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Agranulocytosis with combination of paliperidone and clozapine: a case report

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ABSTRACT

Antipsychotics are the most common psychotropic drugs associated with blood dyscrasias, and clozapine is the most notably implicated when agranulocytosis occurs, although other antipsychotic agents can cause this serious side effect at different levels of risk. We present the case of a 26-year-old man with a treatment-resistant schizophrenia who developed agranulocytosis while under treatment with the combination of paliperidone and clozapine. We discuss the individual and combined implications of both antipsychotics in the development of agranulocytosis and the importance of haematological monitoring for combined antipsychotic treatment in general, and not only when clozapine is used. To the authors' knowledge this is the first report of agranulocytosis with the combination of clozapine and paliperidone.

Keywords: paliperidone, clozapine, risperidone, agranulocytosis, neutropenia, antipsychotics

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Introduction

Psychotropic agents have been reported to cause blood dyscrasias and amongst them, antipsychotics, are the most commonly associated with neutropenia and agranulocytosis. Neutropenia can be defined as an absolute neutrophil count (ANC) of ≤ 1500/μl, and may occur either by decreased production or by peripheral destruction [1]. Agranulocytosis (ANC ≤ 500/μl) is a potentially life-threatening uncommon side effect to antipsychotic drugs, most notably clozapine. This side effect is dose-independent and occurs more commonly in the first months of treatment, but can occur at any time during treatment [2]. Current pathogenesis theories of clozapine-induced agranulocytosis highlight the potential role of hapten-based mechanisms and genetic predisposition [2]. Contrary to clozapine, the other antipsychotic drugs do not have an haematological monitoring regulatory process, although they may cause blood dyscrasias at a variable level of risk [3].

We report the case of a patient with a treatment-resistant schizophrenic disorder who developed agranulocytosis while under treatment with paliperidone and clozapine. After discontinuation of both drugs, the patient was later initiated on risperidone and developed neutropenia. Both blood dyscrasias were reversed with the use of a granulocyte colony-stimulating factor (G-CSF). The patient was later medicated with haloperidol, with no recurrence of granulocytopenias. Consent was received from the patient to publish the case and information has

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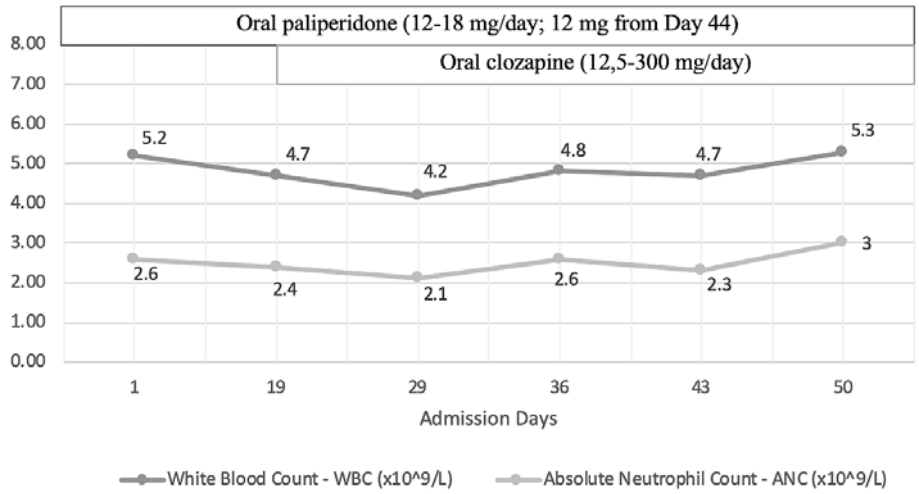


Figure 1. WBC and ANC evolution on first trial with combination of paliperidone and clozapine

been de-identified to protect anonymity.

Case report

The patient is a 26-year-old Caucasian man, non-smoker and without known prior health conditions or substance use, diagnosed with schizophrenia according to the International Classification of Diseases 10th Revision diagnostic criteria, since September 2017 when he was first admitted to the in-patient unit. During a two-month hospital stay, he was first medicated with aripiprazole, titrated to 30 mg/day without improvement. Switch to olanzapine 20 mg/day was made with partial response. Nonetheless, because of increased risk of non-adherence, and since olanzapine depot is not available in Portugal, zuclopenthixol decanoate was introduced and increased to 400 mg every two weeks, and olanzapine was suspended. At discharge, November 2017, some clinical improvement was present, although maintaining positive symptoms and lack of insight, and ANC was normal ($3,7 \times 10^9$/L; reference value 1,8-6,9 $\times 10^9$/L). After six months, medication was abandoned with recrudescence of symptoms and he was readmitted in June 2018. At admission, ANC was normal ($2,6 \times 10^9$/L). On Day 1 paliperidone was started and titrated to 18 mg/day over one week. On Day 19, and since there was no clinical improvement with paliperidone monotherapy, clozapine was initiated and titrated to 300 mg/day over four weeks with normal weekly control hemograms (Figure 1). Paliperidone was reduced to 12 mg/day on Day 44 and paliperidone palmitate was introduced because of non-adherence (150 mg Day 45, 100 mg Day 52). After discharge in August 2018 (Day 60), clozapine was immediately abandoned and no additional laboratory tests were performed. Clinical worsening occurred and he was readmitted in December 2018. At admission ANC was normal ($4,0 \times 10^9$/L). On Day 1, he was started once again on clozapine (12,5 mg/day) and paliperidone (9 mg/day). Clozapine was titrated to 350 mg/day (divided in two doses) over four weeks and paliperidone to 18 mg/day over one week. During this period, control hemograms were normal (Table 1). However, on Day 42, he presented a fever (38°C) with tonsillitis symptoms, and laboratory tests revealed white blood cell (WBC) count of $0,9 \times 10^9$/L (reference value 4,0-11,0 $\times 10^9$/L) and ANC of 0,0 $\times 10^9$/L, so a drug-induced agranulocytosis was assumed. All antipsychotics were abruptly stopped, and biperiden 8 mg/day was introduced in order to prevent cholinergic rebound, being gradually suspended afterwards. Treatment with G-CSF was promptly initiated and on Day 48, ANC started to increase, normalizing on Day 51 ($3,6 \times 10^9$/L). On Day 62, risperidone 4 mg/day was initiated. Two days later, a fever developed but hemogram was normal. However, on Day 65, ANC revealed neutropenia ($1,0 \times 10^9$/L) so risperidone was stopped and G-CSF was reinitiated. Four days later, leukocytosis and neutrophilia ensued so G-CSF was discontinued. On Day 76, WBC count and ANC were in the normal range ($6,9 \times 10^9$/L and $3,3 \times 10^9$/L respectively). Haloperidol 5 mg/day was then initiated and titrated to 20 mg/day over 20 weeks with subsequent normal hemogram controls (weekly controls for 2 months, and fortnightly till discharge) (Figure 2).

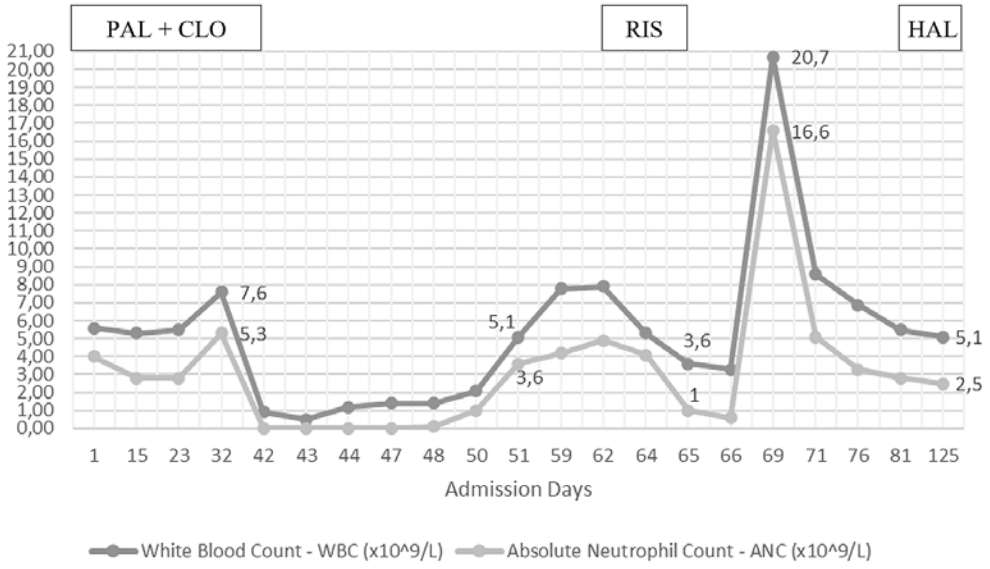
Table 1. Treatment Course and Neutrophil Count Evolution of second trial with combination of paliperidone and clozapine

Day	Medication	Dosage (mg)	WBC ($\times 10^9$/L) Ref. Range: (4,0-11,0)$\times 10^9$/L	ANC ($\times 10^9$/L) Ref. Range: (1,8-6,9)$\times 10^9$/L
1	Clozapine	12,5	5,6	4,0
	Paliperidone	9		
15	Clozapine	125	5,3	2,8
	Paliperidone	18		
23	Clozapine	225	5,5	2,8
	Paliperidone	18		
32	Clozapine	350	7,6	5,3
	Paliperidone	18		
42[a]	Clozapine	350	0,9	0,0
	Paliperidone	18		
43	-	-	0,5	0,0
44	-	-	1,2	0,0
47	-	-	1,4	0,0
48	-	-	1,4	0,1
50[b]	-	-	2,1	1,0
51	-	-	5,1	3,6
59	-	-	7,8	4,2
62	Risperidone	4	7,9	4,9
64	Risperidone	4	5,3	4,1
65[c]	Risperidone	4	3,6	1,0
66	-	-	3,3	0,6
69[d]	-	-	20,7	16,6
71	-	-	8,6	5,1
76	-	-	6,9	3,3
81	Haloperidol	5	5,5	2,8
125	Haloperidol	20	5,1	2,5

a) G-CSF first initiation
b) G-CSF first suspension
c) G-CSF second initiation
d) G-CSF second suspension
WBC, white blood cell; ANC, absolute neutrophil count.

Discussion

Although there is a lack of uniformity in the definition of treatment-resistant schizophrenia (TRS), it is generally assumed as the absence of satisfactory clinical improvement despite the use of at least two antipsychotics (one should be an atypical) at recommended doses and for the adequate duration [4]. In this clinical case, TRS was assumed after lack of consistent clinical response with various antipsychotics, namely: aripiprazole, olanzapine (only partial remission of positive symptoms and maintaining poor insight), zuclopenthixol and paliperidone, the latter being titrated to high dosage in search of a better clinical response, and since there was no evidence of side effects. Although general evidence does not support the use of high dose antipsychotics, this is a relatively frequent option in clinical settings [5]. There appears to be some evidence that high dose paliperidone (15 and 18 mg) does not cause more side effects than the maximum recommended dose of 12 mg/day [6, 7], and this was the case in this clinical report. Since a consistent clinical response to high dose paliperidone wasn't observed, clozapine was initiated, and paliperidone was maintained in association considering the possibility of introducing a long-acting injectable (LAI) because of probable non-adherence. The rationale for LAI introduction was to prevent a more serious relapse if clozapine was later abandoned and to connect the patient to the mental health outpatient unit, being acknowledged that co-utilization



PAL= Paliperidone; CLO= Clozapine; RIS= Risperidone; HAL= Haloperidol

Figure 2. WBC and ANC evolution on second trial with combination of paliperidone and clozapine

of different routes of administration is typically a justifiable reason for antipsychotic combination in clinical practice [8]. Additionally, there is some evidence supporting the efficacy and safety of this specific antipsychotic combination in clozapine-resistant schizophrenia, without reference to major side effects such as agranulocytosis [9, 10]. To our knowledge this is the first report of agranulocytosis with the combination of clozapine and paliperidone.

It should be noted that the patient only developed agranulocytosis on the second trial with this antipsychotic combination. To our understanding, if clozapine alone is to be considered the culprit, this may be explained as an idiosyncratic event, since clozapine titration was performed in both instances over 4 weeks (median of less than 12,5 mg/day increments), and agranulocytosis occurred in week 5, being known that this phenomena is more frequent between weeks 4 and 20 of treatment and is dose-independent [2]. As for paliperidone, it was increased over one week to the same dose of 18 mg in both instances, and there are case reports of agranulocytosis [11] and neutropenia [12, 13] with this antipsychotic. The main differences between both trials were the clozapine final dose, which was higher in the second trial (350 mg/day), and the fact that both antipsychotics were started at the same time in the second trial, contrary to the first trial, when paliperidone was initiated firstly and maintained as monotherapy for 18 days.

Given the difficulty in understanding the role of each antipsychotic in the development of agranulocytosis, the Naranjo scale of adverse drug reaction [14] was applied. A score of 5 was obtained for clozapine and of 6 for paliperidone, implying both agents as probable causal factors of agranulocytosis, but not permitting to define which one was the main responsible for this event. Nonetheless, adding the fact that paliperidone scored higher, to the fact that the patient was later started on risperidone and developed a neutropenia, leads us to think that paliperidone was more responsible for the agranulocytosis than previously presumed, since paliperidone is the primary active metabolite of risperidone [15]. Additionally, a recent meta-analysis suggests that other antipsychotics cause agranulocytosis at an incidence similar to that of clozapine, and that this phenomena may be wrongly attributed to clozapine especially when cross-titration of clozapine with the preceding antipsychotic is performed [16].

Although literature does not seem to find an increased risk of more serious adverse events such as blood dyscrasias with the combined use of antipsychotics, these results are based in very low-quality evidence [17]. Thus, it cannot be excluded in this case that agranulocytosis was due to the combined use of both antipsychotics. While clozapine is the most frequently associated antipsychotic to agranulocytosis, being this association dose-independent, it is suspected that the major mechanism underlying drug-induced agranulocytosis is bone marrow toxic-

ity, which is typically determined by the dosage of medication [1]. Thus, the two main differences between the two trials of this drug combination may be of some explanation to the development of agranulocytosis in the second trial, namely the fact that clozapine was combined with paliperidone 18 mg/day at a higher dose (350 mg/day), and that this combination was maintained for a longer period of time, since paliperidone dose was not reduced. In this sense, the combination of clozapine and paliperidone, especially with higher doses, could have increased the toxic effects in the bone marrow leading to agranulocytosis.

We conclude that regardless of the most probable explanatory hypothesis, patients should be more carefully monitored in general for blood dyscrasias when under combined antipsychotic treatment, especially if higher doses are used.

CONFLICT OF INTEREST

Dr. Dehanov reports non-financial support from Janssen-Cilag Farmacêutica, non-financial support from Lundbeck Portugal - Produtos Farmacêuticos, non-financial support from Angelini Farmacêutica Lda, outside the submitted work;

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Dr. Gonçalves reports no conflicts of interest;

Dr. Maia Correia reports non-financial support from Janssen-Cilag Farmacêutica, non-financial support from Lundbeck Portugal - Produtos Farmacêuticos, non-financial support from Eli Lilly and Company, non-financial support from Servier Portugal - Especialidades Farmacêuticas Lda, non-financial support from Astrazeneca PLD, non-financial support from Wyeth Lederle Farma, Lda, outside the submitted work.

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