Reduced Anticoagulant Effect of Dabigatran in a Patient Receiving Concomitant Phenytoin

Objective —

Interaction of dabigatran with phenytoin in a patient with Cerebral venous thrombosis

Introduction-

Dabigatran, a direct thrombin inhibitor, is an oral anticoagulant that was approved for use in the United States in 2010. It is currently indicated for the prevention of stroke in patients with atrial fibrillation (AF) and for treatment and prevention of deep vein thrombosis and pulmonary embolism.[1] It is a pro drug which acts as a substrate for permeability glycoprotein (P-gp). Medications that induce P-gp (e.g., carbamazepine, rifampin, and phenytoin) can reduce the bioavailability of medications that are P-gp substrates. It mainly results in suboptimal anticoagulation and increases risk of stroke and venous thrombosis. [2]There are recent studies which supports use of NOACS in CVT patients.Phenytoin is anti epileptic drug which is a potent enzyme inducer which reduce efficacy of drugs metabolized by P 450 enzyme system. P-gp induction by phenytoin has only been demonstrated in animals (Phase I studies) [3, 4].

Among elderly population , epilepsy is reported in 30-40% of stroke patients [5] . AEDS can either reduce or increase absorption of NOAC metabolism leading to reduced efficacy of this drugs. A reduced NOAC metabolism can increase significantly the risk of

bleeding in these patients.The clinical relevance of the interaction between dabigatran and phenytoin has not been well described.

We describe case of interaction between Dabigatran and phenytoin in a patient with cerebral venous thrombosis.

Case report

A 25 years old male patient with no significant history presented as focal seizures. He was diagnosed as CVT.He was started on full dose phenytoin and enoxaparin . He started gradually improving with near complete recovery in 2 days. He was discharged on Dabigatran 150mg twice a day and phenytoin 100mg three times a day. Around 2 months later he presented with recurrence of right focal seizures. Repeat MRI brain showed increase in filling defect in superior sagittal sinus. He had gradual clinical improvement with no further seizures and was discharged in next 3 days .So inspite on full dose NOACS (dabigatran) , he had repeat Venous thrombosis.

3. Discussion

Dabigatran does not interact with the cytochrome P450 system. It acts as a substrate for permeability glycoprotein (P-gp) . So drug interactions are restricted to absorption across the intestinal wall only where P gp is present. Drugs that induce cell efflux transporter P-glycoprotein (P-gp) and/or CYP450 may decrease DOAC plasma concentrations and increase the risk for thromboembolic events, while drugs that inhibit P-gp and/or CYP3A4 may increase DOAC concentrations and therefore increase bleeding risk.

Medications that induce P-gp (e.g., carbamazepine, rifampin, and phenytoin) can reduce the bioavailability of medications that are P-gp substrates, such as dabigatran. This can result in suboptimal anticoagulation, increasing the risk of stroke and venous thrombosis. [2]

In current literature the relevance of interaction between dabigatran and phenytoin has not been well described. Few case reports have been reported.

The U.S. labeling for dabigatran are less clear. The product label for these agents cites only an example of a P-gp inducer but does not list all of those that may affect the efficacy of dabigatran. Although it should be intuitive that phenytoin is an inducer, it is not specifically listed in the prescribing labeling, which could easily lead to oversight and subsequent prescribing of this combination.

Conclusion -

In conclusion, interaction between dabigatran and phenytoin is important and clinicians should be aware of such potential interactions

References -

1. Prescribing information. Pradaxa (dabigatran etexilate). Ridge- field, CT: Boehringer Ingelheim Pharmaceuticals, Inc., 2010.
2. Stöllberger, C. and Finsterer, J. Relevance of P-glycoprotein in stroke prevention with dabigatran, rivaroxaban, and apixaban. *Herz*. 2015; 40: 140–145)
3. C. Sto¨llberger and J. Finsterer, "Interactions between non- vitamin K oral anticoagulants and antiepileptic drugs," *Epilepsy Research*, vol. 126, pp. 98–101, 2016.
4. T.HellwigandM.Gulseth,"Pharmacokineticandpharmacody- namic drug interactions with new oral anticoagulants," *Annals of Pharmacotherapy*, vol. 47, no. 11, pp. 1478–1487, 2013.
5. Wang JZ, Vyas MV, Saposnik G, Burneo JG. Incidence and management of seizures after ischemic stroke. Neurology (2017) 89:1220–8. 10.1212/WNL. 0000000000004407

Biography -

I am Dr. Shalin Shah , finished my DM neurology last year from prestigious amrita institute of medical science ,kochi ,India . My mentor was Dr. Anand kumar who is head of department in amrita institute. I had done work and thesis of vascular headache. At

present I am doing my Stroke and neurointervention fellowship at Artemis institute , gurgaon , india under DR. Vipul Gupta . I want to present a case report on commonly missed interaction

Title - Reduced Anticoagulant Effect of Dabigatran in a Patient Receiving Concomitant Phenytoin

I can present it as oral or poster presentation ..

Thankyou