Hi my name is Jomy George

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Today Ill actually be going through a casestudy focused on Transporter Mediated DrugDrug Interactions and this will actually be anapplication of the presentation that was provided to you by Dr Ware on drug transporters andad me and drug absorption

So lets get started with the patient case

This is a year old male with a medicalhistory significant for HIV hypertension and left lower leg deep vein thrombosis orDVT who presents the clinic today with a fiveday history of recurrent nosebleeds andfeeling fatigued

His current medications include the following:the antiretroviral elvitegravir cobicistat tenofovir alafenamide and emtricitabine givenas one tablet by mouth daily

The antihypertensive a amlodipine 0 milligramsby mouth daily and the oral anticoagulant used to treat his DVT provided at 0 milligramsby mouth twice daily and this started about a week ago

So when we take a look at this particularcase we need to take a couple of steps at least to identify the problem and identifyingthe problem is important because we can come up with logical solutions on how to actuallybest manage these challenges and provide optimal care for this particular patient

So in looking at whats highlighted in redthe statement thats provided there pretty much provides a lot of information thatsextremely important for management of this patient

So this individual has a medical historythat has a number of comorbidities that require multiple modalities of drug therapy whichare implicated in a number of drugdrug interactions

Also of note whats significant is that thisindividual presents in side effects presumably from his oral anticoagulant that startedabout a week ago and when we take a look

at his regimen his medication list we reallyneed to think about are any of these particular drugs have clinically relevant drugdrug interactions?

And this is important because this individualsactually presenting with side effects again presumably from his oral anticoagulant

When we take a closer look in fact thereis actually an interaction between cobicistat which is a PK booster or a pharmacokineticbooster or enhancer thats provided as part of his antiretroviral regimen and his antioralcoagulant dabigatran

So our next step is understanding how togo about figuring out what resources we need to use to provide and help support is theredata to support this drug interaction and is this drug interaction clinically relevantand could it possibly explain why this individual has developed this side effect from dabigatran?

And what Ive pulled for you here are tworesources that are reputable resources one being from the University of Liverpool andthe second being from Lexicomp and these are simple searches that were provided usingtheir drug interaction checker online

So if you take a look at these recommendationstheyre actually a little bit different

However the data that is used to supportthese recommendations are similar

By the recommendations provided by the Universityof Liverpool as you can see here their recommendation is actually do not coadminister these particularmedications and the data here is to support it is based on a theoretical interaction thatcobicistat can actually increase the exposure of dabigatran and well go through the mechanismof the interaction in a few slides

If we look towards the other side of the slidewhere Lexicomp provides also a drug interaction checker the actual risk here is not to actuallydo not coadminister its actually to monitor therapy and really look at the patient andunderstand the benefit versus risk ratio and if there needs to be any dosage modificationsor avoidance of coadministration

So having said that lets take a look specificallyat the drugs that are implicated in this particular drug interaction

So cobicistat as Ive mentioned is a pharmacokineticbooster or enhancer it doesnt have antiretroviral properties per se but its really main focusor function if you will is to enhance the exposure of cocompetent medications namelythe antiretrovirals that are combined within the tablet and Dabigatran as Ive mentionedis the oral anticoagulant

When you pull data on how these drugs aremetabolized or transported you will note that cobicistat actually goes through CYPAmediatedmetabolism

Specifically as highlighted here its astrong inhibitor for CYPA as well as a substrait for it it also inhibits CYPD to some extentbut when we take a look at transporters and the transporters that are implicated for thisparticular drug we actually see a number of transporters that are involved for thisparticular medication including Pglycoprotein BCRP MATE and OATPIB and these areall different functions and these transporters are located all throughout the body in differentindifferent areas but whats important to understand and appreciate is that Dabigatran happensto be a pretty sensitive substrait for Pglycoprotein

The FDA defines a sensitive substrait asone that in the presence of other Pglycoproteins its exposure will increase more than twofold

So in its drug development program thereis data for Dabigatran in combination of other PGP inhibitors however it is not been studiedwith cobicistat

So the natural question again is is thisa clinically relevant interaction and could this interaction be explaining the side effectprofile for this particular medication in this patient?

So lets take a closer look at the actualmechanism and really breaking down what actually is happening

What the picture here is depicting for youis the intestinal membranes specifically in the enterocytes where Pglycoprotein islocated and Pglycoprotein as youve learned from the lecture is located all throughoutthe body

Pglycoprotein is indeed an efflux transporterand it has its specific function and role

in mitigating or facilitating a transporterdiffusion across different membranes

So looking at the intestinal membrane thereis a apical side which faces the intestinal tract or the lumen the basolateral sidewhich faces the blood

Now when an individual ingests Dabigatranin the absence of any transporter inhibition or induction Dabigatran sits as a Pglycoproteinsubstrait but in the presence of cobicistat cobicistat actually inhibits this efflux ofdabigatran

So essentially whats happening here isthat youve got almost a stoppage if you will of this carriermediated efflux and keepin mind that theres always constant concentration gradient that can go from the apical to thebasolateral side which really determines the absorption of a medication or the intestinalabsorption of the medication or it can go from the basolateral to the apical side whichreally determines its exertive gradient

What happens when you inhibit this particulartransport?

You increase the concentrations or you actuallyincrease the intestinal absorption or bioability of oral dabigatran and what happens youhave an accumulation of the drug within the blood which then really translates to higherconcentrations higher exposure of the blood

But again the question is is this relevant?

Is this exposure high enough such that thisrequires a dosage modification or recommendation in avoiding these medications all together?

So Ive pulled for you here the FDAapprovedlabel for dabigatran and Ive specifically highlighted for you the section on drug interactions

If you take a look these labels are actuallyquite complicated to go through and as clinicians wed have to make sure that were lookingat these medications for the right indication and we understand what data is available andif that data can be extrapolated to other drugs of interest in other target populations

It should be noted that most of the drug interactionstudies that are included within a drug label are conducted in a healthy volunteer populationand not within the target population

So things to consider are other patient covariantsthat are not actually accounted for in the actual clinical trials

So what this section actually outlines foryou are particular recommendations based on the absence or presence of the concomitantmedication that could be interacting or interfering with drug transport

It also highlights for you in the presenceof kidney disfunction or renal impairment if those recommendations change and specificallyfor dabigatran Dabigatran is actually eliminated via glomerular filtration by 0 percent ofit

So from a clinical standpoint this is actuallyvery very important to appreciate and to incorporate into our final recommendationto this particular patient

So Id like to focus right here where itsays The use of PGP inhibitors specifically when its called out are verapamil amiodaronequinidine clarithromycin and ticagrelor

All of these particular medications were studiedwith Dabigatran and the exposure although there were increased in the presence of thesePGP inhibitors they were deemed to have there was a margin if you will that of efficacyand safety for that particular exposure that was deemed to be clinically irrelevant

Or really what that means is it did not requirea dosage adjustment but whats important is the next statement also

These results should not be extrapolated toPGP inhibitors

So then the question comes up in this particularcase cobicistat which happens to be a PGP inhibitor what do you do?

How do you manage this patient appropriately?

Is it appropriate to continue to dose thisindividual in the presence of this side effect or do we need to dose suggest perhaps themedication?

And this leads essentially a research gapin data and in response if you will to help fill this research gap there was a publicationthat was put out by Gordon et al in circulation

in about 0 which really sought out tohelp fill this gap and to study the drug interaction

impact of cobicistat on dabigatran

I should note here that the study actuallylooks at this particular interaction in healthy volunteers but this is a comparison betweenthe impact of ritonavir which is also a PK booster but this is an older PK booster thathas fallen out of favor namely because of side effects and because of the fact thatcobicistat is now available and is better tolerated

So this particular study actually looks atboth ritonavir and cobicistat

As you can see here panel A focuses on ritonavirand panel B or arm B focuses on cobicistat

These are very simple concentration versustime curves where Dabigatran plasma concentration is plotted for you on the Yaxis the timeof administration posted Dabigatran administration posted is plotted for you on the Xaxis

Both of these arms had three different phases

The first phase in both arms was to providehealthy volunteers Dabigatran alone

The second phase included providing or givingDabigatran two hours before either ritonavir or cobicistat and the thought here is thatbecause this drug interaction is mediated or modulated by Pglycoprotein perhaps separatingtheir administration to mitigate this interaction would help in perhaps being able to providethese medications together

So that was actually studied if two hourswas actually enough and if that separation actually did mitigate that interaction

And that third phase was simultaneous administrationof Dabigatran with ritonavir or cobicistat

And as you can see here you can visuallyappreciate that there are significant differences between both of these arms

Particularly in the setting of simultaneousadministration of Dabigatran and cobicistat versus Dabigatran and ritonavir you can seea significantly increased Cmax and overall exposure of Dabigatran in the presence ofcobicistat

Whats interesting here is that actually ritonavirand cobicistat are both PGP inhibitors so this actually speaks to what the label actuallyindicates as well that the ability to extrapolate data to PGP inhibitors may not be appropriatein all patient populations

And this really focuses and calls out thatin the absence of data extrapolation may not be entirely appropriate and you needto take a case by case benefit versus risk ratio for each of your patients

So again even though this PK study providedquantitative data it provides you a percentage increase

It provides you metrics as far as how muchthe drug is increased in the setting of cobicistat and ritonavir but again the question isis that exposure increase clinically relevant?

Would this exposure put individuals at riskfor bleeds namely?

So in this healthy volunteer study itsapparent that CoB did have much more profound effect as a PGP inhibitor but extrapolationof this data may not be entirely appropriate to all target populations

Staggering the dose actually did not havean expected pronounced effect and it actually did not mitigate the interaction and likelythe mechanism is that CoB is indeed a potent intestinal PGP inhibitor whereas ritonavirmay be acting as an inducer a mixed inducer and inhibitor or Pglycoprotein

The clinical relevance right now at this momentis really unknown however because our particular patient is experiencing side effects thisreally cannot be ruled out that possibly the cobicistat is propagating or perpetuatingthe drug interaction with dabigatran

The therapeutic options for this individualand really any individual based on this PK data is either to avoid its concomitant usealtogether provided that there is an appropriate alternate option for the patients

Second would be to space apart perhaps themedications for more than two hours

In the case of dabigatran it should be notedthat Dabigatran is already being given twice

a day in this particular patient and reallyall patients for Dabigatran is typically dosed twice a day so really spacing these drugsapart for more than two hours really doesnt provide a chance for patients to be actuallyadherent to their medications and could actually negatively impact adherence so it may notbe the best optimal choice

And then lastly does it make sense to reducethe Dabigatran dose?

But the question then is how much do youreduce the dose and would that actually have negative impact namely on efficacy?

And remember that theres a delicate balancebetween efficacy and safety

This is a drug thats being given to an individualto essentially anticoagulate them after having identified thrombosis so we do need to carefullyfigure out the balance between efficacy and safety and if that reduction of dose is trulytherapeutically appropriate

And for all of those reasons this reallyprovides or introduces many different management challenges

Ive pulled for you here a number of FDA USproduct labels for other direct oral anticoagulants

Select ones that are listed here for youRivaroxaban Apixaban Dabigatran and Edoxaban

If you look across the drug interaction potentialactually both rivaroxaban and Edoxaban plausibly actually pose a higher drug interaction potentialbecause theyre substraits for both CYPA as well as Pglycoprotein

The label recommendations essentially provideguidance saying that rivaroxaban drugs like cobicistat should be avoided altogether

Apixaban you could use it but you may needa dosage reduction depending upon the indication for the drug and the patient population andthe covariants

Dabigatran we already went through the labelrecommendation for that and Edoxaban which is a fairly newer direct antioral coagulantfor that thats available

The data thats actually with Edoxaban ifyou actually dont hear for in the product label is that with specific PGP inhibitorsyou actually might be able to use it without

any dosage suggestions but I would cautionor advise that we have a patient here thats developed a side effect plausibly becauseof the antioral coagulant so the question of being able to safely administer in thepresence of his antiretroviral regimen really should be questioned and Im not entirelysure if switching him to Edoxaban would be the most appropriate option

But having said that we have to do somethingfor our patient

We have to make a decision

So we did identify the relevant drug interaction

Were essentially deeming this to essentiallybe clinically relevant for this particular patient case as hes developed side effectspresumably from his dabigatran and because hes feeling fatigued remember he could havelost actually quite a bit of blood but we dont have other laboratory markers to reallysupport that but really it should cause concern given that hes had recurrent nosebleeds reallytemporally associated with the time of initiation of his dabigatran

And really what we need to do is think aboutand ask advice from specialists and really take a multidisciplinary approach in reallymanaging this particular patient

So really it would be great to work withhis HIV provider to discontinue his cobicistatbased antiretroviral therapy and really constructan alternative regimen which poses a much lesser drug interaction risk

And in this situation you could actuallycontinue his Dabigatran and treat him for his DVT or other options could potentiallybe for whatever reason he cannot tolerate or cannot be switched to an alternative antiretroviralregimen

We do need to think about switching him toanother oral anticoagulant but would need very frequent monitoring to ensure that hedoesnt continue to have side effects from his oral anticoagulant

So in summary drug transporters are implicatedin many clinically relevant drug interactions

It may not be important to extrapolate druginteraction data generated from healthy volunteers to a target population or rather for drugof interest other drugs of interest

It is important to practice a multidisciplinaryapproach in the management of these patients who do present with rather complex comorbiditieswhich end up having very complex drugdrug interactions

Thank you and I hope this presentation washelpful