

the solid dots are closed

open circles

are open capillaries

and so by regulating the number of open

capillaries

the the body has a way to regulate the

permeability coefficient surface area

product its the surface area obviously

thats changed when you close

increase the number of closed

or open capillaries or

or reduce them

and the way that happens physiologically

has been shown in microvessel studies

that

with angiotensin ii

youre

increasing postcapillary sphincters

more than precapillary synctus so

youre getting an increase in total

peripheral resistance

that keeps at the same time in the

capillary open

whereas with arginine vasopressin and

norepinephrine

youre closing only the precapillary

sphincter and the capillary inside

collapses

so that results in what we call

capillary decrepit derecruitment

so here is a system where you have

lets say eight open capillaries in the

skeletal muscle bed this is an animation

of the crows study

and you see if you reduce and now only

have four open capillaries

oxygen has to travel a greater distance

to get over to the tissues supplied by

that capillary

now

its perhaps not surprising that you

decrease skeletal blood flow by 90

some people might get cramps

the paradox is not everybody gets cramps

so how do we explain that

in terms of the physiology

well

because these patients have renal

disease thats where the renin is made

so they have an impaired

arena angiotensin system

and when that has happened they may have

a sympathetic nervous response to the

volume distress of hemodialysis thats

not modulated by the reninangiotensin

system so they close down

capillaries

and most of the noncrappers actually

also have a defective sympathetic

nervous system so they dont close

anything down

if you put them on the tail table their

blood pressure drops precipitously

so they have

a doubly impaired homeostasis than for

volume stress

well thats the end of my particular

section and

well continue to to hear uh from uh

more novel

methods of extracurricular

drug removal

that are less stressful to patients than

hemodialysis thank you