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Interaction of Fluvoxamine with Warfarin in an Elderly Woman

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ABSTRACT

An 80-year-old woman presented with an embolic stroke secondary to atrial fibrillation and mitral stenosis. She was initially on intravenous heparin and was subsequently maintained on oral warfarin. She was also given digoxin for atrial fibrillation and colchicine for gouty arthritis as well as fluvoxamine in her fourth week in hospital, to treat her depression. However, her INR (international normalised ratio) became markedly elevated within a week. Fluvoxamine and warfarin were stopped immediately. When warfarin was reintroduced 6 days later, her INR value increased again. The coagulation profile only became stable after 2 weeks of cessation of fluvoxamine. Low dose fluvoxamine can interact significantly with warfarin in the elderly and the effect may persist for up to 2 weeks of stopping the anti-depressant.

Keywords: embolism, anticoagulation, cytochrome P-450, drug interactions, geriatric

INTRODUCTION

Elderly patients are known to require a reduced dose of warfarin to achieve the same anticoagulant effect[1]. There have been two recent reviews[2,3] that highlight the potential interaction between fluvoxamine and warfarin. Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), is used in the treatment of depression and is known to inhibit oxidative drug metabolising enzymes in the liver. We could only locate one case report[4] using MEDLINE, that reports on this interaction. We report here a case of an elderly woman who had an unexpectedly labile anticoagulation profile with warfarin while on fluvoxamine.

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CASE REPORT

An 80-year-old woman was admitted to hospital with a left hemiparesis. Her medical history revealed a chronic heart problem which was diagnosed more than 20 years earlier. Before her current stroke, she was living alone for more than 10 years and had been functionally independent. Examination revealed atrial fibrillation with a health rate of 130/min. No cardiac murmurs were detected and examination of the other systems was normal. She weighed 45 kg.

Her full blood count, renal panel, serum glucose, liver function tests, coagulation profile and serum lipids were within normal laboratory limits. Her ECG showed atrial fibrillation with a ventricular response of 133/min. Her chest X-ray showed borderline cardiomegaly with a straight left heart border. Initial CT scan of the head showed multiple small infarcts in the right frontal lobe and right basal ganglia, and a large infarct in the left parieto-occipital lobe with surrounding oedema. Echocardiogram showed severe mitral stenosis with an orifice of 0.9 cm^2. The left atrium was moderately dilated but no thrombus was present. The left ventricle was normal with an ejection fraction of 55%. Thickening of the aortic and tricuspid valves were seen.

Her heart rate was controlled with intravenous digoxin. On day 2 of admission, she complained of dyspnoea. Chest X-ray showed upper lobe venous diversion and she was given a dose of intravenous frusemide with improvement. On day 3, she developed inflammation in the left knee. There was an effusion and movements of the knee were limited by pain. Forty mls of straw coloured fluid was aspirated from the knee joint. Serum uric acid level was raised and uric acid crystals were present in the knee aspirate. There was no previous history of gout or arthritis. She was started on colchicine 0.5 mg t.i.d. from day 3 to day 17 of hospitalisation.

A repeat CT scan done 2 weeks after the stroke did not show any haemorrhagic transformation. She was started on intravenous heparin because of the high risk of another embolic stroke. The therapeutic target was to achieve an international normalised ratio (INR) of between 2 and 3. She was started on warfarin concurrently. The initial warfarin dose was 2 mg daily for 3 days. This was reduced to 1.5 mg daily for another 3 days and she was subsequently maintained on 1 mg daily. Her INR on days 18 and 21 were 2.49 and 3.00 respectively.

However, she had another attack of gout (this time over the left metatarsophalangeal joint) during the fourth week of admission. Colchicine was restarted on day 24 and continued to day 42. On day 26, she was started on fluvoxamine 25 mg daily because of depression. INR on day 26 was 1.8. In view of the potential interaction of fluvoxamine with warfarin, the dosage of warfarin was left at 1 mg daily despite the sub-therapeutic INR.

She had worsening of the left hemiparesis on day 29 and the dosage of warfarin was increased to 1.5 mg daily. A repeat CT scan did not show a new stroke or haemorrhagic transformation. On day 32, the INR was found to be extremely high at 9.96. A repeat test was done to exclude laboratory error – the repeat INR was 11.30. Warfarin was stopped immediately and one unit of fresh frozen plasma (FFP) was given. Fluvoxamine was also stopped although colchicine was continued due to persistent joint pain. Check INR on the following two days were 3.18 and 3.08 respectively.

Warfarin was recommenced on day 38 at 1 mg daily without additional loading dose. The INR 4 days later was again elevated, at 11.80. Colchicine was stopped and the patient was only maintained on oral digoxin. One unit of FFP was given. She was restarted on warfarin a few days later and eventually stabilised on a dose of 1 mg daily with INR values of between 2.0 and 2.5. Fig 1 shows the trend of the INR between days 13 and 60 of the patient's hospital stay.

DISCUSSION

In this patient, the critical clinical decision was the timing of commencement of anti-coagulant once the echocardiogram and CT scan head results were available. Mitral stenosis was not suspected initially because of the absence of any cardiac murmurs. However, it is well known that tight mitral stenosis may not produce any murmurs[5]. Although we were aware of the high risk of recurrent emboli in the setting of atrial fibrillation and mitral stenosis, anti-coagulation was not started immediately because of the risk of haemorrhagic transformation in the new large infarct in the brain. The safety of immediate anti-coagulation in the presence of a large cortical infarct remains a controversial issue[6].

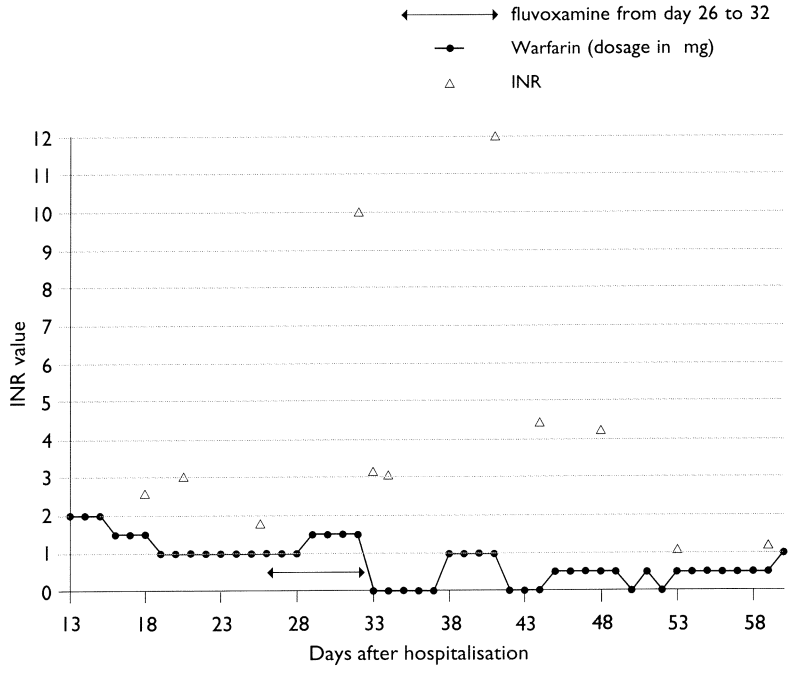

Fig 1 – INR values during hospital stay.

Colchicine was used to treat the patient's gouty arthritis initially since anti-coagulation was planned. There have been no previous documented interaction between colchicine and warfarin in the literature. In an extensive review by Wells et al[7], MEDLINE and TOXLINE databases from 1966 to October 1993 did not highlight any significant interaction between the two drugs. An updated review by Harder and Thürmann[8] in 1996 also did not mention any significant interaction. A non-steroidal anti-inflammatory agent was not chosen for the initial treatment of the gout because of the increased risk of gastrointestinal bleeding in the presence of anti-coagulation[9].

The patient was started on a selective serotonin reuptake inhibitor (SSRI) for the treatment of depression since a tricyclic anti-depressant was not ideal in the presence of her cardiac condition. The two standard SSRIs available in the Ministry of Health, Singapore are fluoxetine and fluvoxamine. Fluvoxamine was chosen because the patient was also experiencing insomnia from her depression and the drug has the desirable side-effect of somnolence in some patients[10]. As there have been recent reviews highlighting the possible interaction between fluvoxamine and warfarin, the patient was started cautiously on a low dose of fluvoxamine.

Fluvoxamine is well absorbed through oral administration with a mean half-life of 15 hours and a range of between 9 and 28 hours. Its disposition is altered by hepatic but not renal disease. Data from pharmacokinetic studies suggest only a modest need for dose adjustment if needed in the elderly[13-14]. Phase I oxidation of the drug occurs in the liver through the cytochrome P-450 enzymes (CYPs) although the parent drug produces no active metabolites. The specific cytochrome isoenzymes involved in the hepatic elimination of the drug are undefined at the moment. However, it is known that fluvoxamine has a high affinity for the CYP1A2 isoenzyme, less affinity for the CYP3A4 and CYP2C19 isoenzymes, and minimal affinity for CYP2D6. CYP inhibition may affect the metabolism of other drugs that are substrates for these isoenzymes with potential serious consequences. In particular, R-warfarin and S-warfarin (the active form) are metabolised by CYP1A2 and CYP2C9/10 respectively and are expected to interact with fluvoxamine.

Although the dose of warfarin was also not increased in our patient despite a subtherapeutic INR value, the INR shot up to an extremely high value of 9.96 at the end of 6 days of therapy with low-dose fluvoxamine. This is probably caused by the interaction of the two drugs with the cytochrome oxidase isoenzymes as explained earlier. It is interesting to note that interaction occurred even at a very low dose of fluvoxamine. When warfarin was restarted 6 days later at a dose of 1 mg daily, the INR value 4 days after the recommencement of warfarin was again elevated. This second elevation of the INR is likely to be the persisting effect of fluvoxamine because the drug was only stopped a week earlier and the patient was only on 2 other drugs (digoxin and colchicine).

It is possible that our patient could be a poor metaboliser of fluvoxamine as an experimental study has shown that poor metabolisers of the CYP2D6 test drug dextromethorphan, developed higher steady-state serum concentrations when they were given fluvoxamine[15].

Our patient was finally stabilised on 1 mg of warfarin daily after another week. Her neurological status improved and she was able to walk independently with the aid of a walking frame at the end of 2 months' hospitalisation. Her mood also improved with the gradual recovery in her functional status without further consumption of antidepressants.

CONCLUSION

Our patient illustrates the difficulty of adjusting the dose of warfarin in the presence of another drug which can cause significant interaction. Fluvoxamine can interact significantly with warfarin even at low doses in the elderly. The effect can occur within a week and persist for at least 2 weeks after stopping therapy. Doctors treating patients with depression should be aware of this and monitor the INR closely.

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