

Serotonin Syndrome and the Anaesthetist

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SUMMARY

Serotonin syndrome results from excessive activation of serotonin (5-hydroxytryptamine; 5-HT) receptors in the nervous system, on the surface of platelets, and on the vascular endothelium. The clinical manifestations are a triad of altered conscious state, autonomic dysfunction, and neuromuscular excitability. Clinical diagnostic criteria remain poorly defined and unvalidated, and there are no available investigations to confirm the diagnosis. The syndrome is caused by the administration of one or more drugs possessing serotonergic activity. Severe forms of the syndrome usually result from overdose, but can be induced by monotherapy. The exact incidence of serotonin syndrome remains unknown, but is likely to be increasing due to increased prescription of selective serotonin reuptake inhibitor antidepressants and tramadol, as well as recreational use of amphetamine-like substances. Serotonin syndrome may complicate the administration of drugs frequently used in anaesthetic practice, including pethidine and tramadol. Although the majority of cases improve with symptomatic and supportive care, severe cases need intensive care and frequently require mechanical ventilation. Neuromuscular excitability is likely to be the cause of rhabdomyolysis seen in severe cases and should be treated with benzodiazepines and muscle relaxants. Supportive therapies are required to treat hyperthermia and autonomic dysfunction. Cyproheptadine is the most commonly administered serotonergic antagonist, but is unavailable in parenteral form.

Key Words: SYNDROME, SEROTONIN: serotonin uptake inhibitors, tramadol, 5-hydroxytryptamine, rhabdomyolysis, cyproheptadine

Serotonin syndrome is a cluster of symptoms and signs resulting from excessive activation of serotonin receptors. The exact incidence of the serotonin syndrome is unknown for several reasons. First, the diagnostic criteria are purely clinical and poorly validated¹. Second, up to 85% of general practitioners prescribing selective serotonin reuptake inhibitor (SSRI) antidepressants are unaware of the serotonin syndrome². Third, milder cases may go unreported by patients. Finally, the clinical features of the serotonin syndrome are relatively non-specific and may be seen in a variety of other settings.

In a post-marketing surveillance study of selective serotonin reuptake inhibitor (SSRI) antidepressants prescribed by general practitioners in the United Kingdom, the incidence of serotonin syndrome was

estimated to be 4 cases per 10,000 patient months of treatment².

Although the serotonin syndrome seems uncommon, the increasing use of agents that act on the serotonergic system may lead to an increase in incidence. Dispensing of oral formulations of tramadol increased from 23,000 in 2000 to 1,100,000 in 2002³. Depression affects 1 in 16 Australians⁴, and from 1998 to 2001, prescription of the various SSRI-antidepressants increased by 13 to 66%⁵. In 2001, prescriptions for the SSRI-antidepressants outnumbered those for tricyclic antidepressants by two to one⁶. Up to 85% of the prescriptions for antidepressant drugs are written by general practitioners⁷, who may have limited knowledge of the syndrome².

In this review we aim to summarize the pathogenesis and diagnostic criteria of the serotonin syndrome. Important differential diagnoses and an approach to treatment are also discussed.

PHYSIOLOGY OF THE SEROTONERGIC SYSTEM

Serotonin does not cross the blood-brain barrier and must be synthesized from dietary L-tryptophan in neurones in the pons and brainstem. The only

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Accepted for publication on December 2, 2004.

peripheral source of serotonin is the intestinal enterochromaffin-like cells⁸. Once synthesized, serotonin is stored in vesicles within platelets and pre-synaptic neurones. There are at least seven different classes and 15 subpopulations of serotonin receptor, based on ligand specificity as well as their distribution and function within the body^{9,10} (Table 1). Receptors act either by functioning as a ligand-gated Na⁺/K⁺ ion channel (5-HT₃ receptors) or by coupling to G-protein (all other subclasses studied)¹¹. Second messenger systems associated with G-protein activation include cAMP (e.g. 5-HT_{1A}) and phosphatidylinositol (e.g. 5-HT_{2A}). In the central nervous system (CNS) serotonin receptors have important functions in mood, alertness, sleep regulation, and thermoregulation. Low levels of serotonin in the CNS have been linked with depression, obsessive compulsive disorder, aggression, anorexia, and impaired sleep latency¹². In the CNS, serotonergic neurones are often co-located with neurones containing neuropeptides (such as substance P and somatostatin) as well as other monoamines (such as dopamine, tyramine, and adrenaline)¹². Serotonergic neurones comprise the major output of the ascending excitatory arousal system from the dorsal raphe nucleus of the mid-brain¹³. Blockade of serotonin receptors, particularly

5-HT_{2A} subtypes, results in depression and drowsiness. Similarly, activation of these receptors is thought to produce the agitation observed in the serotonin syndrome¹¹.

AETIOLOGY AND PATHOGENESIS

The peripheral clinical manifestations of the serotonin syndrome are similar to those seen in patients with carcinoid crisis (the severe form of the carcinoid syndrome). In carcinoid syndrome there is an increased production of serotonin from enterochromaffin-like tumour cells¹⁴. Central manifestations such as altered conscious state and confusion are much less common in carcinoid syndrome than the serotonin syndrome, because serotonin does not cross the blood-brain barrier. Serotonin syndrome is most commonly due to drugs that either increase the availability of serotonin at the neural endplate¹⁵ or lead to direct receptor activation^{16,17}. Increased availability of serotonin at the endplate may occur by a number of mechanisms^{8,16-18} (Table 2). The clinical manifestations arise principally from activation of the 5-HT_{1A} and 5-HT_{2A} receptor subtypes. Activation of receptors in the raphe nucleus of the brainstem and frontal cortex produce alterations in conscious state⁸. Serotonin neurones (esp via 5-HT_{1A}) have also been

TABLE 1
*Location and function of serotonin receptor subclasses implicated in the serotonin syndrome**

Receptor subclass	Anatomical location	Function and clinical implications
5-HT _{1A}	Dorsal raphe nucleus projecting to frontal cortex Median raphe nucleus projecting to hippocampus, cortical limbic areas, amygdala, and lateral hypothalamus. Skeletal muscle	ascending excitatory arousal system hypothalamic cardiovascular and thermoregulatory control muscle differentiation increased glucose uptake
5-HT _{1B}	Presynaptically in substantia nigra, globus pallidus, and dorsal subiculum	thermoregulation, respiration, appetite control, aggression, anxiety
5-HT _{2A}	Smooth muscle cells Cell surface of platelets Endothelium Post synaptic neurones of frontal cortex	vasoconstriction platelet aggregation and degranulation increased capillary permeability increased release of nitric oxide appetite control, thermoregulation, sleep, and pathogenesis of depression and anxiety
5-HT _{2B}	Pulmonary vasculature Skeletal muscle	pulmonary arterial vasoconstriction increased muscle contractions
5-HT ₃	Chemo-receptor trigger zone in area postrema Frontal cortex and hippocampus	emesis agonists may help in treating anxiety, depression, memory loss and dementia
5-HT ₄	Stomach and small bowel Hippocampus	receptor activation increases gastric and intestinal peristalsis receptor levels markedly decreased in patients with Alzheimers disease

*Table compiled from previously published information^{9-11,19}.

implicated in hypothalamic control of cardiovascular function and thermoregulation¹¹. Hypertension, circulatory shock and fever have all been described as manifestations of the serotonin syndrome¹⁰. Peripherally, serotonin modulates vascular tone in the systemic¹¹ (5-HT_{2A}) and pulmonary¹⁹ (5-HT_{2B}) circulations, and also increases platelet aggregation and intestinal peristalsis. Right heart failure²⁰, disseminated intravascular coagulation and diarrhoea have all been described in the serotonin syndrome¹⁰.

The precise mechanism of death from severe cases of serotonin syndrome is unknown. Case reports of fatality often include severe rhabdomyolysis, disseminated intravascular coagulation, as well as renal failure and circulatory failure²¹⁻²⁵. It is likely that patients die from a combination of these factors.

Serotonin syndrome may be associated with drugs that are commonly prescribed for patients undergoing anaesthesia (Table 2). The syndrome may result from combinations of these agents taken in therapeutic doses, or from a single agent taken in overdose¹⁸. Severe forms of the syndrome are usually seen in massive overdoses, or when overdose involves the presence of an uptake inhibitor such as moclobemide (MAO inhibitor) or an SSRI-antidepressant^{3,18}. However, severe cases may be seen with monotherapy^{3,24}.

CLINICAL FEATURES AND DIAGNOSIS

The diagnosis of the serotonin syndrome is clinical and confirmed when a patient displays symptoms of the syndrome following commencement or dose increase of drugs that act on the serotonergic system (Table 3). The clinical features of serotonin syndrome can be described under the categories of alterations in conscious state, autonomic function, and neuromuscular status (Table 4). The presence of fever, altered conscious state, autonomic instability and increased limb rigidity (especially in the lower limbs) in a patient on drugs with serotonergic activity should strongly raise the possibility of the diagnosis. The requirement for three of the eleven clinical features to be present to confirm the diagnosis is arbitrary, and based on the original suggested diagnostic criteria²⁹.

The differential diagnosis for serotonin syndrome is extensive^{30,32-36} (Table 5). Because the manifestations of many of the differential diagnoses include altered conscious state, autonomic instability, or neuromuscular hyperactivity, diagnosis of serotonin syndrome can be difficult^{8,10}. Accordingly, emphasis should be placed upon obtaining an accurate history of the nature of the substances ingested. Differentiating the serotonin syndrome from neuroleptic

TABLE 2
Medications commonly implicated in inducing the serotonin syndrome

Mechanism of induction	Example	Clinical use of medication
Increased 5-HT release	Amphetamines and Ecstasy	
	Ethanol Cocaine Dopamine agonists L-dopa ²⁶ Bromocryptine	Local anaesthetic
Reduced 5-HT uptake	SSRI ²⁷	Parkinsons disease Treatment of NMS* and prolactinoma Depression, anxiety disorder, PTSD‡
	Fluoxetine, sertraline, Paroxetine TCA† Amitriptyline, imipramine Tramadol ³ St. Johns wort Pethidine	Depression, neurogenic pain analgesic non-prescription antidepressant opioid analgesic
Reduced 5-HT catabolism	MAO§ inhibitor Moclobemide Selegeline Linezolid ²¹ St. Johns wort	Depression and anxiety disorder Parkinson's disease Antibiotic for treatment of MRSA#
Direct activation of 5-HT receptors	Lithium Sumatriptan Pethidine ⁶ LSD	bipolar disorder migraine
Other	Olanzapine	Atypical antipsychotic

*NMS = neuroleptic malignant syndrome
‡PTSD = post-traumatic stress disorder
†TCA = tricyclic antidepressant
§MAO = monoamine oxidase
#MRSA = methicillin resistant Staphylococcus aureus

TABLE 3
*Diagnostic criteria for serotonin syndrome**

1. Onset of symptoms following commencement or increase in dosage of serotonergic drug
 - a. This may also include introduction of a drug, which is known to interact with and enhance the effects of a pre-existing serotonergic drug
2. Clinical features consistent with the syndrome (a minimum of 3 of the following 11 features)
 - a. change in conscious state
agitation, confusion, coma
 - b. Autonomic dysfunction
fever, diaphoresis, diarrhoea, shivering
 - c. Neuromuscular changes
Hyperreflexia, incoordination, tremor, myoclonus
3. Other aetiologies have been excluded (infectious, metabolic, substance overdose and withdrawal)
4. No introduction or alteration in dosage of neuroleptic anti-psychotic medication prior to the onset of these symptoms

*Criteria represent a composite of those previously published^{8,16,17,29,31,32}.

TABLE 4
*Clinical manifestations of the serotonin syndrome**

Alterations In Conscious State

Confusion and disorientation>agitation>coma>anxiety, hypomania>lethargy>seizures>hallucinations

Autonomic dysfunction

Hyperthermia, sweating, tachycardia>hypertension, dyspnoea>dilated pupils>non-reactive pupils>flushed skin>hypotension>diarrhoea>abdominal cramps and salivation

Neuromuscular changes

Myoclonus and hyperreflexia>muscle rigidity (especially in the lower limbs) and tremor>ataxia and incoordination>shivering>nystagmus

Other

Rhabdomyolysis, acute renal failure, disseminated intravascular coagulation, metabolic acidosis, death.

*The relative frequency of each feature is derived from the series described by Mills¹⁰.

malignant syndrome (NMS) is important for two reasons. First, dantrolene^{32,33} has been successfully used to treat NMS but has not been shown to be of benefit for serotonin syndrome. Second, chlorpromazine has been advocated as a potential therapy for the serotonin syndrome³⁸, but is contraindicated in a patient with suspected NMS. Other important differentials to entertain include sepsis and malignant hyperthermia, as their treatment also differs from that of the serotonin syndrome.

MANAGEMENT OF SEROTONIN SYNDROME

There are no prospective randomized controlled trials for the management of the serotonin syndrome²⁹. Management principles, based largely on case series, include supportive measures, specific anti-serotonergic therapies, and therapies directed toward the neuromuscular excitability (Table 6). In

a case series of 127 patients, 70% of patients with serotonin syndrome recovered in 24 hours, 40% required intensive care admission, and 25% required mechanical ventilation¹⁰.

Mild cases usually respond to cessation of the culprit drugs and may not require hospital admission. Patients with progressive cognitive changes, fever, autonomic instability, or neuromuscular excitability should be admitted to hospital and referred to intensive care. The mainstay of managing increased muscle tone is neuromuscular paralysis and benzodiazepine infusions. Although it is unknown how important it is to control increased muscle tone early on, it is likely to be the cause of the rhabdomyolysis seen in severe cases of the syndrome¹⁰. Haemodynamic support of severe cases usually requires vasopressor therapy for hypotension. Hypertension and tachycardia may also be seen, especially in milder cases. The β -blocker propranolol is usually used in such cases, partly because of its actions as a 5-HT_{1A} antagonist^{8,16}.

The most widely prescribed 5-HT antagonist is cyproheptadine, which can only be given orally or via nasogastric tube. Cyproheptadine acts primarily on 5-HT₂ receptors, and produces rapid (within one hour) resolution of symptoms, particularly of the CNS effects⁴². Because of recurrence of symptoms, a dose of 4-8 mg should be given every 1-4 hours⁴⁰. Ketanserin also has anti-serotonergic properties but is not readily available in Australia. Chlorpromazine should not be routinely used to manage serotonin syndrome, especially if the patient is hypotensive and/or NMS can not be excluded. If chlorpromazine is used, careful titration of dose is suggested (starting at 25 mg) because of the potential to induce hypotension.

SEROTONIN SYNDROME AND THE ANAESTHETIST

Although the serotonin syndrome is uncommon, it may complicate the administration of drugs frequently used in anaesthetic practice. Given the lack of information regarding individual susceptibility and dose-responsiveness for activation of the syndrome, anaesthetists should consider avoiding the use of combinations of drugs known to precipitate the syndrome. This will often mean avoiding drugs such as tramadol or pethidine in patients who are taking SSRI-antidepressants or monoamine oxidase (MAO) inhibitors. It is conceivable such that a patient given tramadol intra-operatively may develop fever, tachycardia, and increased muscle tone, leading to concerns about the possibility of malignant hyperthermia. Unexplained fever, agitation, increased limb

TABLE 5
Differential diagnosis of the serotonin syndrome

Differential diagnosis	Features supporting diagnosis over serotonin syndrome
<i>Overdose/toxic states</i>	
Neuroleptic malignant syndrome ^{32,33}	History of ingestion of neuroleptic antipsychotic medications Onset and resolution over days to weeks Hypersalivation, mutism, fever, and incontinence more common Rigidity is lead pipe rather than myoclonic Agitation, confusion, hyperreflexia and myoclonus are uncommon ⁵ Rhabdomyolysis, leukocytosis, metabolic acidemia, and elevated hepatic transaminases more common
Anticholinergic syndrome ³⁴	History of use of TCAs or anaesthetic agents with anticholinergic activity Dry mouth, blurred vision, flushed skin, urinary retention, emesis, dizziness Prolonged QRS, ventricular arrhythmias (uncommon in serotonin syndrome), conduction blocks Hallucinations, choreo-athetoid movements relatively common Detection of agents in urine and response of features to physostigmine
MAOI syndrome/cheese reaction ³⁵	Onset is usually delayed and slow to progress Features persist following withdrawal of agent Hypertension is marked Hypotension is late and occurs following catecholamine depletion
Lithium	Onset of symptoms 1-4 hours after ingestion Nausea, vomiting, diarrhoea predominate in the initial phases Hyperglycaemia, glycosuria, and nephrogenic diabetes insipidus (confusion, ataxia, tremors, myoclonus and coma may occur) Falsely elevated serum Cl ⁻ with low anion gap
<i>Infective states</i>	
Meningo-encephalitis ³⁶	Variable onset of headache, fever, nuchal rigidity, nausea, vomiting and photophobia. Seizures may occur Diffuse rigidity/myoclonus uncommon Petechial rash of meningococcus may occur Blood cultures, CSF, CT or MRI may help distinguish Focal cranial nerve signs and papilledema
Severe sepsis ³⁶	Hypotension, WBC >20,000 cells/ μ l (uncommon in serotonin syndrome ³⁷) toxic changes on blood film, detection of organisms or polymorphs in sterile body fluid. Radiographic evidence of focal infection
Tetanus ³⁶	Seen in inadequately immunized individuals following puncture wounds, lacerations or abrasions Muscle rigidity predominates, initially in the head and neck and then the back and proximal muscles. Patients develop severe muscle spasms which are increased with provocation Conscious state is relatively preserved and autonomic dysfunction is typically seen in only severe cases Identification of organisms or spores from wound
<i>Metabolic states</i>	
Hyperthyroidism	Eye signs, subacute onset, rhabdomyolysis and D.I.C. uncommon Thyroid function tests diagnostic
Malignant hyperthermia ³⁰	Patient may have a family history of the condition Follows administration of halogenated volatile anaesthetic agents or depolarizing muscle relaxant agents Sudden onset of sinus tachycardia, ventricular tachycardia or cardiac arrest Rapid rise in ET CO_2 in intubated patients Profuse perspiration and hyperthermia, metabolic and respiratory acidosis Hypoxaemia, elevated Ca ⁺⁺ and K ⁺
Hypoglycaemia	Tachycardia, confusion and agitation, sweating

tone, or incoordination in postoperative patients receiving serotonergically acting drugs should also raise the possibility of the diagnosis.

Further research is required to more accurately

define the incidence of the serotonin syndrome. In addition, work is needed to determine a dose-responsiveness for its activation with administration of various drugs, particularly when they are used in com-

TABLE 6
Management of the serotonin syndrome

Principle	Comments
<i>Diagnostic tests</i>	
Drug screen	urine for amphetamines and cocaine serum for TCAs
TFTs	investigation for hyperthyroidism
culture of body fluids (including CSF) and appropriate radiological imaging	work-up for septic state
serum glucose	to test for hypoglycaemia
Investigations for complications	CK, clotting studies, fibrinogen and d-dimer levels, U&E, renal function, calcium, phosphate, ABGs, LFTs
<i>Supportive therapies</i>	
Stop offending agent(s) and consideration of charcoal lavage	most patients improve with supportive therapy only
Intravenous fluids and/or NaHCO ₃ to prevent renal dysfunction from myoglobinuria	
Active cooling for hyperthermia	
FFP, cryoprecipitate for D.I.C.	
Renal replacement therapy for ARF and to dialyse lithium	
Intubation and mechanical ventilation	for impaired conscious state
<i>Specific anti-serotonergic therapy</i>	
Cyproheptadine ³⁹⁻⁴³ 4-8 mg every 1-4 h to max 32 mg ⁴⁰	cyproheptadine is a 5-HT ₂ >5-HT ₁ receptor antagonist only available in enteral formulation and may have anticholinergic side effects that are potentiated by MAO inhibitor ³⁹
Methysergide ²⁹ 2 mg bd	therapy described in case reports only
Chlorpromazine ^{15,38} 25-100 mg I.M.	has the advantage of I.M. administration 70% potency 5-HT _{2A} and 5-HT _{2B} receptor antagonism compared to cyproheptadine ⁵ should not be given if patient is hypotensive or NMS is suspected ²
Ketanserin ⁴⁴	1.8 times more potent 5-HT _{2A} antagonist than cyproheptadine ⁵ has been used intravenously (10 mg boluses) for the treatment of carcinoid syndrome ³¹
<i>Haemodynamic therapy</i>	
Fluid and vasopressor administration for hypotension	
β-blocker therapy for hypertension and tachycardia	blockade of sympathetic overactivity propranolol is also a 5-HT _{1A} antagonist ^{6,8}
Propranolol 20 mg tds ^{1,3,6,8}	
<i>Treatment of neuromuscular abnormalities</i> ¹⁰	
Benzodiazepines	
Diazepam or midazolam most commonly used	reduce muscle spasms and treat seizures
Neuromuscular paralysis	aims to counter myoclonus to prevent rhabdomyolysis

bination. An appropriate starting point for such epidemiological research may be a central registry of cases.

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