Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/focus-on-pharmacy/anticoagulant-treatments-for-special-patient-populations/3796/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Anticoagulant Treatments for Special Patient Populations

ANTICOAGULATION AND GENETIC TESTING IN GUIDING WARFARIN THERAPY.

Several factors impact the safe and effective prescribing of anticoagulation therapy. Issues that come into play include genetics, weight, renal impairment, and the potential for drug-induced thrombocytopenia. How can we best use this knowledge to augment our approach in anticoagulation? Welcome to Focus On Pharmacy. I am your host, Dr. Charles Turck, PharmD. Our guest is Dr. Kate Phillips, PharmD, clinical specialist in Cardiology and Anticoagulation at the Boston Medical Center. Dr. Phillips also recently authored a review article on anticoagulation in special patient population that was published in the American General of Health System Pharmacy.

DR. CHARLES TURCK:

Dr. Phillips, welcome to the program.

DR. KATE PHILLIPS:

Thank you.

DR. CHARLES TURCK:

Anticoagulation therapy certainly received notice from accrediting bodies like the joint commission. In recent years, it has become a focus of one of the organizations national patient safety goals. Why is it that anticoagulation is receiving such close attention?

DR. KATE PHILLIPS:

The class of anticoagulants is extremely effective medications; however, they are difficult to manage. They require vigilant dosing. It requires extensive monitoring in order to minimize the risk and improve safety when these medications are used. They are lifesaving medications. In the recent years, there have been some efforts to really start identifying new anticoagulants that work in different mechanisms that may require decreased monitoring.

DR. CHARLES TURCK:

Warfarin is the drug that has been around between 50 and 100 years in our clinical use. Why do some clinicians continue to find drug dosing so challenging?

DR. KATE PHILLIPS:

You know, because warfarin has been around for so long. They are just so many factors that can affect warfarin dosing and it is challenging. It's probably the most challenging medication that we have right now. The pharmacokinetics of warfarin may get difficult. So it has a very narrow therapeutic range. We are targeting you know an INR between 2 and 3, which can be somewhat narrow especially when there is so much interpatient variability with dosing requirements. So, age, weight, concomitant disease state, varying nutrition status, liver function, concomitant medications, and drug interactions as well as now we are hearing about recent genetics that may come in to play as well, so all of these factors really do come into play with this interpatient variability. The half-life of the medication is a little bit long and typically about 1 to 3 days and as well as far as the mechanism of action so how warfarin actually interacts with and depletes the clotting factor, so all of these different factors sort of come into play and make warfarin extremely challenging for practitioners to manage.

DR. CHARLES TURCK:

We are talking about difference of say days between the time that one clotting factor is, you know, “depleted” and that other factors are as well, is that right?

DR. KATE PHILLIPS:

Right, so the clotting factors that warfarin works on are II, VII, IX, and X, and they do vary, the longest being factor II thrombin, which can take up to 4 to 5 days to actually be depleted for the systems, so we do not see warfarin’s initial anticoagulant effect until the factors that are currently hanging around the body are actually depleted. So it takes typically we say 4 to 5 days to see initial effects of warfarin.

DR. CHARLES TURCK:

What are some of the different Cytochrome P450 enzymes involved in warfarin metabolism?

DR. KATE PHILLIPS:

So warfarin is made up of 2 enantiomers – R warfarin and S-warfarin. S-warfarin is more potent and is metabolized through the Cytochrome P450 2C9 pathway. So, the enzyme 2C9 is involved as well as something caused vitamin K epoxide reductase enzyme, which mediates warfarin’s effects. Those are the 2 main enzymes that are related to be sort of talked about the genetic determinants of warfarin metabolism. Cytochrome P4502C9 polymorphisms are linked to sort of classifying patients as poor metabolizers. So patients that may have a polymorphism in the CYP2C9 gene will have an extended half-life of warfarin, so that half-life of warfarin that is usually can be about 2 to 4 days will actually be extended in these patients, will require lower doses of warfarin. Patients that may have a polymorphism to the vitamin K epoxide reductase enzyme or VKOR have variant resistance to warfarin dosing as well. So these patients as well can require higher doses of warfarin in order to see its effects.

DR. CHARLES TURCK:

Which patient populations out there are most likely to be affected by these variating genetics?

DR. KATE PHILLIPS:

As of now literature does show that there is a link to ethnicity. The VKORC1 to the vitamin K epoxide reductase enzyme polymorphism is often associated with Asian Americans that typically require lower dosing requirements and it is less common in African-Americans that in clinical practice they often require higher doses of warfarin. So there has at this point been some link to different ethnic groups and having the frequency of these polymorphisms.

DR. CHARLES TURCK:

How much is warfarin in your patient dosing variability attributable to genetics, do we have any idea?

DR. KATE PHILLIPS:

It is a little less unknown there are a few studies out there that really look at these 2 major polymorphisms that I have mentioned, so the VKORC1 polymorphism and the Cytochrome P450 2C9 polymorphism, so they have looked at those 2 genetic factors as well as some of the other variable factors that we know such as age, weight, disease state, and found that that accounts for about 55% to 65% of dosing variability, which still leaves quite a bit of percentage that you know it is not attributed to those factors, so there may be other genetic factors. I think there is sort of a little bit often a best of what actually fully relates to the variability of this dosing.

DR. CHARLES TURCK:

Editorials and review articles in the publications like New England Internal Medicine and Pharmacotherapy have questioned the utility of genetic testing of warfarin suggesting that it is perhaps a little too early to practically incorporate knowledge into clinical decision making. Do you agree with an assessment and what are some of the challenges facing clinicians who want to employ genetic profiling?

DR. KATE PHILLIPS:

So, genetic study testing states that it will lead to better control of your patient's INR and better control of warfarin management, it has been shown in some studies to increase time to therapeutic INR and it has been shown to decrease risk of bleeding because these patients are "managed more appropriately." However, there have been some negative studies today as well that really show no difference in patients that are dosed with an algorithm that takes genetics and to account versus one that does not. So, I think a few of the barriers would be either genetic testing is really only useful in patients that are initiating warfarin, so what about our patient that we see in the clinic that are extremely hard to manage, that are constantly up and down and they does not seem to be, you know, an evident reason why genetics testing is not really going to help so much. There is an argument that practitioners can actually detect what the genotype may be in patients after seeing the response of warfarin after 3 to 4 doses. The genetic testing is really just helping us out in figuring what that initial dose is to start the patient, would it be a lower dose or would they necessarily need a higher dose? We still need to monitor these patients, so because we have, you know, a genetic polymorphism we can necessarily assume that they are going to require lower doses and that will be therapeutic and that will be fine. We still have to do this same amount of monitoring because as mentioned other factors do come into play with affecting dosing. The time for response so at our hospital and I think at lot of hospitals across the country we do not have the ability in our labs to test for this genetic polymorphism, so we have to send it out. It won't come back typically for, you know, 5 to 7 days, which at that point patients received a week of warfarin therapy and we can essentially see

how their INR responded. It has been added healthcare cost, the cost of the machine itself to actually do these lab tests, it is thousands of dollars, so it increases healthcare cost sort of around the board and we have not seen yet in the literature cost benefit analysis that really states that this is the most cost effective or cost beneficial way to manage our patients.

DR. CHARLES TURCK:

If you are just joining us, you are listening to focus on pharmacy; I am your host doctor Charles Turck. Our guest is Dr. Kate Phillips, PharmD, clinical specialist in Cardiology and Anticoagulation at Boston Medical Center. We have been talking about anticoagulation and genetic testing in guiding warfarin therapy.

DR. CHARLES TURCK:

And returning just sort of to more general topic of anticoagulation. I was wondering what sort of characteristics you look for when you initially start to treat a patient presenting with say, idiopathic venous thromboembolism with warfarin therapy?

DR. KATE PHILLIPS:

So in a brand new patient, the first questions that we really look for are you know what other risk factors, what other concomitant disease states that may have led them to forming an idiopathic venous thromboembolism? There are other concomitant disease states as well can let us know sort of how we may need to manage the patient's warfarin, want to look for sure at concomitant medications that the patient is taking because warfarin has an extremely high number of drug interaction, talked to the patient about what their diet is, if they drink alcohol if that can also affect INR levels, want to evaluate their compliance level as well as this medication. In the beginning we need to monitor INRs on a weekly basis and then move towards, you know, every 2 weeks or every once a month.

DR. CHARLES TURCK:

Upfront what is the importance of overlapping parenteral anticoagulation with warfarin therapy?

DR. KATE PHILLIPS:

Sure, so, the half-life of warfarin itself is about 1 to 3 days, so the Reach study states its going to take about a week. Furthermore if warfarin should work in its mechanism of action, it needs to deplete the currently circulating clotting factors II, VII, IX, and X that are vitamin K dependent. It will take at least 3 to 4 days to deplete some of these factors as they can hang around in the body for an extended period of time. In addition during those first 4 days of warfarin therapy it also depletes protein C and S in your body, which are your natural anticoagulant. At this time, the patient is in a slightly increased hypercoagulable state, so warfarin as well as an IV unfractionated heparin or subcutaneous low molecular weight heparin should be started ideally on the same date that warfarin is started as well and they should be continued overlapping the patient until the patient gets therapeutic on warfarin and sort of bridging them through this time about hypercoagulable state in the initial few days. The bridge ideally should last up at least 4 to 5 days and after 2 consecutive INRs that are greater than 2.0 or greater than your targeted INR goal and this overlap is extremely important and as well we mentioned that joint commission in the national quality form really has anticoagulants under high alert as well this overlap of 4 to 5 days is a potential performance measure that we may say come out in the next few months as well.

DR. CHARLES TURCK:

And of course, we do not typically bridge or even parenterally anticoagulate somebody who has started warfarin therapy for something

like atrial fibrillation, but it is for the reason of the depletion of the natural anticoagulants, protein C and S that we in particular overlap anticoagulation therapy.

DR. KATE PHILLIPS:

Correct, in a patient with atrial fibrillation, their risk is a little bit lower than a patient that actually has an active DVT or PE and again you want to sort of feel little bit more cautious with those patients and cover them upfront.

DR. CHARLES TURCK:

We have been talking with Dr. Kate Phillips about employing what we know about differences and warfarin metabolism and genetics at clinical practice. Thank you, Dr. Phillips for being our guest.

DR. KATE PHILLIPS:

Thank you very much.

DR. CHARLES TURCK:

Please be sure to visit our website at www.reachmd.com featuring on-demand pod casts of our entire library. I am your host, Dr. Charles Turck and thank you for listening.