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Olanzapine-induced Agranulocytosis A Case Report And Review Of The Literature

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Abstract

Clozapine's pharmacological and structural characteristics are shared by the new antipsychotic olanzapine. Olanzapine was thought to be a safer option because, up until recently, no cases of haematological toxicity had been associated with its use. The authors analyse the literature and present a case of agranulocytosis brought on by olanzapine.

Keywords: Olanzapine-induced agranulocytosis

Introduction

Olanzapine is a powerful 5-HT2 and lesser D2 receptor agonist that belongs to the thienobenzodiazepine class of serotonin-dopamine antagonists. It shares similarities in its structural and pharmacological profile with that of the atypical antipsychotic clozapine, and both drugs are more tolerable than traditional antipsychotics (Beasley et al., 1997). Despite clozapine's effectiveness in treating refractory schizophrenia, only 0.5–2% of patients who take it develop agranulocytosis (Alvir et al., 1993; Casey, 1997). This prevents clozapine from being used widely. Early research including 2500 patients, summarised by Beasley et al. (1997), indicated that olanzapine had a safety profile and that using medication was not linked to major haematological side effects. In fact, it was anticipated that olanzapine would be a secure substitute for clozapine in the treatment of patients with psychotic illnesses. Patients who had previously had clozapine-induced granulocyte count impairment during pivotal trials did not have neutropenia when taking olanzapine (Beasley et al., 1997). In addition, further studies (Finkel et al., 1998; Oyewumi and Al-Semaan, 2000; Swartz et al., 1999) demonstrated that olanzapine was effective in treating patients with typical and atypical antipsychotic-associated agranulocytosis without recurrence of haematological side effects. But according to recent research, olanzapine might also cause haematological damage. Several occurrences of neutropenia or leukopenia following olanzapine treatment have been recorded (Benedetti et al., 1999; Gajwani and Tesar, 2000; Meissner et al., 1999; Schuld et al., 2000; Steinwachs et al., 1999), as well as two cases of agranulocytosis (Dettling et al., 1999; Naumann e al , 1999) . In addition, those who started taking olanzapine while recovering from clozapine-induced granulocytopenia experienced longer-lasting granulocyte depression than those who did not (Flynn et al., 1997).

Case report

The authors provide a case of agranulocytosis brought on by olanzapine that was previously presented at the most recent C.I.N.P. meeting (Tolosa et al., 2000). A 46-year-old man who was receiving therapy with olanzapine and cyanamide was taken to the hospital due to a fever, chills, and odinophagia. Physical examination revealed no notable symptoms or indicators other than a purulent discharge covering an ulcerated right tonsil. His neutrophil count was 0.36 109/l and his white blood cell count was 0.5 109/l. The results of blood and urine cultures were both negative, and chest radiographs were normal. After stopping olanzapine and cyanamide and starting piperacillin and amikacin instead, clinical improvement appeared three days into the empirical treatment. His leukocyte count was 1 109/l 48 hours after admission, and it increased to 2.31 109/l the following day with a neutrophil count of 0.51 109/l. On the sixth day of olanzapine discontinuation, the white blood cell count returned to normal. Because of his white blood cell count's fast recovery, a bone marrow cytology was not performed. His medical history included intermittent 45 mg daily therapy for cyanamide for

persistent enolism and no prior haematological abnormalities. Due to the presence of a delusional condition, olanzapine 5 mg/day was administered 15 days before to admission. The onset of agranulocytosis and the administration of olanzapine occurred concurrently.

Discussion

Agranulocytosis is a potentially fatal but luckily uncommon medication side effect. On this subject, it was anticipated that the brand-new antipsychotic olanzapine would be a secure substitute for clozapine. But according to recent findings, olanzapine may also cause haematological damage. Eleven cases of granulocyte count impairment brought on by olanzapine have been documented (Table 1), with ages ranging from 20 to 81. The majority of the time, this haematological toxicity manifested within the first month of treatment, but in three instances, it did so within six months. It happened on the 13th month in just one patient. After stopping olanzapine, the neutrophil count often increased. Additionally, as documented with olanzapine's structural counterpart clozapine (Sperner-Unterweger et al., 1994), the myelosuppressive impact of olanzapine in two individuals was self-limiting despite the continuation of the antipsychotic medication (Gajwani and Tesar, 2000; Schuld et al., 2000). Leukocyte and neutrophil numbers were found in one of them were below the upper limits of normal before therapy, and Recovery occurred while the patient was receiving treatment with lithium, a medication known to stimulate granulocyte colony to cause leukocytosis growth component (Tisman et al., 1973). In the alternative, Leukocyte development occurred voluntarily (Schuld et al.,2000). Five of these patients had previously had hemotoxic side effects while receiving clozapine medication. attributes of Table 1 provides a summary of all cases with age range of 20 –81 years old.

	Patient								
Reports	Age (years)	Sex[b]	Dose time	Diagnosis	Haematological side effect[a]	Other drugs	Evolution	Toxicity with other drugs	Observations
Meissner et al. (1999)	56	F	15 mg/day, 4 months	Psychosis related to L-DOPA, Parkinson and dementia	Leukopenia	L-DOPA, Pergolide, Donezepile	Recovery after olanzapine withdrawal	Leukopenia with clozapine	–
Meissner et al. (1999)	58	M	5 mg/day, 13 months	Psychosis related to L-DOPA, Parkinson	Leukopenia	L-DOPA	Recovey after olanzapine withdrawal	Leukopenia with clozapine	–
Dettling et al. (1999)	24	F	15 mg/day, 5 days	Schizophrenia	Neutropenia	–	Recovery after olanzapine withdrawal	–	–
Dettling et al. (1999)	27	F	5 mg/day, 4 months	Brief psychotic disorder	Agranulo cytosis	Amitriptylina	Recovery after stopping both drugs	–	–
Steinwachs et al. (1999)	81	F	5–10 mg/day, 17 days	Schizophrenia	Neutropenia	–	Recovery after olanzapine withdrawal	–	–
Steinwachs et al. (1999)	44	M	20 mg/day, 6 months	Schizophrenia	Neutropenia	–	Recovery after olanzapine withdrawal	Neutropenia with olanzapine and perazine	–
Naumann et al. (1999)	27	M	40 mg/day, 9 days	Schizophrenia	Agranulo cytosis	–	Recovery after olanzapine withdrawal and G-CSF treatment[c]	–	Previous treatments with olanzapine and clozapine without side effects
Benedetti et al. (1999)	31	F	5–10 mg/day, 7 days	Eating disorder	Neutropenia	Flurazepam	Recovery after olanzapine withdrawal	Neutropenia with clozapine	Laboratory tests showed moderate anemia
Gajwani and Tesar (2000)	20	M	5–10 mg/day, 5 days	Schizophrenia	Neutropenia	–	Recovery: reversal with lithium	Neutropenia with risperidone	Basal neutrophil count at the lower limit: $1.64 \times 10^9/l$
Schuld et al. (2000)	26	F	5–10 mg/day, 14 days	Schizophrenia	Neutropenia	–	Recovery despite continuing treatment	Neutropenia with clozapine	Levels of G-CSF not detectable in plasma
Tolosa et al. (2000)	46	M	5 mg/day, 15 days	Delusional disorder, alcoholism	Agranulo cytosis	Cyanamide	Recovery after stopping both drugs	–	Chronic cyanamide treatment without side effects

Table 1 Reports of olanzapine-related haematological toxicity

This haematological damage primarily manifested within the first month following the beginning of therapy, but in three instances, it manifested itself within six months It happened on the 13th month in only one patient. Following olanzapine, the neutrophil count increased. The standard was withdrawn. Additionally, as documented with olanzapine's structural counterpart clozapine (Sperner-Unterweger et al., 1994), the myelosuppressive impact of olanzapine in two individuals was self-limiting despite the continuation of the antipsychotic medication (Gajwani and Tesar, 2000; Schuld et al., 2000).

One of them, lithium (Gajwani and Tesar, 2000), a medication known to cause leukocytosis by stimulating granulocyte colony growth factor, had leukocyte and neutrophil counts that were below the lower limits of normal prior to treatment. However, when the patient was receiving lithium treatment, recovery began to occur (Tisman et al., 1973). In the alternative situation, leukocyte improvement occurred on its own (Schuld et al., 2000). Five of these patients had previously had hemotoxic side effects while receiving clozapine medication. Table 1 summarises the features of all instances.

Given that it also happens with its structural equivalent clozapine, the mechanism underpinning olanzapine-induced neutrophil toxicity is currently poorly known. However, given that the two compounds have a similar chemical composition and can produce similar reactive polypeptide metabolites, this detection does not seem very remarkable (Liu and Uetrecht, 1995; Gardner et al., 1998a,b). According to Uetrecht et al. (1995) and Waldhauser and Uetrecht (1991), other medications that cause neutropenia or agranulocytosis are also metabolised to reactive intermediates that covalently bind to macromolecules. Genetic variables have also been linked to this defective granulopoiesis, albeit a toxic or immune-mediated mechanism may be the primary culprit (Dettling et al., 1999). Gardner et al. (1998a,b) recently looked at any potential differences between the toxicity of clozapine and olanzapine. They showed that, similar to clozapine, olanzapine can be bioactivated to a reactive nitrenium ion, the main oxidant of human neutrophils (Liu and Uetrecht, 1995). They did find some elements, though, that would help to explain why, in theory, olanzapine would not cause neutrophil poisoning. Compared to clozapine, the reactive metabolite of olanzapine appears to covalently bind to human neutrophils to a significantly lesser level in vitro, which suggests that it may have reduced direct toxicity. Additionally, this olanzapine reactive metabolite also exhibited a propensity to bind to a distinct fraction of greater molecular weight neutrophil polypeptides. Clozapine was also discovered covalently linked to human neutrophils during these in vivo experiments. However, neutrophils isolated from olanzapine-using patients did not exhibit any drug-modified polypeptides. This disparity may be partially explained by the lower plasma concentration attained with olanzapine treatment and/or the method's failure to detect it. These investigations indeed demonstrate some covalent binding of clozapine and olanzapine to neutrophils, at least in vitro, although it is less obvious how this relates to the production of agranulocytosis.

Unknown is the frequency of olanzapine-induced neutropenia. Given that only 11 occurrences of olanzapine-induced neutropenia have been documented since the drug's introduction to the market in 1996, it appears to be less common than the incidence of neutropenia in patients receiving clozapine. In 1300 patients receiving olanzapine treatment, a collaborative German-Swiss study group found just two cases, and they estimated the unique data on this subject to be 0.15%. (Steinwachs et al., 1999). Given the low prevalence of olanzapine-induced neutropenia, it has been proposed that there may be additional unidentified risk factors that could impair granulopoiesis, such as immune reactions in some susceptible individuals, impaired G-CSF secretion, or interactions with particular elements of the bone marrow extracellular matrix (Guest and Uetrecht, 1999).

Conclusion

Although this probably happens less frequently, it appears that the new antipsychotic olanzapine can also impair granulopoiesis through clozapine-like routes. The norm is for the neutrophil count to increase after olanzapine cessation, although occasionally the granulocyte count increased even while olanzapine medication was continued. It may be wise to routinely check the white blood cell count when taking olanzapine until more information is available.