Serotonin syndrome following introduction of venlafaxine following withdrawal of phenelzine: implications for drug washout periods

Sarah J. Yates, Niraj Ahuja, Sarah E. Gartside and R. Hamish McAllister-Williams

Introduction

We report here a case of serotonin syndrome (SS) following initiation of venlafaxine 2 weeks after withdrawal of a monoamine oxidase inhibitor (MAOI), phenelzine, and also following repeated retrials of venlafaxine initiation. The case has clinically important implications regarding the period of time necessary for monoamine oxidase biosynthesis following use of an irreversible MAOI.

SS is characterized by the presence of autonomic nervous system symptoms (such as hyperthermia, diaphoresis, mydriasis, nausea, shivering, hypertension, tachycardia, and diarrhoea), mental status changes (such as agitation, hypomania, and confusion), and neuromuscular abnormalities (such as myoclonus, incoordination, hyperreflexia, tremors, clonus, and muscle rigidity [Sternbach, 2003]). SS can be a life-threatening condition and occurs acutely due to markedly increased serotonin levels in brain, often following a coprescription or overdose of serotonergic drugs. These drugs can increase serotonin levels by inhibiting metabolism (such as MAOI), increasing formation (such as l-tryptophan), inhibiting reuptake (such as selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCAs)), increase release (such as amphetamines) or increasing postsynaptic receptor sensitivity (such as lithium). Overdose with a SSRI alone results in mild SS in about 15% of people but does not usually lead to severe toxicity [Isbister *et al.* 2007]. The occurrence of the syndrome is highest with a combination of SSRIs and MAOIs, though it is also reported with other serotonergic drug combinations.

Sternbach described criteria to diagnose SS (Table 1) and highlighted the importance of identifying it since it is usually reversible following discontinuation of the offending drug(s), supportive treatment and addition of a serotonin antagonist (such as cyproheptadine or chlorpromazine) in more severe cases [Sternbach, 1991].

There have been previous case reports of patients who experienced an SS when a serotonin reuptake inhibitor (SRI) has been introduced after the traditionally recommended 2-week washout from an irreversible MAOI [Sternbach, 2003]. However, we have been unable to identify any instance in the literature where a patient has been rechallenged with a SRI (such as an SSRI, SNRI or a TCA) after a further period of washout following the occurrence of SS.

Case report

The patient was a 42-year-old woman who was being treated for an episode of major depression that had lasted several years and had failed to adequately respond to four previous trials of antidepressants. These had included a period of treatment with venlafaxine (375 mg once daily (OD)) augmented with lithium (lithium carbonate, modified release, 800 mg daily; serum level 0.8 mmol/l) in 2009. At the time of referral to our specialist Regional Affective Disorders Service (RADS) in 2010, she was being treated with a combination of lithium (serum level of 1.0 mmol/l) and phenelzine to which she had also not responded. A decision was made to discontinue the phenelzine and re-start venlafaxine since there was a suggestion that there may have been at least a partial response to this.

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Correspondence to:
Dr R. Hamish McAllister-Williams, BSc, MBChB, PhD, FRCPsych, MD
Academic Psychiatry,
Campus for Ageing and
Vitality, Westgate Road,
Newcastle upon Tyne, NE4
6BE UK
r.h.mcallister-williams@ncl.ac.uk

Sarah J. Yates, MBBS
Core Trainee in Psychiatry,
Northern Deanery,
Waterfront 4, Goldcrest
Way, Newburn Riverside,
Newcastle Upon Tyne, UK

Niraj Ahuja, MBBS, MD, MRCPsych
Consultant Psychiatrist,
Wallsend Community
Mental Health Team,
Wallsend, UK and
Honorary Clinical Lecturer
in Psychiatry, Institute of
Neuroscience, Newcastle
University, Newcastle
upon Tyne

Sarah E. Gartside, BSc, DPhil
Lecturer in Biological
Psychiatry, Institute of
Neuroscience, Newcastle
University, Newcastle
upon Tyne, UK

Table 1. Sternbach's criteria [Modified after Sternbach 1991].

1. Presence of at least three of these signs following an addition or increase in serotonergic drug(s): agitation, diaphoresis, diarrhoea, fever, hyperreflexia, incoordination, mental status changes (such as confusion/hypomania), myoclonus, shivering and tremor.
2. Exclusion of other causes (such as infections/substance misuse).
3. Exclusion of starting or increase in dose of a neuroleptic (antipsychotic) medication.

Owing to the severity of her illness and the potential complications of medication switches of this nature, the patient was admitted to the RADS inpatient unit to facilitate the switch in medication. On admission, she was taking phenelzine 15 mg three times daily (TDS) which was reduced to 15 mg OD for 4 days and then stopped completely. On the basis of current recommendations, a period of 2 weeks was allowed before she was started on 75 mg venlafaxine. Unfortunately, within an hour of receiving this dose the patient became unwell with restlessness, uncontrollable shivering, sweating, dilated pupils, nausea and vomiting, elevated blood pressure (186/111 mmHg) and tachycardia with a rate of 130 bpm. On the basis that these symptoms met Sternbach's criteria (Table 1), a diagnosis of SS was made and the patient was transferred to a medical admission unit for monitoring purposes. She did not require any supportive medication and recovered within a few hours.

Clinically, the opinion was that venlafaxine was still indicated for the treatment of the patient. As a consequence, it was decided to continue with the original treatment plan, but to wait a further 2 weeks (i.e. 4 weeks since phenelzine discontinuation) and then to start venlafaxine at a lower dose of 18.75 mg. This was done but within 1 hour the patient became unwell again. She felt nauseous, was sweaty with some mild shivering. Her blood pressure was elevated at 167/99 mmHg with a pulse of 101 bpm. We had anticipated that a further reaction may happen and the patient was given 25 mg of chlorpromazine orally. Chlorpromazine is a 5-HT_{1A} and 5-HT₂ receptor antagonist and was administered to mitigate some of the effects of SS. Her symptoms settled within an hour.

As discussed below, it was felt that the lithium may be exacerbating the patient's reaction to venlafaxine, since lithium can enhance serotonergic activity. Her lithium was subsequently slowly reduced and then stopped. At this point, 10 weeks after stopping the phenelzine, the

venlafaxine was re-introduced at 18.75 mg and then, the following day, 37.5 mg. Unfortunately, an hour or so after taking 37.5 mg dose the patient experienced nausea, shivering and sweating. However, this reaction was milder than previously with no increase in blood pressure and lasted only around 30 minutes or so. This reaction was not felt to be caused by anxiety about the re-introduction of venlafaxine, as the change in her presentation (observed by ward staff) occurred while she was engaged in other activities. The patient was keen to continue with venlafaxine but after a week of these continuing adverse effects, each time she took a dose, other medication options were considered.

Other than a severe depressive illness, the patient had no other significant medical concerns. She was on lymecycline for acne, zopiclone for insomnia, levothyroxine and paracetamol for headaches. Her blood results, including renal function, liver function, thyroid function and full blood count were all within normal limits through this course of treatment. The patient is also a nonsmoker.

Discussion

The washout period between discontinuing an irreversible MAOI, such as phenelzine, and starting venlafaxine, or any SNRI, SSRI or TCA, is to allow for biosynthesis of MAO to replace enzyme which has been irreversibly inactivated. Current clinical recommendations in the UK [Bazire, 2010; BNF, 2010; Taylor *et al.* 2009] suggest a washout period of 2 weeks. However, there are previous cases in the literature of SS when switching from phenelzine to venlafaxine after 14 days, with two patients developing SS after a gap of 14 days [Diamond *et al.* 1998], one after 15 days [Diamond *et al.* 1998] and one after 16 days [Kolecki, 1997]. Reviewing the literature, we can find little evidence to support the traditional 2-week recommendation. MAO has two subtypes, MAO-A and MAO-B. Although it is believed that 5-HT is preferentially metabolized by MAO-A, MAO-B may also play a significant role in the metabolism of 5-HT, particularly

when MAO-A is inhibited. There is a paucity of human data regarding MAO-A turnover, although there is a report that following irreversible blockade with l-deprenyl, MAO-B recovery has a half life of around 6 weeks [Fowler *et al.* 2005]. How relevant this is to the washout period when switching from a nonselective irreversible antagonist (phenelzine) to an SRI is not known. However, our experience demonstrates that, at least in some individuals, a washout period of even 4 weeks (as has been suggested by some [Ruiz, 1994]), may be insufficient to guard against SS.

While SS has been reported with venlafaxine treatment alone [Pan and Shen, 2003], we think this is not the situation in our patient given the previous use of the drug. It is also not possible to be sure of the role of lithium in this particular instance of SS. Certainly, the combination of lithium plus venlafaxine has been reported as leading to SS [Adan-Manes *et al.* 2006; Bertschy *et al.* 2003; Mekler and Woggon, 1997]. It may be that the combination of continued lithium treatment and possible slow biosynthesis of MAO meant that this patient required a much longer washout period than the standard 2-week recommendation. However, it is important to note that our particular patient had previously been treated with lithium and venlafaxine in combination (375 mg of venlafaxine) without incident. Nevertheless we did decide to withdraw lithium prior to the third attempt at introducing venlafaxine.

In conclusion, this case demonstrates that the standard recommendation of 2-week washout following the use of an irreversible MAOI may be insufficient prior to starting a SRI, and that even after periods as long as 10 weeks symptoms of SS may occur. We would therefore recommend clinicians proceed cautiously when introducing a SRI following MAOI discontinuation, with careful monitoring of patients symptoms such as on an inpatient or day hospital basis, even when this is done more than 2 weeks post-MAOI withdrawal as per current recommendations.

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Conflict of interest statement

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