Serotonin syndrome

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SYNOPSIS

Serotonin syndrome is a toxic state caused mainly by excess serotonin within the central nervous system. It results in a variety of mental, autonomic and neuromuscular changes, which can range in severity from mild to life-threatening. Most cases are self-limiting. Severe serotonin syndrome is nearly always caused by a drug interaction involving two or more 'serotonergic' drugs, at least one of which is usually a selective serotonin reuptake inhibitor or monoamine oxidase inhibitor. Management involves withdrawal of the offending drugs, aggressive supportive care and occasionally serotonin antagonists such as cyproheptadine. Treatment of the condition for which the serotonergic drugs were prescribed should be reviewed.

Index words: selective serotonin reuptake inhibitors, drug interactions, cyproheptadine.

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Introduction

The treatment of depression in Australia has evolved greatly over the last two decades. Tricyclic antidepressant use is decreasing, while the use of selective serotonin reuptake inhibitors (SSRIs) is increasing. In 2001, prescriptions for SSRIs outnumbered those for tricyclics by two to one.[1] Other new antidepressants with serotonergic properties are also being introduced. Although SSRIs and the other 'atypical' antidepressants are generally regarded as having lower toxicity than tricyclics, minor toxic effects are common, and serious toxicity can occur.

Serotonin syndrome refers to a drug-induced syndrome that is characterised by mental, autonomic and neuromuscular changes. It is not an idiosyncratic adverse reaction, but a dose-related range of toxic symptoms that are largely attributable to increasing serotonin concentrations in the central nervous system. Serotonin syndrome was first described in 1955, but during the 1990s reports became increasingly common, as the signs, symptoms, and precipitants became more widely recognised. Although severe cases have been reported with an overdose of a single drug, they usually only occur with a combination of two or more 'serotonergic' drugs (even when each is at a therapeutic dose), presumably leading to an excessive rise in serotonin concentrations. The true incidence of serotonin syndrome is unknown, because of a lack of large case series, a wide spectrum of symptoms and variations in the definition.

Pathophysiology

Serotonin (5-hydroxytryptamine, 5-HT) is synthesised from the amino acid tryptophan. It has central and peripheral effects and there are at least seven different types of serotonin receptors. Centrally, serotonin acts as a neurotransmitter with influences on mood, sleep, vomiting and pain perception. Depression is often associated with low concentrations of serotonin. Peripherally, the primary effect of serotonin is on muscles and nerves. The majority of serotonin is synthesised and stored in the enterochromaffin cells of the gut where it causes contraction of gastrointestinal smooth muscle. Serotonin is also stored in platelets and promotes platelet aggregation. It also acts as an inflammatory mediator.

The pathophysiology of serotonin syndrome remains poorly understood. It is thought to result from stimulation of the 5-HT_{1A} and 5-HT_{2} receptors, and the drug classes implicated in serotonin syndrome reflect this theory. These include serotonin precursors, serotonin agonists, serotonin releasers, serotonin reuptake inhibitors, monoamine oxidase inhibitors (MAOIs) and some herbal medicines (Table 1). Commonly used migraine medications such as sumatriptan and dihydroergotamine are also regarded as 'serotonergic' drugs. There are isolated case reports of mild/moderate serotonin syndrome associated with these drugs. Most cases will involve either an SSRI or an MAOI and at least one other medication. Generally, drugs with two different mechanisms of action on serotonin must be present for a severe serotonin syndrome to develop.

Table 1

Drugs implicated in severe serotonin syndrome*

Drug	*Mechanism*
L-Tryptophan	Serotonin precursor
Selective serotonin reuptake inhibitors	Inhibit serotonin reuptake
Tricyclic antidepressants	Inhibit serotonin reuptake
Monoamine oxidase inhibitors (A>B)	Inhibit metabolism of 5-HT
Pethidine	Serotonin agonist
Tramadol	Inhibits serotonin reuptake
LSD	Partial serotonin agonist
Buspirone	Partial serotonin agonist
Amphetamines and anorectics	↑ 5-HT release & ↓ reuptake
Atypical antidepressants	Various
St John's wort	All of the above?
Lithium	Unknown

* Note: Interactions are more severe between drugs with different mechanisms of increasing serotonin.

Some other drugs may cause serotonin syndrome although how this happens remains unclear. Drugs with effects on catecholamines, tryptamine and dopamine may have secondary effects on serotonin release or reuptake.

Diagnosis

The diagnosis of serotonin syndrome is purely clinical. It is based upon recognising a varied combination of signs and symptoms in the presence of selected 'serotonergic' medications. The diagnosis should not be made without identifying a cause. Serotonin syndrome most commonly occurs after a dose increase (or overdose) of a potent serotonergic drug or shortly after a second drug is added. Some of the drugs involved have very long half-lives (e.g. fluoxetine) and may have been ceased weeks before. There may be a history of recent overdose or use of illicit drugs, particularly ecstasy, amphetamines or cocaine. Herbal medicines may be implicated (St John's wort, ginseng, S-adenosyl-methionine).

The clinical features of serotonin syndrome are highly variable, reflecting the spectrum of toxicity (Table 2). The onset can be dramatic or insidious. The most useful features in the diagnosis of serotonin syndrome are hyperreflexia and clonus (inducible/spontaneous/ocular). However, many patients taking SSRIs may display one or more of the clinical features without gross toxicity.

Investigations are generally unhelpful in the diagnosis of serotonin syndrome, but may assist in treatment and in ruling out a differential diagnosis. The white cell count is often mildly raised and elevations in creatine kinase levels may occur.

The differential diagnosis includes neuroleptic malignant syndrome, dystonic reactions, encephalitis, tetanus, thyroid storm and sepsis, as well as poisoning by anticholinergic drugs, amphetamines, cocaine, lithium, MAOIs, salicylates and strychnine. Serotonin syndrome can also be confused with the withdrawal of antidepressant treatment.[2] Serotonin syndrome and the other agitated deliriums share many clinical features, but clonus, hyperreflexia and flushing are the most specific signs.

Time course/complications

In most cases, serotonin syndrome is a self-limiting condition and will improve on cessation of the offending drugs. Mild to moderate cases usually resolve in 24–72 hours. In severe cases patients require intensive care as the syndrome may be complicated by severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation and/or adult respiratory distress syndrome.

Treatment

Recognising the possibility of serotonin syndrome and diligent supportive care are the mainstays of treatment. All patients with moderate or severe serotonergic symptoms should be admitted to hospital. Those with hyperthermia should be admitted to an intensive care unit. All serotonergic medications should be ceased, and care taken that other precipitants are not inadvertently administered. Intravenous hydration is given, to ensure an adequate output of urine. Careful monitoring of temperature, pulse, blood pressure and urine output is required. Aggressive cooling techniques may be required for hyperthermia. This may involve cool water sprays, ice packs, and even paralysis and ventilation. Benzodiazepines may be used to control seizures and muscle hyperactivity. Specific treatment of hypertension is usually not required.

Table 2

Clinical features of serotonin syndrome

Cognitive	Confusion, agitation, hypomania, hyperactivity, restlessness
Autonomic	Hyperthermia, sweating, tachycardia, hypertension, mydriasis, flushing, shivering
Neuromuscular	Clonus (spontaneous/inducible/ocular), hyperreflexia, hypertonia, ataxia, tremor

Hypertonia and clonus are always symmetrical and are often much more dramatic in the lower limbs.

Serotonin antagonists have been used in management of moderate to severe serotonin syndrome. Cyproheptadine is possibly the most promising drug.[3] The initial dose is 4–8 mg orally. This may be repeated in two hours. If no response is seen after 16 mg it should be discontinued. If there is a response then it may be continued in divided doses up to 32 mg/day (e.g. up to 8 mg four times daily). Other drugs that have been suggested include chlorpromazine and propranolol, but these have more contraindications and adverse effects.

After the patient has recovered reconsider the ongoing treatment of the condition for which the serotonergic drug was prescribed.

Prevention

The prevention of serotonin syndrome involves awareness of the toxic potential of serotonergic drugs. The manufacturer's advice about washout periods should be carefully considered when switching antidepressants and patients should also be educated about possible drug interactions.

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FURTHER READING

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Conflict of interest: none declared