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Olanzapine-associated neuroleptic malignant syndrome: Is there an overlap with the serotonin syndrome?

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Abstract

Background: The neuroleptic malignant syndrome is a rare but serious condition mainly associated with antipsychotic medication. There are controversies as to whether "classical" forms of neuroleptic malignant syndrome can occur in patients given atypical antipsychotics. The serotonin syndrome is caused by drug-induced excess of intrasynaptic 5-hydroxytryptamine. The possible relationship between neuroleptic malignant syndrome and serotonin syndrome is at present in the focus of scientific interest.

Methods: This retrospective phenomenological study aims to examine the seventeen reported olanzapine – induced neuroleptic malignant syndrome cases under the light of possible overlap between neuroleptic malignant syndrome and serotonin syndrome clinical features.

Results: The serotonin syndrome clinical features most often reported in cases initially diagnosed as neuroleptic malignant syndrome are: fever (82%), mental status changes (82%) and diaphoresis (47%). Three out of the ten classical serotonin syndrome clinical features were concurrently observed in eleven (65%) patients and four clinical features were observed in seven (41%) patients.

Conclusion: The results of this study show that the clinical symptoms of olanzapine-induced neuroleptic malignant syndrome and serotonin syndrome are overlapping suggesting similarities in underlying pathophysiological mechanisms.

Background

The neuroleptic malignant syndrome (NMS) is a rare but potentially fatal condition associated with antipsychotic medication. It is mainly characterized by fever, extrapyramidal symptoms, autonomic instability and an altered state of consciousness. It is primarily caused by dopamine (D_2) receptors blockage in the nigrostriatal tract, mesocortical pathway and hypothalamic nuclei [1]. Recently, many authors have expressed the view that NMS is not caused by dopamine block alone. Other aminergic systems have also been implicated such as serotonin, norepinephrine, GABA e.t.c. [1,2]. There are controversies as to

Table 1: Serotonin syndrome clinical features presented in NMS cases induced by olanzapine

Case	Reference	MS	A	MY	H	D	S	T	DI	I	F
1	Johnson & Bruxner [10]	+								+	+
2	Filice et al[11]	+				+		+			+
3	Moltz & Coeytaux[12]	+	+			+					+
4	Henel et al[13]	+			+	+		+			
5	Burkhard et al [14]	+	+							+	+
6	Emborg[15]	+									+
7	Apple & Van Hauer[16]	+				+		+			+
8	Hickey et al[17]					+					
9	Margolese & Chouinard[18]										+
10	Carcia Lopez et al[19]	+				+			+		+
11	Levenson[20]	+				+		+			+
12	Gheorghiou et al[21]				+						+
13	Haggarty et al[22]	+	+								
14	Nyfort-Hansen & Alderman[23]	+		+	+						+
15	Jarventausta & Leinonen[24]	+	+								+
16	Stanfield & Privette[25]	+						+			+
17	Sierra-Biddle et al[26]	+				+		+			+

MS, Mental status changes; A, Agitation; MY, Myoclonus; H, Hyperreflexia; D, Diaphoresis; S, Shivering; T, Tremor; DI, Diarrhea; I, Incoordination; F, Fever

whether atypical antipsychotics can cause "classical" forms of NMS [3–5].

During the last years, a condition of serotoninergic hyperstimulation called "serotonin syndrome" (SS) has been described. It is mainly associated with administration of antidepressive medication. The most frequent clinical features of this syndrome are changes in mental status, restlessness, myoclonus and hyperreflexia [6].

The difficulty of differentiating between NMS and SS has been well recognized [7,8].

Olanzapine is an atypical antipsychotic, which exhibits greater affinity to serotonin (5-HT_2) receptors than to dopamin (D_2) receptors [9].

The aim of this study was to examine the recently reported NMS cases induced by olanzapine regarding SS clinical features and to elucidate phenomenological similarities between the two syndromes.

Methods

A MEDLINE search related to olanzapine-induced NMS cases reported in the international literature from January 1996 to March 2001 was conducted. On the basis of the titles and information included in the abstracts, seventeen case reports were found [10–26]. Olanzapine-induced NMS cases have been presented and critically reviewed elswhere [27]. All cases were re-analyzed against SS clinical features according to Sternbach diagnostic criteria [6].

Results

NMS associated with olanzapine has been reported in twelve males (mean age 44.5 ± 20.9 years) and in five females (mean age 54.2 ± 22.4 years). Schizophrenia was the primary diagnosis in nine of the patients (53%). The mean olanzapine dosage was 10.7 ± 4.3 mg/day.

As shown in table 1, the SS clinical features presented in cases initially diagnosed as NMS were the following: fever (82%), mental status changes (82%), diaphoresis (47%), tremor (35%), agitation (23%), hyperreflexia (18%), incoordination (12%), myoclonus (6%), diarrhea (6%). There was no report on shivering.

Three out of the ten SS clinical features set by Sternbach [6] were concurrently observed in eleven (65%) patients. Four clinical features were observed in seven (41%) patients and five clinical features in two (12%) patients.

Discussion

According to Sternbach [6], for the establishment of the diagnosis of SS, the following three criteria should be fulfilled: a. presence of at least three of the ten proposed clinical features, b. addition to the therapeutic regiment or increase of a known serotonergic agent, and c. a neuroleptic had not been started or increased in dosage. If the last two criteria of drug use were excluded, the SS diagnosis in olanzapine-associated NMS cases could be made in eleven patients (65%). This means that there is a phenomenological overlap between NMS and SS symptoms in patients on olanzapine treatment. According to several authors NMS and SS can be differentiated with difficulty in many

cases induced by antipsychotics or selective serotonin-receptor inhibitors (SSRI's) [7,8].

The atypical or moderate forms of NMS attributed to novel antipsychotics (that have greater affinity to serotonin 5-HT_{2A} receptors than to dopamine D_2 receptors) and the overlapping in clinical features between SS and NMS observed in patients treated with olanzapine, reinforce the view that the two syndromes may share the same underlying pathophysiology, i.e. imbalance between aminergic systems, despite differences in the causative drugs [28].

According to Fink [29], NMS and SS are non-specific generalized neurotoxic syndromes. This author recommends the immediate withdrawal of the offending agent and the administration of benzodiazepines in the early stages in both these syndromes.

Further studies, particularly of prospective nature are warranted in patients receiving conventional or atypical antipsychotics as well as serotoninergic agents in order to elucidate the common elements between NMS and SS regarding phenomenology, pathophysiology and treatment response.

Study limits

This is a retrospective analysis of the reported NMS cases induced by olanzapine. The fact that the data were collected from published case reports by other authors, has an inherent bias. The major limitation of this study stems from the lack of detailed information provided regarding the SS clinical symptoms, since the authors were mainly focusing on the description of NMS symptomatology.

Competing intrests

None declared.

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