The Necessary Evil: Balancing the Risks and Benefits of Fluvoxamine in a Patient with Treatment Refractory Depression on Warfarin. A Case Report.

By:

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Abstract

Warfarin, a commonly prescribed anticoagulant, has a narrow therapeutic index; and is metabolised by a number of cytochrome P-450 isoenzymes. Fluvoxamine is an effective antidepressant. It is a potent SSRI, with proven efficacy on obsessive-compulsive symptoms, anxiety, and psychotic depression. It is also a potent inhibitor of a number of cytochrome P-450 isoenzymes and has the potential to cause pharmacokinetic interactions with warfarin, resulting in elevated International Normalised Ratio (INR).

We report a case of an elderly man, who was on warfarin for atrial fibrillation. He also suffered from severe and complex depressive episodes, with marked anxiety, and obsessive-compulsive symptoms which at times were impervious to reassurance and rational explanations.

The depression responded inadequately to a number of trial of antidepressants, including a combination of antidepressants. Hence a decision was taken to commence Fluvoxamine. Co-administration resulted in the marked and rapid elevation of INR, necessitating adjustment in the dose of Warfarin.

Although Fluvoxamine, by dint of its pharmacokinetic profile as a Selective Serotonin Reuptake Inhibitor (SSRI) has a high likelihood of interaction with Warfarin, there are very clinical few case-reports of such an interaction.

Over the years, the use of Fluvoxamine in clinical practice has declined following the availability of other SSRIs that have less effect on the cytochrome enzyme system. However, in certain clinical situations where the use of Fluvoxamine is warranted, careful consideration of the drug interactions is highly recommended

The case demonstrates the necessity of close monitoring when Fluvoxamine is co-administered with Warfarin, as the INR is elevated and the risk of haemorrhage increases even at small doses of Fluvoxamine. This close monitoring becomes even more relevant in the elderly because of prolonged half-life of Fluvoxamine in this population.

Introduction

Warfarin is a widely used anticoagulant, primarily for the prevention of thrombosis and thromboembolism. Warfarin is used as a prophylactic agent in conditions such as atrial fibrillation and coronary artery thrombosis.[1]

Although effective and safe, treatment with Warfarin is associated with risks. Because of its narrow therapeutic index, patients require regular blood monitoring for the international normalised ratio (INR) to determine the safe yet effective dose of Warfarin.

Warfarin has interaction with several medications which affect the availability of Warfarin. One class of drugs which is very commonly prescribed is the selective serotonin reuptake inhibitors (SSRIs) antidepressants.

Due to their supposedly favourable side-effect profile, e.g. less cardiotoxicity, and safety in overdose, SSRIs have become the first-line antidepressant [2], preferred over tricyclic antidepressants (TCA). However, SSRIs, have other serious side-effects including increased tendency to bleed, particularly gastrointestinal bleeding. SSRIs may increase the risk of bleeding due to the secondary effect of serotonin release which is essential for platelet aggregation. [3] This effect is especially significant when combined with anticoagulants. [1]

Several of the SSRIs are inhibitors of the cytochrome P 450 enzyme system, which is responsible for the metabolism of some medications, including Warfarin. Both SSRIs and anticoagulants are frequently prescribed in the elderly population.

Fluvoxamine is a SSRI which is licensed for use in the treatment of depressive disorder, obsessive-compulsive disorder (OCD) [1], and is also used in the treatment of social phobia. While an interaction between Fluvoxamine and Warfarin is to be expected because of Fluvoxamine's inhibitory action on a number of cytochrome P 450 enzymes, there have not been many case reports of the interaction between Fluvoxamine and Warfarin.

A Medline search revealed only two case reports of an interaction between Warfarin and Fluvoxamine. [4,5]

We report a case of an elderly man who developed elevated INR when he was started on Fluvoxamine for the treatment of depression, while on Warfarin.

Case Report

A 75-year old male was admitted to the acute psychiatric unit with complaints of anxiety, depressed mood and suicidal ideation. In the previous months, he had developed a pre-occupation that his bowels were not functioning properly and that he would not be able to open his bowels. He was using excessive laxatives secondary to this preoccupation. He also described other depressive symptoms: anhedonia, insomnia with early morning wakening, poor concentration, and low motivation.

The patient was diagnosed with depression two years previously, requiring Electroconvulsive therapy (ECT). He was discharged on Mirtazapine 45mg and Venlafaxine-XL 150mg. Following a deterioration in mental state, the Venlafaxine-XL dose was increased to 225mg three months before this admission, without much improvement. Risperidone and Olanzapine were trialled as an adjunct without beneficial effect and were discontinued. Compliance with medication was reportedly good.

The patient had multiple physical health complaints: previous myocardial infarctions, hypertension and paroxysmal atrial fibrillation. He was prescribed tamsulosin, bisoprolol, perindopril, atorvastatin, and warfarin.

The patient's preoccupation about bowel movements was, for the most part, deemed to have obsessive quality: he accepted that these worries were repetitive and came to his mind against his wishes. He said that he would rather not have these worries but was unable to distract himself.

The marked subjective anxiety, according to the patient, was entirely linked to the preoccupation. However, when the patient became agitated, it was difficult to persuade him to appreciate the anomalous nature of his thoughts. At such times he insisted that there was something definitely wrong with his bowels and nothing could help him.

Prior to admission, the patient was treated at different times with different antipsychotic medications, which made little impact on the symptoms. Following his admission he was referred to the psychology services, which concluded that he was too unwell to meaningfully participate in psychological therapies. The patient, too, was not keen on this option. He also declined ECT and was deemed to have the capacity to make the decision.

Venlafaxine-XL was switched, in light of the patient's cardiac risk history, to an SSRI known to have an effect on obsessional symptoms. Accordingly, a dose of Mirtazapine was decreased to 30mg, and Venlafaxine-XL was tapered off over ten days.

Fluvoxamine was started at 50mg/day, and the dose was titrated to 150 mg/day over the next week. The dose was further increased to 200 mg/day.

INR was previously stable on warfarin dose of 5mg per day: blood results were between 2.32-2.68. Following fluvoxamine-initiation, INR started increasing: 2.98 after six days. INR increased further, to 3.82, with increase in Fluvoxamine's dose

Warfarin-dose, as a result, was decreased, initially from 5mg to 4mg; however, INR remained above range (3.75). With further reduction in Warfarin's dose, to 3mg/day, INR reduced but was still above range (3.51). INR eventually stabilised when warfarin-dose was reduced to 2mg/day. The dose adjustment took place over ten days.

Discussion

Management of depression in elderly population requires careful consideration of the choice of psychotropic medication, as elderly patients are more likely than younger patients to be on multiple medications for associated physical health problems, which increase the potential for drug interactions. Half-lives of drugs are also extended in the elderly.

The patient was prescribed Warfarin for the management of atrial fibrillation. Warfarin is a racemic mixture of S-warfarin and R-warfarin, of which S-warfarin is more potent than R-warfarin. [6]

Warfarin has the potential to cause pharmacokinetic drug interactions (drugs affecting hepatic cytochrome P 450 enzyme system, which metabolises warfarin), which are thought to be more clinically relevant than pharmacodynamic interactions (highly protein bound drugs displacing Warfarin from its binding site) for warfarin. [6]

Warfarin is metabolised by a number of P450 isoenzymes such as 2C9/2C19, 1A2, and 3A4. [6] Of these 2C9 is thought to be crucial, as it metabolises the more potent S-isomer. Isoenzyme 1A2 is the major route for the metabolism of the R-isomer, while 3A4 and 2C19 are considered to be minor routes.

The psychotropic medications that are thought to have the potential for significant pharmacokinetic interaction with warfarin include Fluoxetine, Fluvoxamine, Quetiapine, and Valproic Acid. [7] Venlafaxine is also considered a high-risk drug in patients taking warfarin. One study found that fluvoxamine and venlafaxine were associated with a more than double risk of having an INR value of 6 or more. [3]

Fluvoxamine by dint of its inhibitory actions on 2C9/2C19, 3A4, and 1A2 [8] inhibits all the isoenzymes that metabolise Warfarin and can be said to have the maximum potential for pharmacokinetic interaction with Warfarin.

National Collaborating Centre for Mental Health guidelines on depression in adults with chronic physical health problems advise avoiding SSRI in patients taking warfarin or heparin and instead offering an alternative antidepressant such as mirtazapine. [9] Therefore, caution is needed when prescribing these medications to patients who fail to respond to other safer options.

At the time of his admission, the patient was on a combination on Mirtazapine and Venlafaxine XL, both at high doses, for several months. Neither of the antidepressants has significant action on the P450 isoenzyme system, although both are substrates of some enzymes, such as 2D6, 1A2 and 3A4. [8] The patient's INR was within normal limits when he was on these two medications (despite the aforementioned potential effect of venlafaxine on INR values).

During the period of admission, a decision was taken to change the antidepressant regime, for clinical reasons. The two antidepressants considered were Fluvoxamine and Sertraline.

It was felt that despite its higher potential to cause pharmacokinetic interaction with Warfarin, Fluvoxamine is chosen ahead of Sertraline (which inhibits 3A4 and 2D6). The more potent action of Fluvoxamine on the $sigma_1$ receptors, which account for its significant anxiolytic properties and therapeutic action in the delusional depression [10] was felt to have the potential of benefit given the patient's clinical symptoms.

It was also felt that Fluvoxamine would also be of more benefit than Sertraline with insomnia which was patient's frequent complaint given its side-effect of somnolence. [11]

Fluvoxamine was started at a low dose (50 mg/day) after Venlafaxine XL was completely withdrawn. The dose was titrated rapidly over the next one week, to 150 mg/day. The INR showed an upward trend within five days of commencing Fluvoxamine, and it exceeded three by the time the dose of Fluvoxamine was increased to 150 mg/day. This necessitated a reduction in Warfarin's dose from 5 mg to 2 mg/day. The INR stabilised to between 2 and 3 when warfarin dose was more than halved.

Fluvoxamine has a half-life of 9-28 hours, and steady-state levels reach roughly after ten days. [8]

The half-life is increased by almost 50% in the elderly. [3] The trajectory of increase in the INR was consistent with the pharmacokinetic of Fluvoxamine: it is a potent inhibitor of CYP4501A2, with a relatively little affinity for the other isoenzymes. The increase in INR was not dramatic, which is different from previous reports. [4] Throughout the period of Fluvoxamine –titration and Warfarin dose adjustment, there was no clinically untoward incident.

In conclusion, this case shows the need for close monitoring when warfarin is combined with another drug which significantly enhances warfarin's anticoagulant effect. At the same time, it can be done safely, even in patients such as the elderly, who can be at a higher risk of adverse effects of interaction, when appropriate steps to monitor the patient are in place. The case also demonstrates the necessity of using clinical judgment while applying the guidance in individual patients.

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