Warfarin-quetiapine interaction causing hemorrhage

Sir,

Psychotropic drugs have been reported to have a drug-drug interaction with warfarin, raising the international normalizing ratio (INR), with a potential to develop hemorrhage.\(^\text{[1]}\) We report a rare case of warfarin-quetiapine interaction causing gastrointestinal hemorrhage. Extensive review of literature has revealed only one such case, hitherto.

A 72-year-old female patient developed deep vein thrombosis, 6 months back. She had hypertension since the age of 40 years, for which she was on regular treatment. She was started on warfarin, and in about 3 weeks, her INR readings ranged from 2 to 3, which was the desired range. A month later, she developed sleep disturbance, restlessness, and occasional visual hallucinations at night, for which, quetiapine was started in a dose of 25 mg, given at bedtime. These symptoms subsided within a week. About 1 week later, she complained of passing blood stained stools. Detailed evaluations including upper gastrointestinal endoscopy and colonoscopy were normal. The stool analysis showed plenty of red blood corpuscles, with no other significant finding. Quetiapine-warfarin interaction causing gastrointestinal hemorrhage was made. The INR had risen to 3.2 at this point of time. Quetiapine was immediately stopped and warfarin was continued. There was no bleeding after 3 days, at which time the INR was 2.2 and was within the desired range. She received warfarin for the next 2 months, and when Doppler studies showed no clot and the blood flow was normal, warfarin was tapered and stopped; 10 days after this, the INR was 1.2 which is normal.

Warfarin is metabolized in the liver and is highly protein bound, therefore, increasing the risk of drug interactions, particularly hemorrhagic adverse events, which is further increased by the fact that it has a low therapeutic index. While the interaction of warfarin with many drugs is well studied, there is, in comparison, insufficient research of its interaction with psychotropic drugs.

The available literature on the interaction between psychotropic drugs and warfarin indicates that some drugs such as trazodone and carbamazepine have long been known to lower the levels of warfarin. More recently, bupropion too has been reported to seriously decrease the activity of warfarin.\(^\text{[2]}\)

Of the interactions between psychotropic drugs and warfarin that have been reported, very few are “definite” interactions; the rest are reported as “could possibly be implicated,” as they were used along with drugs known to cause hemorrhage when used with warfarin.

This is the second case of quetiapine reported to cause bleeding, in a patient, on a stable regimen of warfarin. CYP2C9 and CYP1A2 are known to be the major pathways of metabolism of warfarin S and R enantiomer, respectively. CYP3A4 and CYP2C19 are minor pathways of the far less potent R-enantiomer of warfarin.\(^\text{[3]}\) Quetiapine-warfarin reaction occurred, though quetiapine does not have any action on the major pathways mentioned; except in vitro, where CYP 2C9 has been shown to cause this, but not in vivo. CYP3A4 is the only enzyme responsible for the biotransformation of quetiapine,\(^\text{[4]}\) and therefore, inhibition of CYP3A4, a minor pathway, was the cause of the quetiapine-warfarin reaction in both cases.

In the previous reported case, the INR was 3.4 when the bleeding occurred.\(^\text{[5]}\) In this case, the INR was 3.2 when the bleeding occurred. The INR was considerably lower than the levels that generally cause bleeding, in both the cases. The possible reason could be that, in both cases, there were risk factors for hemorrhage; age above 70 years, female sex, and the presence of hypertension.

Though the interactions between psychotropic drugs and warfarin leading to hemorrhage are not many in literature, this case indicates that caution is warranted while combining them. A life-threatening drug interaction, as a result of increased INR with hemorrhage, is known to occur.
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Divalproex sodium leading to sustained significant improvement in tardive dyskinesia in a patient with bipolar disorder
Patient presented again in November 2014 for a detailed work-up. He was euthymic. However these movements were present consistently for a month. The movements were noticeable during the interview and an impression of TD was made. On Abnormal Involuntary Movement Scale (AIMS), these were rated as 3 for lips and perioral area (0–4) and 3 for jaw (0–4), three for awareness (0–4) with moderate distress. During that visit, tablet valproate 1000 mg/day was added as prophylaxis for bipolar disorder. Aripiprazole was continued with a plan to stop it later. The patient was compliant to both medications.

During his next visit after 10 days, patient and informants reported a significant improvement (of more than 90%) in TD. It was now barely noticeable during the interview. The AIMS rating was 1 for lips/perioral movements (0–3) and 0 for jaws (0–3), and 1 for awareness (0–3) with no accompanying distress.

Serum valproate level (12‑h postdose) was 134 µg/ml. Clinically, neurological examination was within normal limits.

Considering that level was on somewhat higher side, an attempt was made to reduce divalproex sodium to 750 mg/day. However, TD re-surfaced almost at previous intensity, as observed after 2 weeks. Consequently, the dosage was increased to 1000 mg/day, which was well tolerated. During the next 4 months, he continued on both divalproex sodium and aripiprazole, with no TD, and periodic review every 2–4 weeks. Aripiprazole

Sir,

Not many therapeutic options are available to treat tardive dyskinesia (TD). Usual algorithm involves a reduction of antipsychotic dosage, clozapine, or tetrabenazine. Apart from that, available literature is scant and inconclusive. We report a case where divalproex sodium at a relatively higher serum concentration leads to improvement in TD.

A 35‑year‑old married male with no family history first visited the outpatient clinic in August 2014 with irritable behavior, “racing thoughts,” referential ideas for 1 week. He had been a known case of bipolar affective disorder (four episodes between 1994 and 2009) and cannabis dependence for 6 months in 2009 (as per subjective and objective corroboration). Between 2009 and 2013, he maintained largely euthymic and occupationally functional while on unknown medications. In December 2013, patient stopped all medications, maintained well for subsequent 8 months until current presentation.

He was prescribed aripiprazole 5 mg/day by the treating doctor (pending a detailed assessment), with which remission was achieved. After being on low‑dose aripiprazole for 2 months, patient started to experience involuntary movements involving lips, mouth, and jaw. As a result, patient reported feeling inhibited while attending to customers at workplace.