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Comedication with Sertraline and Phenprocoumon in Two Patients with Anxiety Disorders

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Abstract

Comorbidity of cardiovascular and affective disorders is common. Many patients with prior cardiac disease receive anticoagulants, such as warfarin or phenprocoumon. While older antidepressants are contraindicated in patients at risk of arrhythmia, selective serotonin re-uptake inhibitors (SSRIs) can interfere with blood clotting. So far, literature on concomitant treatment with phenprocoumon and SSRIs is sparse. We observed comedication of sertraline and phenprocoumon in two patients with anxiety disorders and prior cardiac disease. We found no clear evidence for clinically relevant interaction of sertraline and phenprocoumon. Further research should be conducted to establish an evidence based rationale for antidepressant treatment of patients with cardiovascular complications (German J Psychiatry 2003; 6: 69-72).

Keywords: anxiety, depression, sertraline, phenprocoumon, interaction

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Introduction

In our cognitive behaviour therapy unit we commonly see patients with a coincidence of affective and anxiety disorders and cardiovascular diseases. Comorbidities of cardiovascular and affective disorders have been reported in various publications and are receiving increased attention due to the high incidence and relevance of both disorders (e.g. Hippisley et al., 1998, Gorman et al., 2000). In fact, clinical observations suggest that the two diseases may be linked. Many patients show depressive symptoms after cardiac ischaemia, and depression appears to be a risk factor for cardiovascular disease in itself. Patients with depression are at higher risk of re-infarction (Hippisley et al., 1998).

Antidepressant treatment in general would probably improve the outcome of patients with cardiovascular diseases. However, because of their arrhythmogenic side effects, tricyclic antidepressants are often contraindicated in these patients. This limits the choice of antidepressants significantly. A class of antidepressants that appear to be relatively safe, if not advantageous, are the selective serotonin re-uptake inhibitors (SSRIs). Substances of this class inhibit uptake of serotonin into neurons, and other cells, such as platelets. Thus, an important side effect of SSRIs is their potential to interfere with platelet function. Although it has recently been suggested that this side effect might actually be beneficial in patients with coronary artery disease (Malinin et al., 2001), it has also been accused of placing patients at risk of bleeding complications (Abajo et al., 1999, Walraven et al., 2001).

Interference with blood clotting is of major concern in patients who receive anticoagulation treatment, especially because SSRIs might also interact with the metabolism of coumarins like warfarin or phenprocoumon. These substances are regularly used in patients with severe arrhythmias, or artificial heart valve implants. Phenprocoumon is a substance similar to warfarin that is commonly administered in Germany, Denmark, Belgium, Switzerland and the Netherlands. The interaction of warfarin with various drugs has been assessed thoroughly. It has been found that interaction potential with some SSRIs, as for example sertraline, is relatively low (Sayal et al., 2000,Schmider et al., 1997). To our knowledge, there are no publications on the comedication of SSRIs and phenprocoumon.

Three possible forms of interaction might be of concern to the clinician: firstly, direct effects of serotonin depletion of platelets, secondly, competition for plasma protein binding

of the SSRI and phenprocoumon and, thirdly, competitive CYT P450 turnover.

The direct effects of serotonin on the coagulation system are the mediation of vasoconstriction in the first phase of hemostasis after trauma and the activation of platelets for subsequent aggregation (Li et al., 1997). Since SSRIs lead to serotonin depletion of platelets (Ross et al., 1980), it is likely that SSRIs compromise platelet function to some extent.

SSRIs partially displace coumarin derivatives out of albumin binding (Apseloff et al., 1997). Subsequently, the free plasma level of the coumarin rises transiently, until a new steady state is reached (Harder et al., 1996). This might lead to a transiently increased risk of bleeding (Apseloff et al., 1997,Harder et al., 1996).

Coumarin derivatives are metabolised by the mitochondrial cytochrome peroxidase system (CYP) of the hepatocytes. There are many genetic variants of this enzyme family and the individual variants are mostly substrate specific. Warfarin is metabolised mainly by CYP2C9, as well as 1A2, 2C19 and 3A4 (Sayal et al., 2000). Phenprocoumon is metabolised by 2C8, 2C9, 2A6, 3A4, 3A5 and 3A7 (Flockhart, 2003). SSRIs, notably fluvoxamine, fluoxetine and to some extent sertraline, inhibit CYP2C9 (Schmider et al., 1997). This might lead to increased coumarin plasma levels and thus increase the risk of bleeding.

Case Reports

We observed comedication of sertraline and phenprocoumon in two of our patients. Both patients suffered from depressive as well as anxiety symptoms. While treatment of anxiety disorders with sertraline is still "off label" in Germany, it is well accepted in the USA and its effectiveness has been documented in a multicenter study (Bandelow et al., 2002). Bearing in mind the various mechanisms of interaction described above, we expected to be able to observe interaction by means of laboratory tests for blood clotting and platelet function. The central parameter for blood clotting is the International Normalized Ratio (INR). While the INR in healthy individuals is about 1.0, the desired INR for patients who need anticoagulation therapy should be in the range of 2 to 3.5. The daily dose of phenprocoumon is usually in a range of 1.5 to 4.5 mg. It is however necessary to determine the individual dose for each patient by monitoring the INR and adjusting the dosage regularly until the steady state has been reached. Since the effect of phenprocoumon can be measured by the INR, we expected that an alteration of this effect should be visible either by a change of the INR or by a change of the weekly dose of phenprocoumon needed to keep the INR in the therapeutic range. Additionally, in order to detect direct effects of sertraline through serotonin depletion, we did in vitro platelet function tests.

Patient A

Patient A was a 49-year-old Caucasian female with recurrent depression (ICD-10: F33.1) and somatoform autonomic dysfunction of the cardiovascular system (ICD-10: F45.30). At the time of admission, there were also agoraphobic symptoms and panic attacks (ICD-10: F40.01). She had a mechanical mitral valve prosthesis due to mitral valve insufficiency after rheumatic fever in her childhood, recurrent episodes of sinal tachyarrhythmia and arterial hypertension. She had received anticoagulation therapy with phenprocoumon since implantation of the artificial mitral valve 15 years previously.

Prior to admission to our cognitive behaviour therapy ward, she had developed increasing depressive and anxiety symptoms in spite of being treated with mirtazapine for several months. Due to the apparent non-response to mirtazapine, we decided to treat her with sertraline. At the time of admission, her impairment was severe, due to fear of a heart attack. She had been admitted to an internal medial ward prior to admission to our ward. However, no acute cardiovascular complications could be found.

In the first laboratory tests, prior to beginning with sertraline, in vitro platelet function was normal. On the internal medical ward, treatment with phenprocoumon had been interrupted, as is often done in in-patients, in order to allow for invasive diagnostic procedures. When she was admitted to our ward, phenprocoumon was being phased in at a daily dose of 4.5 mg. The initial INR was 4.55 so that the phenprocoumon dose had to be adjusted. We slowly increased sertraline starting from 50 mg daily, and monitored the INR every 3 days. Over the course of two weeks, we increased sertraline to the final dose of 150 mg. The last lab was done one week later before discharge. At this time, INR was 2.35, in vitro platelet function was not impaired and there were no clinical signs of bleeding. Over the course of phasing in sertraline, INR was within a range of 1.46 to 3.72. The daily phenprocoumon dose needed was between none and 4.5 mg, the weekly average ranging from 0.86 to 2.79 mg per day. We found that we had to increase phenprocoumon transiently when sertraline was started. However, three months after discharge, the general practitioner who sees patient A regularly reported that the steady state dose of phenprocoumon was at about 1.29 mg per day, whereas 14 months before it had been 1.5 mg daily. Apparently, the steady state dose had not changed significantly in the long term.

As to the psychiatric symptoms described above, we found that treatment with sertraline notably reduced depressive symptoms as well as frequency and severity of panic attacks. However, we found only a minor effect on possible cardiovascular complications.

Patient B

Patient B was a 59-year-old Caucasian male who developed agoraphobia with panic disorder (ICD-10: F40.01) and depressive symptoms (ICD-10: F32.1). Additionally, he had intermittent tachyarrhythmia and atrial fibrillation, as well as a history of recurrent gastritis and back pain. He had received anticoagulation therapy with phenprocoumon for about seven years because of the intermittent tachyarrhythmias.

Prior to admission to our cognitive behaviour therapy ward he had been treated with venlafaxine for several months. Nevertheless, he experienced increasing impairment due to his phobic anxiety symptoms, so venlafaxine was discontinued. Due to the apparent non-response to venlafaxine we decided to treat him with sertraline.

With the experience of the case described above, we decided to stop phenprocoumon initially, start medication with sertraline and begin phenprocoumon again, once the steady state of sertraline had been reached. In the meantime, adequate anticoagulation was provided through a low molecular weight heparin. As in Patient A, we assessed platelet function and INR prior to starting sertraline. The INR was 1.64, in vitro platelet function was normal. The average phenprocoumon dose had been in the range of 1.7 to 1.9 mg per day during the last months prior to admission. We started sertraline at 50 mg per day and increased to 100 mg per day after one week. Three weeks later, one week prior to discharge, we started phenprocoumon again at the usual initial dose of 9 mg and then adjusting to the required steady state dose. In the final labs before discharge, the INR was 1.9 and in vitro platelet function was normal. There were no clinical signs of bleeding. Four weeks after discharge, the steady state dose was reported to be 1.9 mg per day on average. In other words, it had not changed significantly.

Over the course of combined psychopharmacological and cognitive behaviour therapy in our ward, agoraphobic symptoms were reduced. However, patient B reported a full relapse of symptoms under ongoing treatment with sertraline two months after discharge, which he attributed to his problematic employment situation. Subsequently, his general practitioner discontinued treatment with sertraline.

Discussion

We observed comedication of sertraline and phenprocoumon in two patients with anxiety disorders and prior cardiac disease. There were no signs of clinically relevant interaction and the steady state dose of phenprocoumon did not change significantly once the steady state of both substances had been reached. However, in patient A, we observed a transient drop of the INR while phasing in sertraline. This made it necessary to increase phenprocoumon. Whether this was a direct consequence of administering sertraline remained unclear. It must be kept in mind that unfortunately in patient A the phenprocoumon dose was not properly adjusted and not in the steady state at the time of admission, so that oscillations of the INR were to be expected.

Nevertheless, since controlled studies with larger samples are not available at present, we cannot rule out the possibility that interaction might be relevant in some patients. A prior publication reported a significant increase in INR associated with sertraline and paroxetine in patients treated with warfarin (Askinazi, 1996). Whether this discrepancy in relation to our observations with phenprocoumon is due to a substantial difference in the way sertraline interacts with phenprocoumon remains unclear.

Our experience suggests that it is legitimate to treat patients with sertraline and phenprocoumon, given that there is a clear indication for both medications. Of course, good clinical practice requires that these patients be monitored closely for signs of bleeding. Regular monitoring should be obligatory until a steady state of both substances has been reached. For phenprocoumon this can take more than 20 days, since its half-life is about 4 to 6 days (Harder et al., 1996). For inpatients we suggest proceeding as described for patient B, i.e. interrupting phenprocoumon until the steady state of the SSRI has been reached. The time required to achieve the steady state is about seven days for sertraline. This approach appears to be more economical and easier to monitor. Care should also be taken when the sertraline dosage is altered.

The population of patients with prior ischaemic heart disease or arrhythmia who would be likely to benefit from antidepressants is considerable. However, pharmacological options are limited and appropriate knowledge and experience is lacking. We suggest that further research on the interaction of anticoagulants and antidepressants be conducted. It is desirable to establish an evidence based and safe rationale for antidepressant treatment of patients with cardiovascular complications.

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