Warfarin-induced raised international normalized ratio is further prolonged by pantoprazole

Sir,

Drug–drug interactions are important to know so that any complication arising can be avoided, especially when it is life-endangering. We present a case where pantoprazole further increased the warfarin-induced raised International normalized ratio (INR) by potentiating warfarin effect. This increase in INR attenuated after stopping the pantoprazole, and a stable INR target was achieved.

Pantoprazole is commonly used in Pediatric Intensive Care Unit (ICU) for prophylaxis of stress-induced ulcers. It probably can interact with warfarin and further prolong INR, which can result in life-threatening bleeding. A 14-year-old patient was admitted in our ICU in view of sepsis with pneumonia and later developed deep vein thrombosis of circumflex vein, common femoral vein, superficial vein, and popliteal vein. Heparin was started, later followed by warfarin in a dose of 0.2 mg/kg (8 mg/day) to maintain a target INR of 2.5. On day 3, her INR rose to 6, but the patient was stable, and there was no bleeding. Hence, we decreased the warfarin dose by 20%. After 2 days, INR was still raised at 5.0. We again decreased the dose and monitored INR. High INR led to a reduction of warfarin to a total dose of 1 mg/day. This usually does not happen in our practice, so we looked for drug interactions which can cause raised INR in patients on warfarin therapy and checked that our patient was not receiving any such drugs or dietary items such as garlic, mango, papaya, or fish. Our patient was receiving ceftriaxone, vancomycin, and pantoprazole. We could not change/stop antibiotics and so decided to stop pantoprazole. After 3 days, INR decreased to 1.4. We had to increase the warfarin dose to increase INR to 2.5. Final dose of warfarin now was 8 mg/day. We observed a 87.5% reduction in dose of warfarin when given concomitantly.

Warfarin is a racemic mixture of stereoisomers where S-warfarin is 3–5 times more potent inhibitor of the Vitamin K epoxide reductase complex than R-warfarin. It undergoes extensive metabolism by the cytochrome P450 (CYP) isoforms. CYP2C9 is responsible for the metabolism of S-warfarin, while R-warfarin is metabolized by CYP1A2, CYP2C19, and CYP3A4.[1] Any drug which can inhibit these cytochrome isoenzymes can lead to decreased metabolism of warfarin and thus prolonged effect of the drug.[2] In a study from Sweden, pantoprazole was shown to strongly inhibit CYP2C9 activity *in vitro*.[3] This may form the basis for the interaction between these two drugs. As warfarin has a low therapeutic index such interaction may lead to life-threatening bleeding. This interaction has also been reported in postmarketing period. However, one study clearly showed a lack of interaction between pantoprazole and warfarin.[4] On application of DIPS scale for drug–drug interaction, this case scored "5" points which shows that interaction between pantoprazole and warfarin is probable and caused a rise in INR.[5] We did not rechallenge/made alterations in the dose of pantoprazole. CYP2C9 polymorphism is unlikely as on stopping the pantoprazole INR again decreased to nontherapeutic range. In conclusion, in spite of a good rationale, there is small evidence for interaction between pantoprazole and warfarin; it would be pragmatic to monitor INR when pantoprazole and warfarin are used concomitantly to avert any serious bleeding.

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Conflicts of interest

There are no conflicts of interest.

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