Antidepressants and the serotonin syndrome in general practice

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SUMMARY

Background. *As a consequence of the greater use of agents affecting the serotonergic system, a syndrome of serotonin hyperstimulation has been recognized more frequently. The serotonin syndrome is characterized by a constellation of symptoms that include mental status changes, agitation, myoclonus, hyperreflexia, sweating, shivering, tremor, diarrhoea, lack of coordination, and fever. Deaths have been reported.*

Aim. *To identify cases of the serotonin syndrome among patients prescribed a new antidepressant in general practice, and to determine doctors' awareness of the syndrome.*

Method. *Patients who were dispensed nefazodone in England between 1996 and 1997 were identified using dispensed prescription data. Prescribing doctors were sent questionnaires as part of a post-marketing surveillance study. Patients reported to have experienced two or more features of the serotonin syndrome were identified, and specific questionnaires were sent to their general practitioners.*

Results. *There was a 96.2% return rate of serotonin syndrome questionnaires. Nineteen cases met criteria for the syndrome (incidence = 0.4 cases per 1000 patient-months of treatment with nefazodone). Eight patients developed symptoms while taking nefazodone alone. Serotonergic symptoms were reported to a similar degree with five other antidepressants studied by the same method. In total, 85.4% of responding general practitioners were unaware of the serotonin syndrome.*

Conclusion. *Improved awareness of the syndrome is needed within general practice. There is a need to distinguish the relatively minor serotonergic symptoms from those of a severe, life-threatening serotonin syndrome.*

Keywords: antidepressants; serotonin; serotonergic system; patient records; questionnaire survey.

Introduction

A GROWING number of serotonergic antidepressants have been marketed, and these are increasingly prescribed in general practice.[1] Serotonin receptors have been demonstrated to have a role in multiple medical and psychiatric conditions, including depression, anxiety, migraine, and vomiting. As a consequence of the greater use of agents affecting the serotonergic system, a syndrome of serotonin hyperstimulation has been recognized more frequently.[2] Case reports describe combinations of myoclonus, rigidity, hyperreflexia, shivering, confusion, agitation, restlessness, coma, autonomic instability, low-grade fever, nausea, diarrhoea, diaphoresis, flushing, rhabdomyolysis, and death.[3] The onset of the serotonin syndrome ranges from minutes after receiving a second serotonergic drug, to weeks, after a stable dose.[2] The most frequent drugs associated with the syndrome have previously been monoamine oxidase inhibitors in combination with other agents. Selective serotonin reuptake inhibitors (SSRIs) have also been implicated in combination with lithium and dextromethorphan.[2]

There have been no population-based studies on the serotonin syndrome. Sternbach reviewed the available literature on animals and humans and suggested diagnostic criteria based on the frequency of reported symptoms.[4] We report 19 cases that meet these criteria, associated with a newly-marketed antidepressant in general practice.

Method

A routine post-marketing surveillance study of nefazodone was conducted by prescription-event monitoring on a cohort of 11 834 patients. The technique has been reported elsewhere.[5-7] Patients were systematically identified by means of dispensed prescription data supplied in confidence by the Prescription Pricing Authority between 1996 and 1997. Questionnaires were sent to the prescribing general practitioners (GPs) six months after the date of first prescription for each patient. Questionnaires requested information on clinical events experienced by patients during treatment. Sternbach's criteria for the serotonin syndrome are shown in Box 1.[4] Criteria involve the presence of three or more specific features. In order to screen for all cases of the syndrome, patients with two or more diagnostic features recorded on the same date and reported either after commencing treatment or increasing the dose of nefazodone were followed up. Patients reported as having taken neuroleptic medication or who had concurrent infection or a metabolic complaint were excluded. Specific questionnaires were sent to patients' GPs requesting more detailed information about symptoms and signs, possible infection, concurrent metabolic disease, concomitant medication, and past medical history.

Prescription-event monitoring studies have been conducted for five additional antidepressants (fluoxetine, sertraline, paroxetine, moclobemide, and venlafaxine) in their immediate post-marketing periods. As with nefazodone, patients with two or more diagnostic features of the serotonin syndrome recorded on the same date (after initiation of treatment or increase in dose) were identified. Incidence rates were calculated and expressed as number of patients per 1000 patient-months of treatment. Rate ratios were calculated with nefazodone as the index drug, using Stata statistical software.[8]

Results

Fifty-three patients treated with nefazodone had two or more diagnostic features of the serotonin syndrome reported on the same date during the study. This compares with similar figures for five other antidepressants (Table 1).

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Sternbach's suggested diagnostic criteria for serotonin sydrome

A. Coincident with the addition of or increase in a known serotonergic agent to an established medication regimen, at least three of the following clinical features are present:

1. Mental status changes (confusion, hypomania),
2. Agitation,
3. Myoclonus,
4. Hyperreflexia,
5. Diaphoresis,
6. Shivering,
7. Tremor,
8. Diarrhoea,
9. Lack of coordination,
10. Fever.

B. Other aetiologies (e.g. infectious, metabolic, substance abuse, or withdrawal) have been ruled out.

C. A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above.

Box 1. Suggested diagnostic criteria for serotonin syndrome. (Taken from: Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991; **148(6):** 705-713. Reprinted by permission.)

The 53 nefazodone patients were followed up. One patient had died and the records were obtained from the local health authority after obtaining permission from the patient's doctor. Fifty-two questionnaires were sent to GPs for the remaining patients and 50 (96%) were returned. Follow-up data were therefore available for 51 patients. Twenty-eight cases failed to meet the diagnostic criteria after follow-up (20 had fewer than three diagnostic features, five had concurrent infection, one had started taking chlorpromazine, one had thyrotoxicosis, and one had insulin-dependent diabetes mellitus). In four additional cases, time to onset of symptoms was more than two weeks after the start of treatment, and these cases were difficult to assess.

There were 19 cases that met Sternbach's criteria for the syndrome; in which symptoms developed rapidly after the start of treatment with nefazodone (Table 2). The incidence rate for the serotonin syndrome as defined was 0.4 cases per 1000 patient-months of treatment with nefazodone.

Sixteen of the 19 (84%) patients meeting criteria for the serotonin syndrome were female and three (16%) were male. The proportion of the original cohort (11 834 patients) who were dispensed nefazodone was 62% female and 38% male. The mean age of the 19 patients was 50 (years (SD = 20) compared with the mean age of 45 (years (SD = 16) for the original cohort. Eleven (58%) patients took another antidepressant before treatment with nefazodone. Table 2 also lists concomitant medication. Seven patients took nefazodone alone, and five of these had received no previous antidepressant. All five patients developed symptoms on 200 mg nefazodone daily; less than the 400 mg daily dose recommended for maintenance therapy.[9]

Twenty of the original 53 cases followed up failed to meet Sternbach's criteria for the serotonin syndrome because they had less than three specified features. However, each patient experienced a combination of serotonergic symptoms. One patient died. This 71 year-old female had known rheumatic heart disease but was otherwise in good general health. She took no regular medications. She was treated with sertraline following a bereavement. Sertraline was withdrawn after three days as a result of headache and nausea. One week later the patient started nefazodone. Three weeks later the entry in the record read, 'having to open bowels four times in the morning ?secondary to nefazodone — not really a problem'. The next entry dated four weeks later reported 'confusion, dizziness, and hallucinations. Getting these since taking nefazodone: stop.' Nefazodone was discontinued on the same date but the patient collapsed in asystolic arrest the same day. The postmortem report commented, 'despite the history of confusion, examination of the brain showed no evidence of acute infarction or haemorrhage'. The report concluded, 'Although rheumatic heart disease does not usually lead to sudden death, it nonetheless can, on occasion, be associated with sudden death, and I am forced to conclude that this has been the case here. There is insufficient evidence of coronary artery atheroma to implicate coronary artery disease.'

The questionnaires asked GPs whether they were aware of the serotonin syndrome. Forty-eight doctors returned 50 follow-up questionnaires (two doctors each had two patients). Forty-one (85%) of the responding doctors were unaware of the serotonin syndrome and seven (15%) were aware.

Discussion

There have been no population-based studies of the serotonin syndrome in humans, and reviews have been based primarily on anecdotal case reports.[3,4] The advantages and disadvantages of prescription-event monitoring have been described elsewhere.[5]

The principal disadvantages of the method are that not all of the questionnaires sent out are returned, and the quality of the information available depends upon the quality of information that is recorded and available to the GPs in their notes and computerized records. However, the information yield is considerable, and 65 prescription-event monitoring studies have now been completed, with a mean cohort size of 11 055 patients. Overall, 57.6% (95% CI = 57.3–57.8) of the questionnaires sent out in these 65 studies have been returned.

All patients who are dispensed a monitored drug are systematically identified during prescription-event monitoring, and duration of treatment is reported for each individual. Incidence rates can be calculated for all reported events and particular cases followed up. A response rate of 96% for the serotonin questionnaire reflects both the interest and concern experienced by GPs. The

Table 1. Patients with two or more reported diagnostic features of the serotonin syndrome; incidence rates, and rate ratios using nefazodone as the index drug.

Drug	Cohort	Patients with two or more features (n)	Percentage of cohort	Incidence rate (number per 1000 patient-months of treatment)	Rate ratio (95% CI)
Fluoxetine	12 962	24	0.2	0.5	0.5 (0.3–0.8)
Sertraline	12 734	35	0.3	0.6	0.6 (0.4–0.9)
Paroxetine	13 741	58	0.4	0.9	0.9 (0.6–1.3)
Moclobemide	10 835	26	0.2	0.5	0.5 (0.3–0.9)
Venlafaxine	12 642	50	0.4	0.9	0.9 (0.6–1.3)
Nefazodone	11 834	53	0.5	1.0	1.0

Table 2. Patients with case criteria for the serotonin syndrome.

Age (years)	Sex[a]	Time to onset	Sternbach's criteria	Previous therapy[b]	'Washout' period	Concomitant medication
76	M	<5 days	Confusion, tremor, lack of coordination	None		Sodium valproate, indoramin, bendrofluazide, nizatidine
68	F	<24 hours	Agitation, sweating, shivering, tremor	TA	<5 days	Temazepam, hydroxyzine, paracetamol, codeine phosphate
28	F	<10 days	Agitation, sweating, shivering, tremor	None		Zopiclone, paracetamol/ dextropropoxyphene
49	M	<3 days	Agitation, sweating, tremor, diarrhoea, lack of coordination	SSRI	None	Warfarin
39	F	<12 days	Confusion, agitation, lack of coordination	TA	None	Diazepam
43	M	<24 hours	Confusion, sweating, lack of coordination	SSRI	>14 days	None
27	F	<3 days	Agitation, sweating, shivering, diarrhoea, pyrexia	TA	<5 days	None
37	F	<24 hours	Agitation, tremor, diarrhoea	None		None
76	F	<24 hours	Confusion, tremor, lack of coordination	None		Lansoprazole
73	F	<14 days	Confusion, diarrhoea, lack of coordination	SSRI	None	Lithium
79	F	<2 days	Confusion, shivering, tremor, lack of coordination	TA	>14 days	Omeprazole, amiloride/cyclopenthiazide
80	F	<24 hours	Confusion, tremor, lack of coordination	TA SSRI	Continued	Dothiepin, paracetamol, salbutamol inhaler
43	F	<24 hours	Confusion, tremor, diarrhoea, lack of coordination	SSRI	None	Zopiclone
18	F	<24 hours	Confusion, agitation, tremor	None		None
69	F	<24 hours	Agitation, tremor, lack of coordination	TA	None	Doctor wrote, 'Not sure'
27	F	<24 hours	Confusion, agitation, sweating, shivering, lack of coordination	None		None
37	F	<24 Hours	Sweating, shivering, tremor	None		None
49	F	<24 hours	Confusion, agitation, tremor, lack of coordination	None		None
41	F	<5 days	Confusion, sweating, shivering, pyrexia, lack of coordination	SSRI	None	Dydrogesterone

[a]F = female, M = male; [b]TA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor.

other antidepressants studied by prescription-event monitoring were on the market from 1989 and a detailed follow-up of patients was no longer considered practical.

The serotonin syndrome appears in different gradations of severity, and this will affect recognition and reporting.[4] There were no specific reports of 'serotonin syndrome' in the prescription-event monitoring study of nefazodone, and clusters of events were unrecognized as such by GPs. We followed up all patients with two or more features of the syndrome in order to screen for all possible cases. The data indicate that clusters of serotonergic symptoms occur to a similar degree with all six antidepressants studied by prescription-event monitoring.

The serotonin syndrome has typically been associated with combinations of drugs, although Sternbach's original clinical reports include two patients taking clomipramine alone, four weeks after stopping clorgyline (a monoamine oxidase inhibitor).[4] In our study, seven cases involved nefazodone alone and, of course, the link between the serotonin syndrome and the drug is strongest in these cases. There were no data on over-the-counter drug use, but other agents implicated in the serotonin syndrome are generally 'prescription only' and reporting doctors should have been aware whether patients were taking them.

The results from this study on nefazodone form a small sample and do not allow any conclusions to be drawn on age and/or sex as predisposing factors for the syndrome.

Although the majority of case reports of the serotonin syndrome have involved relatively minor symptoms, several patient deaths have been recorded.[2] There is a need for clinicians to recognize the syndrome and distinguish relatively minor serotonergic symptoms from those of a potentially life-threatening nature. In practice, case assessment can be difficult for a number of reasons. Four patients in our study satisfying Sternbach's criteria discontinued SSRIs immediately before starting nefazodone (no 'wash-out' period, Table 2). Gastrointestinal disturbance, anxiety, agitation, and problems with balance have all been reported with withdrawal of SSRIs.[10] Agitation and confusion may be part of the underlying psychiatric disorder being treated. The majority of cases of the serotonin syndrome resolve within 24 hours of discontinuation of treatment[2] and, in such cases, resolution of symptoms provides a strong indication of a drug-induced event. Twenty patients with two features of the serotonin syndrome still failed to meet diagnostic criteria despite a spectrum of additional serotonergic symptoms. We describe a case report of a patient who died while taking nefazodone. She developed serotonergic symptoms while taking nefazodone but did not satisfy Sternbach's criteria. The current criteria give weight to features rarely measured in general practice. For example, few GPs would routinely test for myoclonus or hyperreflexia when examining a patient with diarrhoea (no GP reported hyperreflexia). This will lead to under-recognition of cases. Improved awareness of the serotonin syndrome may alert clinicians to such signs.

Between 1993 and 1995, the number of prescriptions for depression increased by nearly 30%, mainly as a result of increased prescribing of SSRIs.[1] Doctors may be unaware of the potential for interaction between serotonergic antidepressants with other classes of drugs (e.g. anti-migraine preparations, antiemetics, cough suppressants). Awareness of the serotonin syndrome among prescribing doctors is poor. In this study, 85% of responding GPs reported that they were unaware of the syndrome. It has been argued that heightened awareness of the serotonin syndrome would help to minimize co-prescription of drugs known to have a higher probability of inducing the syndrome, and, if it develops, this same awareness could lead to prompt institution of measures to resolve it.[4] While antidepressants become increasingly used in general practice, improved awareness of the serotonin syndrome is required among prescribing doctors.

This study provides an example of the importance of the early post-marketing safety surveillance of new drugs. It is known that successful product licence applications in the United Kingdom for new drugs containing new active substances have a safety database comprising a median and range of only 1480 (129–9400) volunteers and patients.[11] The chance of spotting a rare adverse drug reaction from numbers of this order of magnitude is obviously small. It is therefore crucial to monitor very carefully the early clinical experience with new drugs. The Committee on Safety of Medicines' yellow card scheme for spontaneous adverse drug reactions reporting does this, but only if doctors suspect the reaction to be a result of the drug and report their suspicions. The only other national surveillance scheme is Prescription-Event Monitoring, which, in England, has now studied 65 new drugs with a mean cohort size of 11 055 patients. Later on in the life of a drug, computerized systems that allow monitoring of a part of the population become important, but it has to be realised that the support that general practitioners give to the Committee on Safety of Medicines' system and Prescription-Event Monitoring is important in protecting the safety of their patients.

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