were very honored to have dr darren
lecture dr roberts is a physician with a
subspecialty in nephrology clinical
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he completed his medical education at
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his research interests are in the broad
field of pharmacotherapy and nephrology
we hope that you enjoy todays lecture
hello everyone and thanks very much for
the opportunity to come and talk to you
about this topic which i really find is
a very fascinating topic my name is
darren roberts im coming to you from
australia and sydney
my background is ive got training as a
pharmacist and a physician and my main

area of work is that of nephrology and

clinical pharmacology and toxicology i

work at a number of institutions here in

australia and so im going to be talking

to you today about changes in

pharmacokinetics in patients with kidney

disease

by way of overview

these are the topics that well be

covering today

for the first part of this session

so first of all what is the problem well

we know the chronic kidney disease and

acute kidney injury are relatively

common conditions particularly for those

of you who work in acute care settings

such as a hospital and we also know that

drugs are regularly prescribed to

patients with impaired kidney function

what were learning more and more about

is the extent to which kidney function

impacts on the disposition of many drugs

in the body

and so when we are prescribing or

dispensing or reviewing medication

orders for patients who have been who

have kidney disease and are being

treated with medicines

we need to be aware of how these differ

between patients with normal kidney

function

we know the patients with impaired

kidney function are a vulnerable

vulnerable population particularly

theyve already been admitted to

hospital with an acute illness

and the actual changes that we provide

or

would institute for the management of

these patients really depends on a

number of factors including the patient

themselves and the drug were

prescribing and so thinking about the

prescribing of medicines to patients and

pet with impaired kidney function

provides the opportunity for us to

provide patientcentered care

so why dose adjust

well we dont suggest for the purpose of

reducing adverse drug events there are

two sorts of adverse drug events adverse

drug reactions which can relate to an

excessive exposure

but also through

we can get treatment failure if we have

subtherapeutic doses

now so we may have a subtherapeutic

dose because we are so concerned about

the risk of accumulation of a drug that

we reduce the dose too much

so then we need to understand that when

were prescribing

a few features first of all we need to

know what the renal function is at the

time that were prescribing

and if theres any changes to the kidney

function if this is an acute change or a

chronic change compared to for example a

reference population

and when were doing this its largely

based on blood results noticeably the

serum creatinine concentration

but in some cases its also under useful

to understand the etiology of the

impaired kidney function

because this may give insights in terms

of changes in pharmacokinetics

but also whether or not theres going to

be progression and changes

and when were thinking about

pharmacokinetics were thinking about

clearance because this is the primary

factor that relates to the maintenance

dose

so the challenge that we have when we

are

supervising the management of patients

uh with kidney disease or being

prescribed drugs is that there is in

many cases and its quite unfortunate

limited data about the pharmacokinetics

of many drugs in patients with kidney

disease in some cases the data is even

absent this is particularly the case for

new drugs so we need a position to come

from when we are prescribing these drugs

so we need to think about having a

rational approach to prescribing in

every patient with kidney disease

and this involves us having some

attention to the methods for assessing

kidney function but also knowledge about

pharmacokinetic principles

so lets have a brief revision about

some principles about the kidneys

so the kidneys are a key organ for the

elimination of drugs it does this

through a number of mechanisms the first

is filtration this is one wed know the

most filtration is a passive process

which the physiology is well defined and

we quantify the filtration process

through gfr or the glomerular filtration

rate

and in practice this is largely based on

the measurement of serum creatinines

which are then applied to various

formulae

but there is also active secretion and

this is happening to a larger extent

than we previously fully understood

secretion is an active process whereby

theres various transporters

particularly on the proximal tubule but

also in the distal tubule

and this can have a variable

contribution to the overall clearance it

largely depends on the particular drug

and the transporter

there are some drugs for example

metformin that are almost completely

eliminated by the kidney

but their clearance is is about four

times higher than that of gfr because

the

transport through these active

transporters in the proximal tubule is

so active

and so efficient that the amount of drug

which is removed from the kidney far

exceeds that that youd see from the gfr

and the kidneys also have a role for

metabolism where they biotransform some

drugs for example imipenem

similar and victim

and the extent to which chronic kidney

disease and particularly acute kidney

injury impact on this biotransformation

is really very poorly defined

so just a quick overview of

pharmacokinetics and the way i think

about pharmacokinetics when im thinking

about the management of patients with

kidney disease

so as you would be aware

pharmacokinetics is the

um

is describes the effect of the drug on a

body

and it reflects multiple physiological

processes including absorption

distribution metabolism and excretion

and add me is a very useful way to

remember those

each of these processes can be altered

in patients with kidney disease

and they can therefore impact on

therapeutic outcomes so they should be

considered

and the concentration time profile of a

drug reflects the net effects of these

pharmacokinetic pro

processes following drug administration

this is a concentration time profile as

youd be aware so when a drug is taken

orally theres a short gap until it gets

into the bloodstream where the

concentration then increases this is the

absorption phase and the cmax is this

highest concentration thats seen this

occurs at a time known as a tmax

and then it decreases

over time and the rate of elimination

is defined by the elimination halflife

which is the time it takes for the drug

concentration to decrease by half

these are important principles because

were going to be referring to them

multiple times during this talk

but im sure theyre principles that

youre all very well familiar with

theres a number of pharmacogenetic

properties that were interested in the

first one

are the what we call the primary

pharmacokinetics and that relates the

volume of distribution and the clearance

volume of distribution is important

because it determines the c max

clearance is very important because it

determines a maintenance dose clearance

is a key factor that is impacted on by

kidney disease but there can also be

some changes to volume distribution and

well talk about this in more detail

these two factors are used to determine

the halflife and well talk more about

that in a moment there are some other

equations which i use not uncommonly as

part of my clinical practice and im

sure you do too

where we can use these different

pharmacognomic principles to look at

things such as a dosing rate

and also the area under the curve for

interpreting pharmacokinetic data

so lets just remember about clearance

so clearance determines a maintenance

dose im going to say that a few times

during this talk and im sorry to

repeat myself but it is such an

important principle

the total clearance is made up of the

clearance of multiple different pathways

that exist in the body so its the

clearance of the kidney and the

clearance of the liver and other

clearance so in the context of kidney

disease that may relate to for example

dialysis

we wont be talking about dialysis today

because i understand thats been covered

by another presentation

so when were thinking about the total

clearance of a drug we need to think

about all these various parts

as we can imagine in patients with

chronic kidney disease wed usually

assume that this is the only component

that would change

kidney and the others would remain the

same

were going to be talking more about

that later

clearance relates to halflife as such

once if the clearance goes down then the

halflife will go up so itll persist

for longer in the body but im sure

youre all aware of that

these are three patterns whereby drug

clearance varies with gfr now this is a

diagram which really incorporates

pictorially the equation that i just

shown you

this shows how as gfr decreases from

normal down to zero

there are changes in drug clearance so

if we start with drug b for example the

red line we can see that theyre

directly proportional when youve got no

kidney function you have you have no

drug clearance and this would be

described as a drug whereby all of the

clearances due to the kidneys and

examples of that might be for example

with antibiotics a betalactam or for

anticoagulants it could be

to bigatran

drug c is a drug whereby no matter how

gfr changes there is no change in drug

clearance so this would be a drug which

has no kidney clearance

and or very minimal kidney clearance and

all the clearances via

for example the liver

so again if we go back to our examples

of of our antibiotics this may be a

macrolide antibiotic

or for anticoagulants it might be for

example warfarin

and drug a is where theres a

combination so there is some decrease in

drug clearance as gfr decreases but not

all the way there are some other

processes for example the liver and

again if we go back to our examples that

we had before of drug classes

antibiotics an example may be

a fluoroquinolone such as ciprofloxacin

and for an anticoagulant it might be for

example rivaroxaban

so we can see here from this picture

that how we dose adjust various drugs

will depend in part on which of these

patterns they most likely relate to

and the extent to which we change drug b

is quite easy for the halving of the gfr

or kidney function

we get a halving of clearance and

therefore we have the dosing regimen

so just to revise about principles of

dose adjustment

theres a few principles to consider

and im sure these have already been

covered elsewhere we need to consider

our therapeutic target we need to

consider if we need to give an initial

dose or a loading dose what is our

maintenance dose and dose frequency when

we should adjust the dosage

and where possible if we should be

performing some sort of therapeutic drug

monitoring

to be able to consider all of these

factors requires a prescriber or other

healthcare professional

to obtain published pharmacogenetic data

from a comparable patient population

in the case of patients with impaired

kidney function this is often

lacking further and we know this from

any area of pharmacology and

pharmacokinetics we know theres always

marked interpatient pharmacokinetic

variability and so that can always add

some degree of uncertainty to some of

our predictions we will try and address

some examples of this in the

presentation today

so the maintenance dose and the dosing

frequency largely depends on clearance i

mentioned this to you before drug

clearance varies widely in patients with

impaired kidney function depending on

what their kidney function is

the decrease in drug clearance with

impaired kidney function prompts either

a decrease in the maintenance dose

meaning we give a smaller number of

milligrams or an increase in the dosing

interval meaning that we extend

the frequency of the dosing

either of these decisions can be

made

in patients with impaired kidney

function but the specific one we do may

depend on the drug in

question well talk about that with an

example later

it may also depend on the toxicity

profile of the drug whereby giving

bigger doses less frequently may

predispose to some toxicity

this is of course as offset by the fact

that less frequent dosing grenade

compliance with our patients

so when we have a change in the

pharmacokinetics in patients

changing the pharmacokinetics it can

have different impacts on the

concentration time profile if the black

line is showing what happens with normal

pharmacokinetics

if there is a halving of clearance in a

drug thats taken orally we can see what

happens with the red line theres a

slightly higher concentration

and then it persists for longer

if we contrast that to patients who have

a doubling of their volume of

distribution we get what we see in the

blue line whereby the concentration the

cmax wont be as high because theres a

relative dilution its got more volume

to distribute across

and again the halflife of the

limitlight nation is long

so there are these are the differences

exerted by those two

changes in pharmacokinetics

and so then thinking about how that may

impact on therapeutics we see this

with the red line which is a halving of

clearance we can see that there is

accumulation and it occurs rapidly the

concentrations go up

this happens if we do not change the

dosing regimen in the context of

impaired clearance and this is a very

important consideration that we must

always think about in patients with

impaired kidney dysfunction

in contrast to volume of distribution a

doubling of the volume of distribution

we get a lower concentration

but again we get accumulation so we

still do get accumulation to the point

that it can cause toxicity

but it just takes longer to occur than

we see with the halving of clearance

as well outline later you also get a

double you can also get an increase in

volume distribution as well as a

decrease in clearance in patients with

impaired kidney function so both of

these factors may be occurring but what

it does tell us is that we need to be

very certain very careful

about dose adjustments for our patients

because its very important

thats considering the prescribing of

gentamycin to a patient with advanced

kidney disease

i like to use this example because it

always gets the attention of pharmacists

in particular

but all of us who work in healthcare

its a its a bit of a prompt why would

someone prescribe gender mycen to some

with endstage kidney disease

actually there are some tricks around

how we can do that but we wont be

talking about that today

we can see here that prescribing gender

mice and we get the

if we dont make any dose adjustments

then the red line shows were getting

accumulation

so we can address that by doing two

things given that we know that the top

the efficacy of gentamicin is related to

how high the concentration is we know

that we shouldnt be decreasing the dose

what we should instead do is increase

the frequency of dosing

and when we do this for example the

second daily we can see that theres

less accumulation but still there is

accumulation

if we go to third daily dosing then we

can see again that theres less

accumulation so just simply by

prolonging the dosing interval helps to decrease toxicity well we think we do still have a very high area under the curve which may predispose to toxicity and the other issue that we have from gentamicin in this example is that within this time frame weve now only given two doses whereas previously there had been six doses so weve actually possibly compromised some of the benefits of giving gender mice in that case so although were able to make some adjustments to the dosing regimen we may still be compromising patient outcomes and increasing the risk of adverse drug events

lets talk about some more general considerations in patients with kidney disease

so kidney disease as ive already introduced to you has multiple effects on the pharmacokinetics depending on the drug in the clinical context

the two groups are very different

chronic kidney disease is a slowly progressive disease sometimes over

months but more often over years so what

were seeing physiologically is

generally fairly stable the kidney

function does not change

over months neither does a volume of

distribution

in contrast acute kidney injury is a

rapidly evolving state and therefore

theres rapid changes in volume

distribution and clearance

and so each scenario requires a

different approach to drug dosing and

were going to address each of these

individually

patients with kidney disease are prone

to changes in both of these

and theyre also prone to being

coming into a hospital with acute and

chronic conditions

and as ive already demonstrated with

those figures

if there is drug accumulation then that

may actually occur over weeks and so

therefore the onset of drug toxicity is

insidious so we need to anticipate the

potential for this to occur

and to prevent it from happening but we

also need to monitor our patients

closely to identify if it occurs

our job when were prescribing

or having some other oversight of drug

therapy is complicated largely due to

the lack of data in kidney disease

dose recommendations are frequently

based on limited data or theyre just

not made

and there may not be an opportunity

within

for example recommendations to fully

account or understand about

interindividual variability

its older data now but things havent

changed much

a study was produced

which showed that between 00 and 00

only about of new drug applications

to the fda

even examined pharmacokinetics and

kidney impairment and only of those

had data in patients with such severe

kidney impairment that they were on

dialysis

and this reflects an fda policy that

manufacturers factories are not required

to determine the impact of kidney

disease and drug dosing

this is a bit unfair for our patients

because they should also have access to

new therapeutics

for whatever the condition thats being

treated is and its also a challenge for

us to provide guidance in terms of what

dose to prescribe

this is a paper which uh really

fascinated me um

when i first read it back in 00

it was published by a us colleague tom

nolan whos a pharmd

and what he showed here is he looked at

the erythromycin breath test

so

this is where erythemicin is injected

and then its metabolized

and one of the metabolites is a

carbon labeled

and co and so then its breathed off

and so its a method by which we can

look at the pharmacokinetics of a drug

what they did here was they looked at

the pharmacokinetics of erythromycin

immediately before dialysis

and then in another patient they did it

immediately after dialysis

and you can see hips are in the same

patient so you can see here that the

active performing dialysis

caused a change in pharmacokinetics now

this is a drug thats largely

metabolized

and therefore

this increase in the metabolites

suggests that

the active dialysis um uh increase the

activity of the liver enzymes

and thats odd and thats confusing and

thats really interesting because what

that shows us is that in patients with

endstage kidney disease

there is circulating the theory behind

how this works is that theres

circulating uremic toxins and these

inhibit the cytochrome p0 or perhaps

they also inhibit transporters and this

causes um changes in nonrenal clearance

of drugs

and that

also these effects are fairly rapidly

reversible because simply doing dialysis

was able to reverse them

or at least minimize them so what this

tells says to me is that patients with

chronic kidney disease and particularly

patients with acute kidney injury can be

predisposed to changes in nonrenal

clearance

as well

and therefore its something that we

need to understand

unfortunately theres not enough data to

provide clear guidance on this so

instead it becomes a research priority

for the future

well talk more about that as we go

through