Welcome to this segment of the NIH principlesof clinical pharmacology course

recent lectures that you have listened to

My title is Im Lionel Lewis

Im a professor of pharmacology and medicinein Dartmouth Medical School

My title is Victims and Perpetrators inTherapeutics

What I want to do today is discuss with youin analyzing detail a clinical case where there has been a victim and a perpetratorof an adverse outcome in a patient in an unexpected clinical scenario

Lets get into the clinical case in detailand Ill summarize it for you

The case is that of a yearold Caucasianmale

The gentleman had been diagnosed some monthspreviously with colon cancer

And this was now metastatic widely metastaticto his lungs and several lesions in his liver

During this period the patient had receiveda number of chemotherapeutic regimens

Namely he had the SALZ regimen which isIrinotecanFULeucovorin

He also received capecitabine which is oralFU oxaliplatin oral topotecan and lapatinib

And unfortunately the patient had progressedthrough all of these treatments

And at this point in his disease he was nownot able because there wasnt to have any additional therapy and standard of care

So he was considered for a phaseI studyof a novel compound under an IND

And he was found to be eligible for this studyand wanted to participate

The study was of an antiinhibitor of apoptosisdrug which means that the drug itself promotes apoptosis

And he was evaluated screened and enteredthe study

Of note his general health was pretty good

His laboratory testing of his hematologicaland metabolic profiles were normal particularly

his liver function tests

And at the time of entry into the study hewas taking warfarin six milligrams alternating seven milligrams alternate days for a priordeep venous thrombosis that was diagnosed some three months before but remained ontherapy because of the risk of further thromboembolic disease

His other therapy was that of one multivitamintablet a day

And I should add that he was taking no otheroverthecounter medications and no nutraceuticals

And there was no history or evidence of recreationaldrug use

He was a nonsmoker and didnt partake ofethanol

But prior to entering into the study becausethe novel drug is given intravenously it was decided that he needed a port cathetera central catheter for the administration of the infusion

To do this perioperatively around it herequired his warfarin dose to be reduced so that he would reduce the risk of hemorrhage

And he subsequently entered the study to receivethe new drug on a daily basis 0 milligrams per meters squared every day for seven days

At that point as you can see in this slidehis INR was just subtherapeutic

And he was on four milligrams a day of warfarin

And during the period illustrated by the redbar he received the daily therapy of the novel agent

And his INR climbed into the therapeutic rangeand he subsequently remained on four milligrams per day of warfarin

At the end of the seven days treatment hewas then discharged and he subsequently was followed in the clinic with a day breakbefore he would enter the second cycle of treatment with a new agent

As you can see in the slide now on admissionhis INR was in the therapeutic range four

milligrams per day

But over a period of days when he was receivingthe daily novel administration of the novel antiinhibitor of apoptosis drug his INRescalated way out of the range in fact into the severely elevated range of about

At this point we stopped his warfarin andwe instituted some therapy and luckily for us there were no adverse events

There was no hemorrhage

He remained inhouse inhospital and we wereable to carefully monitor his INR as it dropped back into the therapeutic range on no warfarin

At the end of the investigational drug infusionshe was discharged home and we reestablished his INR and warfarin dose as you can seein the graphic

So at this point I want to pose to you somequestions as to what actually we did and what was the appropriate therapy to give this patientto mitigate and reduce the risk of serious hemorrhagic events

And as you can see on this slide Ive doneit as a multiplechoice question

And the options I want to pose to you arethe following: did we give him plasma protein fraction?

Did we give him phytomenadione?

Did we give him idarucizumab?

Did we give him andexanet alfa?

Or did we give him recombinant factor VII?

Im going to pause at this point for about0 to 0 seconds to give you a change to think about your answers and then well go throughthe possible answers in some detail and inform you which was the most appropriate therapeuticaction that we undertook in this case

So hopefully youve collected your thoughtsand youve come to a recommendation of which of these options is the most appropriate wayto go

Lets deal with them one by one

Plasma protein fraction in this situationdoesnt contain the right components and would not be an option one would consider

Idarucizumab which is option C is actuallya fab monoclonal antibody targeted against dabigatran that is a thrombin inhibitor

And because the patient wasnt on a thrombininhibitor would be an inappropriate therapy

Andexanet alfa is a full monoclonal antibodytargeting the oral the novel oral antiXa agent such as apixaban rivaroxaban or edoxaban

And again because he wasnt on those drugsit would not be an appropriate therapy

I should add that option C and D are intravenousand are very expensive

Option E is recombinant factor VII whichcan be used in severe cases of hypocoagulable states where patients are developing severehemorrhagic complications

In this case because the patient was an inpatientwas monitored carefully and did not develop any signs of hemorrhage blood loss or volumeloss we were able in fact to treat him with phytomenadione which is vitamin K

Phytomenadione is available as both an oraland an intravenous formulation

And currently the standards are to preferthe oral formulation to reduce the risk of allergic or anaphylactic reactions to theintravenous formulation

And indeed the studies show that oral formulationadministration several times a day produces a time course of reduction in the INR thatis acceptable and safe

So this is the patients third cycle

And as you can see here as an outpatienthe was maintained on six milligrams of warfarin per day as illustrated by the solid circles

And his INR on admission was just above thetherapeutic range somewhere around three and a half

We started the treatment as indicated inthe red bar and once again over a period

of a very short time only a matter of daysthere was an elevation in the INR which we then spotted early and stopped his warfarinand subsequently his INR dropped back from over six down into the therapeutic range

This to us represented a case where we rechallengedthe drugs together and we found that there was a further abnormal and worrying elevationin the INR

So one thing I want to address with you guysat this point how do you address whether this was an adverse drug reaction?

And there are many strategies to do this

I would take you back to some simple questionsand criteria one can think about that will give you an evaluation of the likelihood ofwhether this was an adverse drug reaction or not

As you can see in this slide the criteriaquestions you ask are the following and these are the Naranjo Criteria: does the timeframe fit which means are the drugs given at the same time?

And did the adverse outcome occur in a framewhich you would expect?

Has it been reported before?

The problem here is that with a drug suchas an under IND its unlikely to be a literature thats in the public domain

And therefore reports of this are unlikelyto be known

And of course in a drug which is still ininvestigation and in phase one first in man there is very little data

Have other causes ruled out?

Well in this situation the patient was aninpatient

We evaluated his liver function his renalfunction and his hematological function which remained stable and his platelets werenormal

His LFTs were normal

We had no evidence of sepsis

We felt that this was other causes hasbeen ruled out

And we were focused on the fact that theremay be a drugdrug interaction here

Does it resolve when dechallenged?

Well when we stopped giving him the novelcompound and reduced his warfarin and restarted his warfarin we were able to reestablishanticoagulation at normal doses for him

And then on cycle three as the previous slideshave demonstrated when we rechallenged the patient on warfarin with a third dose athird cycle dosing of the novel compound

we saw that once again we ran into problemswith an elevation of the INR

So if you score these criteria from not itdoesnt occur it is not applicable to

two it is truly applicable you can see onthis slide that for the first criterion yes

its time frame fitted

We did not have reports

Yes we ruled out other causes

We did have resolution on dechallenge

And we also had recurrence on rechallenge

And this gives us a score of eight out of0 which means theres a highly probable adverse drug reaction in this case

So thinking more mechanistically Id liketo pose you a few additional questions on the likely mechanism of this drugdrug interaction

And here Im asking which proteins do youthink are dysfunctional in this drugdrug interaction?

Is it factor one factor eight CYPACYPA CYPC9 or CYPC9?

Ill give you a few seconds to think aboutthis and then well discuss the options on which is the correct response

So once again I hope youve had enough timeto thoughtfully go through the options

Factor one is fibrinogen and therefore reallynot applicable

Factor eight is not involved in the intrinsicpathway

A and A are not really involved in thedrug metabolism of warfarin

And the drug itself the antiIAP agent ispredominantly renal excreted without very much hepatic metabolism

So C9 is not involved

And the correct answer is CYPC9

So CYPC9 really is the CYP thats involvedin metabolizing the S stereoisomer of warfarin

So here you can I want to just reviewwith you quickly some of which youve heard in the recent lecture about what do CYPsdo

And here you can see on this slide a rotatingvideo of CYPA

The important thing about it is the hemoprotein

Its a monooxygenase

Its found in the endoplasmic reticulum

And it has multiple binding sites at the centerof which is a heme center with a ferric ion

And this is pivotal to the action of theseagents which are effectively oxidoreductases

And they therefore convert and add oxygenwith the removal of an electron from a chemical entity to make it more polar

Many of you will be aware as shown in thispart of the slide that the dominant CYP in drug metabolism is CYPA with about to 0 percent drug metabolism CYPD about 0 CYPC9 about high teens and lessereffects with CYPA et cetera

And many of you have seen this pie chart before

And this next part of the slide just showsthe actual chemical processes that are undertaken by the CYP where it acts the P0 actsvia its heme center to take away an electron

And subsequently with the reductase addingoxygen and subsequently make the chemical molarity more polar and more easily excreted

So to remind ourselves about warfarin metabolismwhich I think is important here this next slides shows that warfarin is a racemic mixtureof the R and S enantiomers

Predominantly in a 00 proportion the Swarfarinis the most potent as its target and inhibits vitamin K epoxide reductase

And in so doing by inhibiting the epoxidereductase it compromises the ability to change oxidize vitamin K to reduce vitamin K Andby blocking this action it subsequently limits the ability of gamma glutamyl carboxylaseto carboxylate the hypofunctional coagulation factors two seven nine and ten

And therefore you get a hypocoagulable statebecause these coagulation factors are not activated and functional

Many of you would be aware from your knowledgeand prior lectures that there are multiple variants of CYPC9

And this subdiagram shows that the wild typehas a higher activity than the star three star three which has a much lower activity

And theres also a [unintelligible] type variabilityin the activity of the vitamin K epoxide reductase

Importantly these two genetic tests thesetwo genetic variants have been brought together in some guidances around how you might usetesting for them to specifically enhance our ability to therapeutically prescribe and appropriatelyuse warfarin

So what PGx tests could be informative here?

And in light of my prior in the prior scribeIm going to run though this rather quickly

The options I put forward in a multiplechoiceformat are: CYPAfactor one Afactor eight AC BCYPC9 CYPC9D CYPC9VKORCor CYPD and factor seven

And of course based on my prior discussionof warfarin metabolism and its target and the genetic variability in the CYP metabolismand the variability in the target the correct answer of course is CYPC9VKCORC testing

We actually did this on our patient

And it is no surprise based on the dosingthat he was on remember alternating six milligrams and seven milligrams alternatedays his CYPC9 was wild type was a heterozygous wild type and star two

And his VKORC was wild type which meanshe had a fairly standard dose of warfarin to give him his normal anticoagulant control

We did this in retrospect because we feltit was important to complete the workup on this patient

As is the case and in the next slide toremind us all that it is very important to report all adverse drug reactions to the FDAparticularly in the context of a drug thats under investigation in an IND situation whereits early in its clinical development

But also for drugs that are already on themarket that have recently been approved or older drugs that have been approved for sometime where there is a significantly unusual reaction

And this we do using the MedWatch form thatsshown in this slide

So before I finish I want to I was ratherhumble and always am by this statement by Paracelsus in the late th and early thcentury that says All substances are poisonous There is none which is not a poison

The right dose differentiates a poison froma remedy

Then to wrap up I would like to tell youin my native tongue Diolch am eich sylw which for those of you not conversant withthe Welsh language means Thank you for your attention

I appreciate your time

I hope youve found this presentation informativeand useful

Thank you very much