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The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity

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Summary

Background: There are difficulties with the diagnosis of serotonin toxicity, particularly with the use of Sternbach's criteria.
Aim: To improve the criteria for diagnosing clinically significant serotonin toxicity.
Design: Retrospective analysis of prospectively collected data
Methods: We studied all patients admitted to the Hunter Area Toxicology Service (HATS) following an overdose of a serotonergic drug from January 1987 to November 2002 ($n = 2222$). Main outcomes were: diagnosis of serotonin toxicity by a clinical toxicologist, fulfilment of Sternbach's criteria and treatment with a serotonin receptor ($5\text{-}HT_{2A}$) antagonist. A learning dataset of 473 selective serotonin reuptake inhibitor (SSRI)-alone overdoses was used to determine individual clinical features predictive of serotonin toxicity by univariate analysis. Decision rules using CART analysis were developed, and tested on the dataset of all serotonergic overdose admissions.
Results: Numerous clinical features were associated with serotonin toxicity, but only clonus (inducible, spontaneous or ocular), agitation, diaphoresis, tremor and hyperreflexia were needed for accurate prediction of serotonin toxicity as diagnosed by a clinical toxicologist. Although the learning dataset did not include patients with life-threatening serotonin toxicity, hypertonicity and maximum temperature $> 38°C$ were universal in such patients; these features were therefore added. Using these seven clinical features, decision rules (the Hunter Serotonin Toxicity Criteria) were developed. These new criteria were simpler, more sensitive (84% vs. 75%) and more specific (97% vs. 96%) than Sternbach's criteria.
Discussion: These redefined criteria for serotonin toxicity should be more sensitive to serotonin toxicity and less likely to yield false positives.

Introduction

Serotonin (5-hydroxytryptamine or 5-HT) is a neurotransmitter, discovered in 1948,[1] and thought to have a major role in multiple states including aggression, pain, sleep, appetite, anxiety, depression, migraine, and emesis.[2,3] Serotonin in the body is derived from dietary tryptophan, which is converted by a number of enzymes to 5-HT. It is then transported into cells by a specific transport

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1. Recent addition or increase in a known serotonergic agent
2. Absence of other possible aetiologies (infection, substance abuse, withdrawal, etc.)
3. No recent addition or increase of a neuroleptic agent
4. At least three of the following symptoms:
   - Mental status changes (confusion, hypomania)
   - Agitation
   - Myoclonus
   - Hyperreflexia
   - Diaphoresis
   - Shivering
   - Tremor
   - Diarrhoea
   - Incoordination
   - Fever

Figure 1. Sternbach's criteria.[3]

system and is degraded mainly by monoamine oxidase (MAO) both within the cell and after release. The MAO-A isoenzyme is more important than the MAO-B isoenzyme in the degradation of serotonin. The breakdown products are excreted in the urine as 5-hydroxyindole acetic acid (5-HIAA).

Central nervous system (CNS) serotonin excess as a clinical problem in humans was first noted by Oates and Sjostrand.[4] They reported patients who developed symptoms after receiving tryptophan while on therapy with a monoamine oxidase inhibitor (MAOI). Insel described two further cases in patients receiving a MAOI and a tricyclic antidepressant.[5] In 1991, Sternbach reviewed 38 cases from 10 case reports and two case series published in the literature, from which he derived diagnostic criteria for what was termed the serotonin syndrome.[3] This was defined as the presence of three or more of the 10 most common clinical features in these case reports (Figure 1), coincident with the addition of or increase in a known serotonergic agent.[3] Other aetiologies needed to have been ruled out and a neuroleptic agent should not have been given.

A significant problem with Sternbach's criteria is the inclusion of four criteria that relate to mental status, which weights the definition towards patients with an abnormal mental state. Sternbach's criteria include confusion, hypomania, restlessness and ataxia (incoordination). Because only three are required to occur for the diagnosis of serotonin syndrome to be made, someone with an anticholinergic delirium would meet the clinical criteria. Ataxia or incoordination is also a problematic feature, since serotonin toxicity does not appear to cause cerebellar features, and any patient who is agitated and confused may appear to be ataxic.

Sternbach recognized the likelihood of reporting bias inherent in reviewing disparate case reports and series.[3] His diagnostic criteria were based upon the categorical presence of symptoms and signs described in published cases, and therefore were unable to include clinical features that may have been present but not recognized by the original authors as related to serotonin toxicity. Despite these concerns, there are increasing numbers of case reports and case series of serotonin syndrome, which are generally based on Sternbach's criteria but may also include other symptoms and signs.

Serotonin excess is best thought of as a spectrum of toxicity, rather than a defined clinical entity (syndrome) with clear prognostic importance.[6] To reflect this, we will henceforth refer to the toxic effects of serotonin excess as serotonin toxicity rather than serotonin syndrome. Serotonin toxicity results from an increase in the intrasynaptic concentration of 5-HT in the CNS. Thus it is a concentration-dependent toxicity that can develop in any individual, rather than an idiosyncratic reaction to a drug such as the neuroleptic malignant syndrome[7] or dystonic reactions. Serotonin toxicity can be thought of as a triad of clinical features consisting of: (i) autonomic signs, (ii) neuromuscular changes and (iii) altered mental status.[8,9] Omitting any of these parts in the assessment of the patient may lead to an inaccurate diagnosis of serotonin toxicity and false assumptions about the most useful diagnostic symptoms. This has resulted in increasing confusion about which medications can cause serotonin toxicity, with misleading case reports that misattribute serotonin toxicity to a number of unlikely drugs.[6,10,11] In some cases this has led to reports of serotonin toxicity for drugs that, from well-defined receptor binding studies,[12] are unlikely to

cause increased levels of CNS 5-HT. Important examples include the 5-HT_{2A} receptor antagonist olanzapine[11,13,14] and the 5-HT receptor antagonist mirtazapine.[10,15,16]

In addition, the currently ill-defined features of serotonin toxicity have misled many authors into suggesting that it is similar to neuroleptic malignant syndrome (NMS) and should be a differential diagnosis for it. A careful assessment of the clinical features of these two reveal this is clearly not the case, with both the time course and particularly the clinical features of NMS differing significantly from those of serotonin toxicity.[6,17] That such confusion arises suggests that serotonin toxicity is currently too incompletely defined to be a prognostically useful clinical diagnosis. Describing serotonin toxicity as a syndrome maintains these potentially unhelpful assumptions and has led us to prefer the term serotonin toxicity.

Others have had concerns about the Sternbach criteria, and several attempts have been made to amend the original criteria. Two such attempts were conducted with the purpose of developing a severity grading. Hegerl *et al*. developed and validated a serotonin toxicity scale for side-effects in depressed patients treated with paroxetine.[18] Their scale was based on a grouping of symptoms with some grading of severity. Their score was positively correlated with paroxetine concentration, and inversely correlated with auditory evoked potential (an indirect measure of serotonergic activity). While this work has limitations in its applicability to patients with self-poisoning, the correlation of drug concentration with serotonergic symptoms is encouraging. A second paper by Randomski, covering the period between 1991 and 1995, conducted a further review of 24 cases since Sternbach's paper.[19] This paper divided cases into: (i) a mild state of serotonin-related problems; (ii) serotonin syndrome; and (iii) toxic states.

Many cases of serotonin toxicity occur in patients who have ingested drug combinations that synergistically increase synaptic 5-HT. The most important is the interaction between MAOIs and drugs with serotonin reuptake inhibiting activity, such as the selective serotonin reuptake inhibitors (SSRIs), which can cause life-threatening serotonin toxicity.[20,21] Serotonin toxicity has been reported following ingestion of a single agent[22] and occurs in 16% of patients ingesting SSRIs in overdose.[23] Thus in developing criteria to diagnose serotonin toxicity, it is important to review both pure serotonergic drug effects (e.g. SSRI-alone overdoses) and drug interactions involving excess serotonin.

We have developed criteria for the diagnosis of clinically significant serotonin toxicity using decision rules, based on consecutive patients admitted to the Hunter Area Toxicology Service (HATS). We determined the clinical features that were significantly associated with patients diagnosed by a clinical toxicologist to have serotonin toxicity, and analysed these using a 'decision tree' algorithm to develop decision rules. To reduce the confounding effects of co-ingested drugs with other than serotonergic actions, the initial dataset was of overdoses of a single SSRI. This was done to obtain features arising from a purely serotonergic drug. To determine the accuracy of these decision rules, a further dataset was used, including any overdose with a serotonergic agent (no exclusions), to test the sensitivity and specificity of the new criteria. The second dataset included the original dataset, and is representative of the spectrum of serotonergic drug overdose presenting to a toxicology treatment unit. The dataset was also searched for life-threatening cases to determine which features were associated with severe serotonin toxicity.

Methods

The HATS is a regional toxicology unit situated at the Newcastle Mater Misericordiae Hospital that serves a population of about 350 000 people and is a tertiary referral centre for a further 150 000 people.[24] All presentations and admissions to HATS with drug overdose are prospectively entered into a clinical database.[25] A preformatted admission sheet is used by medical staff to collect data on admission,[26] and this together with additional information from the medical record is entered into the database by two independent trained personnel who are blinded to any hypotheses being tested at the time.

Detailed demographic and clinical information is recorded. From this dataset, all cases of serotonergic poisoning admissions from 13 January 1987 to 22 November 2002 were identified, and the following information was obtained: details of overdose, clinical effects (temperature, heart rate [HR], blood pressure [BP], Glasgow Coma Score [GCS], akathisia, nystagmus, skin colour, oculogyric crisis, mydriasis, confusion, bowel sounds, ataxia, hallucination, clonus, seizures, myoclonus, diarrhoea, delirium, diaphoresis, reflexes, lacrimation, muscle tone, rhabdomyolysis, shivering, agitation, tremor) and evidence of serotonin toxicity using three different definitions (clinical assessment by the admitting clinical toxicologist, Sternbach's criteria,[3] and use of a 5-HT_{2A} antagonist to treat serotonin toxicity).

Two different datasets were extracted from the HATS database, all containing the same information as above.

Derivation dataset: SSRI-alone overdose

Consecutive SSRI-alone poisoning admissions were extracted from the HATS database between 13 January 1987 and 22 November 2002, based on a history of an SSRI alone being ingested. All admissions where a TCA, MAOI, venlafaxine, nefazodone, or lithium were coingested were excluded, as well as cases where two SSRIs were coingested. In addition, any cases where anti-serotonergic drugs were coingested were also excluded, including cyproheptadine, chlorpromazine, pericyazine, clozapine, olanzapine, quetiapine, risperidone, droperidol, flupenthixol, fluphenazine, pimozide, tetrabenazine, thiethylperazine, thioridazine, trifluoperazine, and zuclopenthixol.

Test dataset: All serotonergic drug overdoses

A dataset of overdoses with any serotonergic drug was obtained from the HATS dataset for the same time period. This included the patients in the above derivation dataset. No exclusions were applied to this dataset.

Life-threatening cases

Life-threatening cases were defined as those requiring endotracheal intubation and assisted ventilation for the management of serotonin toxicity. A review of these patients was undertaken and the clinical features were recorded.

Statistical analysis

Univariate analyses for the outcome variable (based on the diagnosis of serotonin toxicity by a clinical toxicologist) against the predictor variables was conducted using a χ^2 test (or Fisher's exact test where appropriate) for categorical predictor variables or a t-test for the continuous variable. All univariate analyses were conducted using the statistical software SAS version 8.2.[27]

Because of the size of the data set and the large number of predictor variables, it was not possible to use logistic regression to build a multivariate model for each of the outcome variables. As an alternative to logistic regression, the data was analysed using the software package CART (Classification And Regression Trees).[28] CART is a 'decision tree' algorithm that creates a tree-like structure, using statistics rather than experience, to describe a dataset. The decision tree is created by recursively partitioning the dataset into subsets, where the distribution of the outcome variable is successively more homogeneous. This procedure is continued on each subgroup until some minimum subgroup size (default is five) is reached. From the fully-grown tree, a sequence of simpler trees is then constructed by combining subgroups relatively similar to one another. To assess the performance of each tree in this sequence, CART uses cross-validation. The final tree presented is the one that minimizes the overall cross-validated relative error estimate that most accurately predicts data excluded from forming the tree.

One way of interpreting the final decision tree is through a series of 'if-then' decision rules. We consider that presenting the CART results in such a manner is preferable (to a decision tree) because the solutions are more intuitive.

Note that both univariate and multivariate analyses were conducted on the data set containing SSRI overdoses only. However, testing of the decision rules was conducted on the complete data set.

Results

There were 9960 admissions to HATS in the study period. Of these, there were 2222 where at least one serotonergic drug was ingested in overdose.

SSRI-alone overdoses

After excluding nine admissions where two SSRIs were coingested, there were 473 admissions for a single-agent SSRI (SSRI-alone overdose) that also met the criteria discussed in Methods. Of these 473, 73 (15.4%, 95%CI 12.3–19.0) had a diagnosis of serotonin toxicity made by a clinical toxicologist, 70 (14.8%, 95%CI 11.7–18.4) met Sternbach's criteria and 44 (9.3%, 95%CI 6.8–12.3) were treated with a 5-HT_{2A} antagonist.

Univariate analysis of SSRI-alone overdoses

The following categorical variables had a statistically significant association with the diagnosis of serotonin toxicity made by a clinical toxicologist (5% level of significance): hypertension on admission ($p = 0.007$), tachycardia on admission ($p < 0.001$), maximum temperature >38°C ($p = 0.026$), seizure ($p = 0.004$), agitation ($p < 0.001$), akathisia ($p = 0.033$), ataxia ($p = 0.025$), delirium ($p < 0.001$), diaphoresis ($p < 0.001$), diarrhoea ($p < 0.001$),

hyperreflexia ($p<0.001$), inducible clonus ($p<0.001$), mydriasis ($p<0.001$), myoclonus ($p<0.001$), nystagmus ($p=0.009$), ocular clonus ($p<0.001$), shivering ($p<0.001$), spontaneous clonus ($p<0.001$), tremor ($p<0.001$), bowel sounds ($p<0.001$), skin appearance ($p=0.003$), and peripheral hypertonicity ($p<0.001$). The continuous variable age ($p=0.004$) also had a statistically significant association with the diagnosis of serotonin toxicity.

Decision rules

The decision rules, shown in Figure 2, reveal that only the following variables were required for accurately predicting serotonin toxicity: spontaneous clonus, inducible clonus, ocular clonus, agitation, diaphoresis, tremor and hyperreflexia. Rule 5 was added to make sure that the decision rules included patients with severe and life-threatening serotonin toxicity, characterized by high temperature (> 38°C) and hypertonicity/rigidity (see results below). The otherwise highly discriminating neuromuscular features of clonus and hyperreflexia are often not demonstrable in patients with severe rigidity; therefore rule 5 was added despite the fact it was not determined by CART. These life-threatening cases were not included in the learning dataset of SSRI-alone overdoses, because they occur with combinations of serotonergic agents.

Univariate analyses (not shown for Sternbach's criteria and use of 5-HT_{2A} antagonist) confirmed that all of these variables are statistically significant predictors (at the 5% level of significance) of the three outcome variables, the only exception being that maximum temperature was not a statistically significant predictor for use of 5-HT_{2A} antagonist. This is an expected result because high temperature is associated with severe toxicity, which was uncommon in the learning dataset that consisted of SSRI-alone overdoses.

The decision rules were applied to the complete dataset, and were compared to the three outcomes

Hunter Serotonin Toxicity Criteria: Decision Rules

In the presence of a serotonergic agent:

1. IF (spontaneous clonus = yes) THEN serotonin toxicity = YES
2. ELSE IF (inducible clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
3. ELSE IF (ocular clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
4. ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES
5. ELSE IF (hypertonic = yes) AND (temperature > 38°C) AND [(ocular clonus = yes) OR (inducible clonus = yes)] then serotonin toxicity = YES
6. ELSE serotonin toxicity = NO

Figure 2. Decision rules for predicting serotonin toxicity.

Table 1 Predicted serotonin toxicity (based on the Hunter Serotonin Toxicity Criteria) vs. actual serotonin toxicity, determined by: a) diagnosis of serotonin toxicity made by a clinical toxicologist; b) Sternbach's criteria; and c) treatment with a 5-HT_{2A} antagonist – with corresponding sensitivities and specificities

		Predicted			
		No	Yes	Total	
a) Diagnosis of serotonin toxicity by a clinical toxicologist					
Actual	No	1785	62	1847	Sensitivity 84%
	Yes	27	145	172	Specificity 97%
	Total	1812	207	2019	
b) Fulfilment of Sternbach's criteria for serotonin toxicity					
Actual	No	1951	67	2018	Sensitivity 69%
	Yes	64	140	204	Specificity 97%
	Total	2015	207	222	
c) Treatment with a 5-HT_{2A} antagonist (chlorpromazine or cyproheptadine)					
Actual	No	1991	124	2115	Sensitivity 78%
	Yes	24	83	107	Specificity 94%
	Total	2015	207	2222	

Table 2 Predicted serotonin toxicity using Sternbach's criteria (Figure 1) vs. actual serotonin toxicity as determined by a clinical toxicologist

		Predicted (by Sternbach's criteria)		
		No	Yes	
Actual	No	1772	75	Sensitivity 75%
	Yes	43	129	Specificity 96%
	Total	1833	186	

(diagnosis of serotonin toxicity by a clinical toxicologist, fulfilment of Sternbach's criteria for serotonin toxicity, treatment with a 5-HT_{2A} antagonist). The resulting sensitivity and specificity values were 84% and 97%, 69% and 97%, and 78% and 94%, respectively (Table 1). To compare the new Hunter serotonin toxicity criteria with Sternbach's criteria, Sternbach's criteria was applied to the complete dataset and compared to the outcome of diagnosis by a clinical toxicologist. The resulting sensitivity and specificity values were 75% and 96% (Table 2).

Life-threatening serotonin toxicity

A review of all patients who took an overdose of a serotonergic drug and who required endotracheal intubation and assisted ventilation was conducted. Those patients who were intubated purely for worsening serotonin toxicity were distinguished from those that required intubation for decontamination or other reasons by reviewing the medical records. In these patients, hypertonicity and rigidity and high-grade fever (> 38.5°C) were prominent features. Forty-two patients were intubated for either a decreased GCS or the need for decontamination. Six patients were intubated solely for worsening serotonin toxicity. All of these patients had a high fever and multiple features of serotonin toxicity. Review of these life-threatening cases showed that progressive rigidity compromising respiratory function was the precipitating event for intervention in these patients. The preceding signs were a high fever (> 38.5°C) and increasing (particularly truncal) rigidity and peripheral hypertonicity.[20]

Discussion

We evaluated the clinical features of a large consecutive series of patients overdosing on serotonergic drugs, in an attempt to define criteria that would help identify patients with serotonin toxicity warranting observation and clinical intervention. The arbitrary approach taken was mandated by the lack of a gold standard for defining clinically significant serotonin toxicity, and the fact that it is not a discrete syndrome, but rather a spectrum of toxicity.[29] Thus we have used the diagnosis of serotonin toxicity by a clinical toxicologist as the standard, and compared this to both Sternbach's criteria and the use of treatment. Decision tree analysis of a large set of patients produced a simple set of decision rules (the Hunter Serotonin Toxicity Criteria) for diagnosing serotonin toxicity, which are more sensitive and specific than Sternbach's criteria. We thus propose the use of these new criteria, based on the fact that they are simple, both sensitive and specific, and involve the use of only a few well-defined clinical features (clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia and temperature).

Clonus (spontaneous, inducible and ocular) is the most important sign in the Hunter Serotonin Toxicity Criteria. This neuromuscular feature has been strongly associated with serotonin toxicity.[4,6,7,30,31] All types of clonus were common and significantly associated with all three outcomes in the SSRI-alone overdoses (data not shown).

Our analysis has resulted in a reduction in the number of mental status criteria used to determine serotonin toxicity, making the criteria more sensitive to features of serotonin toxicity. This should also reduce the number of other conditions such as anticholinergic and other drug-induced deliriums reaching the diagnostic criteria for serotonin toxicity.

Rigidity did not occur in any of the patients in the original SSRI dataset, but this was recognized in a previous study of SSRI poisoning.[23] Its inclusion was not based on the analysis of the SSRI dataset, but rather its frequent occurrence in cases of life-threatening serotonin toxicity in the literature[20,21] and in six life-threateningly poisoned patients in the full dataset. Because of its clinical importance, hypertonicity/rigidity was felt to be a mandatory inclusion in the final decision rule (decision rule 5).

Although mydriasis occurred commonly (31.6% of patients), it also occurs frequently with anticholinergic drugs, so is unlikely to be a good discriminator of serotonergic excess from other toxidromes. Similarly, tachycardia was frequent (40% of patients), but is a common finding in drug overdose in general, including other toxidromes, such as anticholinergic and sympathomimetic toxicity. However, although tachycardia may not be useful as a diagnostic sign, it may be useful in patients who are already diagnosed with serotonin toxicity (Hunter Serotonin Toxicity Criteria) in determining improvement and response to treatment, as demonstrated previously.[32]

We acknowledge the arbitrary nature of certain decisions in the development of the Hunter Serotonin Toxicity Criteria, and realize this has its limitations. However, we feel the development of this simpler and more accurate set of criteria for serotonin toxicity will aid clinical practice in diagnosing and treating clinically significant serotonin toxicity.

In our clinical practice, a 'yes' decision on any of the decision rules indicates definite or significant serotonin toxicity of sufficient clinical significance to require consideration of treatment with specific 5-HT_{2A} antagonists. Such patients require admission and observation for signs of worsening serotonin toxicity. We also found that the presence of a temperature $\geq 38.5^{\circ}C$ and/or marked hypertonia or rigidity (particularly truncal) indicated severe serotonin toxicity with a high risk of progression to respiratory compromise, requiring urgent active intervention. This included active measures to reduce fever as well as consideration of elective neuromuscular paralysis, endotracheal intubation and assisted ventilation. In this context, the presence of a rising pCO_2 indicated a medical emergency requiring urgent respiratory support.

The decision rules will need to be validated in other settings, including other toxicology treatment centres, emergency departments and psychiatric units. Prospective studies of the usefulness of the decision rules in predicting treatment required and outcomes in patients taking both toxic and therapeutic amounts of serotonergic drugs will be needed.

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