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Olanzapine and pancytopenia with severe folate deficiency

F. Maurier[1], N.Petitpain[2], J-F. Guichard[1], L. Javot[2], P. Tréchot[2]

[1] Department of Internal Medicine, Vascular Medicine and Clinical Immunology, Ste Blandine Hospital, Metz, France

[2] Department of Clinical Pharmacology, Pharmacovigilance Center, University Hospital, Nancy, France

Corresponding author:

Nadine Petitpain

Department of Clinical Pharmacology

Pharmacovigilance Center

CHU Nancy

29 av Mal de Lattre de Tassigny

54035 Nancy, France

Tel : 00 33 3 83 85 27 60

Fax : 00 33 3 83 32 33 44

Email : n.petitpain@chu-nancy.fr

For Peer Review

To the editor :

Olanzapine, a thienobenzodiazepine serotonin-dopamine antagonist, is a recent atypical antipsychotic agent, the structural and pharmacologic profile is similar to that of clozapine. Although clozapine is effective in refractory schizophrenia, its use is limited by the occurrence of hematologic adverse effects, such as agranulocytosis which occurs in 0.5%-2% of treated patients [1]. Many studies have suggested a better hematologic safety profile for olanzapine, but impaired granulocytopoiesis and thrombocytopenia have recently been reported [2-6]. No case of pancytopenia with megaloblastic anemia has been described with the use of olanzapine. We report a case of pancytopenia with severe folate deficiency in a schizophrenic patient treated with olanzapine.

A 56-year-old man, who worked as a painter, was a heavy smoker, had bad dental health, and a history of chronic psychosis was hospitalized on 11 August 2008 with severe pancytopenia, suggested by purpura. He had been living with his brother and had been treated for many years with haloperidol decanoate (3 mg every 3 weeks), loxapine (100 mg/day), amisulpride (800 mg/day), tropatepine (10 mg/day), diazepam (10 mg/day), and clorazepate (50 mg/day). Because of recent worsening of his psychotic symptoms, olanzapine was introduced (20 mg/day) in May 2008.

The laboratory data on admission and during the early period of hospitalization are shown in Table 1. The hemogram and reticulocyte count revealed pancytopenia with macrocytic normochromic aregenerative anemia. The folate plasmatic level was dramatically decreased, total protein and cobalamin were slightly decreased and renal and hepatic functions were normal. Shortly after admission, only olanzapine was discontinued. The patient received probabilist cobalamin supplementation with no immediate hematologic improvement. On 14 August, he began to receive intravenous folate supplementation (50 mg/day). Ten days later, a huge reticulocyte crisis was observed, whereas the white blood cell and platelet counts were significantly increased (Table 1). Meanwhile, the results of bone marrow aspiration confirmed the diagnosis of megaloblastic anaemia. The patient was supplemented with folic acid over 2 weeks. Because the medical staff decided against restarting olanzapine, the loxapine dosage was increased to 150 mg/day with a good response. Computerized tomography imaging showed hepatic abnormalities consistent with portal hypertension. On 4 September, the macrocytic anemia recovered and folate supplementation was discontinued.

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One month after admission, gastric endoscopy revealed grade I peptic esophagitis without esophageal varix. The biopsies were all negative, thus ruling out celiac disease. At this time, his laboratory data only showed a slight macrocytosis with no anemia. At the 3-month follow-up, olanzapine had not been restarted and the patient had a perfect clinical examination, despite discontinuation of folate supplementation.

Cases involving pancytopenia with olanzapine are rare [2], and no case of megaloblastic anemia has been reported with this drug. For our patient, we observed pancytopenia due to folate deficiency. The sequence of events strongly suggests that olanzapine was responsible for this hematologic disorder with i) a 3-month delay of onset, ii) the absence of recurrence after drug withdrawal, despite cessation of folate supplementation, and iii) delayed reticulocytosis after vitamin supplementation .

Folate deficiency is usually linked to decreased intake or decreased proximal small bowel absorption. The poor dental health of our patient is likely to have slowly favored decreased folate intake, but endoscopic examination did not reveal abnormalities consistent with impaired small bowel absorption. However, chronic inadequate folate intake is not sufficient to explain the association of pancytopenia that occurred 3 months after the beginning of olanzapine treatment. Other hypotheses, based on anticonvulsant and recent cough mixture cases of drug-induced folate deficiency imply methylenetetrahydrofolate reductase (MTHFR) polymorphism and hyperhomocysteinemia [7,8]. Unfortunately, neither MTHFR phenotype and homocysteine level were determined in our patient. Olanzapine, with less neutrophil toxicity than clozapine, is expected to be a safer alternative. However, olanzapine can induce impaired granulocytopoiesis and prolonged granulocyte depression in patients switched from clozapine to olanzapine [3]. The mechanism underlying olanzapine-induced neutrophil toxicity remains unclear. Toxicity of olanzapine on granulocyte-macrophage progenitors has been demonstrated *in vitro* [9], and like other neutropenic drugs, olanzapine generates a reactive metabolite that is able to bind to human neutrophils [1,10].

The link between olanzapine treatment and thrombocytopenia is less well documented [4-6]. One case of fatal thrombocytopenia 3 weeks after the start of olanzapine was reported in a 78-year-old patient with a history of idiopathic thrombocytopenic purpura and mild renal insufficiency [4]. This patient had a plasma level of olanzapine 10 times higher than expected. In our patient, renal function was normal and the plasma level of olanzapine was not determined on admission. It is noteworthy that our patient received other treatment when pancytopenia was diagnosed. Haloperidol, loxapine, and amisulpride are associated with

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hematologic adverse effects, like many other neuroleptics. As none of these medications were discontinued, it is unlikely that haloperidol, loxapine, or amisulpride were causal. Moreover, the loxapine dosage was increased after olanzapine withdrawal with no recurrence of any blood cell dyscrasia.

This first case of pancytopenia with severe folate deficiency associated with olanzapine underlines the necessity of hematologic controls during the administration of this drug.

Table 1: Summary of laboratory data

	Units/ [normal range]	11/8	13/8	14/8	18/8	20/8	25/8	27/8	2/9	18/9
Hemoglobin	g/l [130-180]	82	91	85	75	85	71	83	97	129
MGV	Fl [78-94]	124.6	111.1	104.2	104	104.8	118.2	116.3	112.9	102
White blood cell count	10^9/l [4-11]	1.1	1.7	1.58		3.89	12.12	17.77	5040	6100
Platelets	10^9/l [150-400]	39	28	27	16	52	174	323	507	121
Reticulocytes	10^9/l*			15.2			368	158	235.6	
Cobalamin	ng/l [>300]	141								
Folate (serum)	nmol/l [4.5-21]	0							>45.4	
Folate (erythrocytes)	nmol/l [400-1300]								>3100	
Protein	g/l [65-80]	65				61				
Creatinine	mg/l [5-12]	10.3				8				10

*: reticulocytes>80.10^9/l are consistent with regenerative anemia

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Corresponding author:

Nadine Petitpain

Department of Clinical Pharmacology

Pharmacovigilance Center

CHU Nancy

29 av Mal de Lattre de Tassigny

54035 Nancy, France

Tel : 00 33 3 83 85 27 60

Fax : 00 33 3 83 32 33 44

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