Bupropion-warfarin Combination: A Serious Complication

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ABSTRACT
Depressive illness and thromboembolic disorders are both highly prevalent. Warfarin is frequently combined with an antidepressant drug, the choice of which depends mainly on the risk of a hemorrhagic complication. Patients requiring the warfarin are often in the older age group, where the newer antidepressants with a better safety profile are preferred over tricyclic antidepressants. We report herein, a patient who was on bupropion for depression, when he developed deep vein thrombosis high-risk. Warfarin was started. While on this combination bupropion was abruptly stopped. This caused a more than two-fold elevation of international normalized ratio (INR) above the level, which is considered a high-risk for a hemorrhagic complication. INR reverted back to the desired level on reintroduction of bupropion. This indicates that a bupropion-warfarin combination should be used with the caution, though there has been no reported interaction so far.

Key words: Bupropion, international normalized ratio, warfarin

INTRODUCTION
Antidepressants are widely used in the treatment of depression, which is the most common psychiatric disorder with an enormous burden globally. For a long time, tricyclic antidepressants (TCAs) were the mainstay of drug treatment of depression. Only much later, a number of other classes of antidepressants became available. Thromboembolic phenomena are also very common and need treatment with anticoagulants. Of the oral anticoagulants, warfarin is the most widely used drug.

A large number of patients need to take warfarin along with the antidepressants. Studies of drug interaction between warfarin and antidepressant drugs show that bleeding is the most common and also the most feared manifestation of the interaction.

We report a patient who was started on warfarin for treatment of deep vein thrombosis (DVT), who was receiving bupropion for depression. While the international normalized ratio (INR) had been stable at the desired level, bupropion was stopped and this resulted in an alarmingly high INR. Higher values of INR than the desired levels for adequate anticoagulation indicate a high risk of bleeding.

To our knowledge, there is no reported case so far, of drug interaction between bupropion and warfarin.

CASE REPORT
A 55-year-old male was on treatment for dysthymic disorder (DSM IV TR) since 12 years. He was a heavy smoker. The treatment was mainly with psychotherapy, with periods of antidepressants off...
and on. He was mostly on bupropion, in doses ranging from 150 mg/day to 300 mg/day. He responded well to treatment, had few depressive symptoms intermittently, and his smoking had decreased to about 6-8 cigarettes a day. A year back, he developed DVT, at which time, the dose of bupropion was 300 mg/day. He was put on warfarin and the desired level of INR, that is, 2-3, was achieved. At this time, the surgeon did not know that the patient was taking bupropion 300 mg/day. After a couple of weeks, when the patient informed him of this, bupropion was abruptly stopped. The subsequent blood test showed an alarming INR level of 8.0. The patient was under observation, and the surgeon put him back on bupropion, 300 mg/day. The INR returned to the desired level, with no complication. The warfarin was stopped after DVT resolved. The patient remained free of depression and so, bupropion was gradually tapered off.

**DISCUSSION**

Warfarin is a very commonly prescribed anticoagulant all over the world. It is among the 15 most prescribed drugs in the United States, with more than 1 million prescriptions/year and 75.7% of those on warfarin are elderly. Considering that antidepressant drugs are so widely prescribed across all age groups need to study the drug interactions between warfarin and antidepressants is obvious.

Warfarin has a narrow therapeutic range, and for most patients on this drug the target INR usually is 2.0-3.0. A higher target INR of 3.0-4.0 is recommended for patients with the mechanical prosthetic heart valves. Above a level of 4.0, the risk of bleeding is very high, especially intracranial hemorrhage. In our patient, the INR was 8.0, which is potentially life threatening. The average dose of warfarin to achieve the desired level of INR ranges from 2 mg/day to 10 mg/day. The dose of warfarin can vary according to the individual sensitivity to it. In a sensitive individual, a dose of less than 1.5 mg may suffice. And if there is warfarin resistance, a dose in excess of 20 mg may be required. The list of drugs and other factors like diet and food supplements containing vitamin K, that affect the action of warfarin, is prodigious and expanding; for example, acetaminophen, barbiturates, phenytoin, rifampin, phenylbutazone, sulfinpyrazone, metronidazole, disulfiram, allopurinol, cimetidine, and ingestion of large amounts of alcohol.

There are four hypothetical mechanisms by which antidepressants or any other drugs can alter warfarin levels: By decreasing absorption; by inhibiting cytochrome P2C9 (CYP2C9) isoenzyme - causing an increase of INR, by enzyme induction of CYP2C9 causing decrease in INR; by increased protein binding of the drug, resulting in dislodging warfarin, which is highly bound to plasma albumin.

Drugs that alter warfarin levels do so mainly through the CYP450 isoenzyme system. While more than 40 hepatic enzymes have been identified, only six isoenzymes (1A2, 3A4, 2C9, 2C19, 2D6, and 2E1) significantly affect the metabolic clearance of more than 90% of all drugs. For warfarin, the isoenzyme 2C9 is the most important, followed by 1A2.

In recent studies, specific serotonin reuptake inhibitors (SSRIs) have been studied the most and TCAs the least in terms of interaction with warfarin. This is probably due to the pattern of warfarin usage. As mentioned earlier, about three-fourth of all patients on warfarin are older people. In this population, SSRIs are the most commonly used antidepressants. Reported drug interactions between antidepressants and warfarin, of which bleeding is the commonest, are seen most with fluoxetine and fluoxamine. Paroxetine appears to have a lower risk. Sertraline and citalopram have the lowest reported drug interactions among all classes of antidepressants. Ironically, the safest and the most dangerous drugs both belong to SSRI’s.

TCAs, serotonin norepinephrine reuptake inhibitors–venlafexine, duloxetine and desvenlafexine, and mirtazapine are relatively, safe and have no clinically significant interaction with warfarin. This perhaps is due to their minimal or no inhibitory action on relevant CYP450 isoenzymes, 2C9 and 1A2.

There are no reports or empirical data suggesting that there is any risk in using the combination of bupropion and warfarin. It needs to be mentioned though that bupropion has been much less studied compared to SSRIs.

Bupropion acts predominantly on 2D6 and has no action on 2C9. This makes the bupropion-warfarin interaction, in this case, difficult to explain in the light of available evidence. It is possible that there is a hitherto unknown mechanism of action that causes an adverse interaction with warfarin.

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