Psychiatry Research 256 (2017) 275–282

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Clozapine versus other antipsychotics during the first 18 weeks of treatment: A retrospective study on risk factor increase of blood dyscrasias

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ARTICLE INFO

Keywords:
Agranulocytosis
Anemia
Leukocytosis
Neutrophilia
Eosinophilia
Benzodiazepines
Mood stabilizers

ABSTRACT

Blood dyscrasias excluding agranulocytosis received limited attention in antipsychotic-treated patients during the first 18 weeks of therapy, although severe clinical conditions have been reported in a few cases. We extracted data records of 285 Caucasian patients after 18 weeks of antipsychotic treatments to investigate risk factors of blood dyscrasias. We observed a higher risk to develop both transient and persistent anemia, neutrophilia and eosinophilia in clozapine-treated patients, whereas in those treated with other atypical antipsychotics when compared to a reference group under typical antipsychotics, emerged an increased risk for transient neutrophilia and eosinophilia. Male patients revealed a higher risk of persistent eosinophilia, neutrophilia, and leukocytosis. Concomitant treatments with mood stabilizers or benzodiazepines proved to be risk factors for transient anemia, antidepressants for transient eosinophilia. Severe complications emerged in 3 cases of agranulocytosis. Cross-tabulation analysis showed a higher probability of a poor response in clozapine-treated patients with persistent anemia and a positive with persistent neutrophilia and eosinophilia. Our data evidenced that emerging blood dyscrasias were not associated with critical adverse effects, and only agranulocytosis required a treatment interruption. Other atypical antipsychotics might represent a viable alternative to potentially harmful clozapine and typical antipsychotics at the onset of life-threatening haematological alterations.

1. Introduction

In the last twenty years, several epidemiological studies have reported value accuracy of the incidence of clozapine-related agranulocytosis, yet not being the sole blood dyscrasia potentially induced by this atypical antipsychotic. In fact, the constant haematological monitoring of clozapine-treated patients often reveals the presence of other temporary blood alterations whose relevance and underlying mechanisms are still unidentified (Heimpel, 1996; Lambertenghi Deliliers, 2000; Popli and Pies, 1995). There is growing evidence that psychiatrists' lack of experience with clozapine may contribute to a high discontinuation rate along with potentially serious adverse effects, among which haematological alterations are of major concern (Nielsen et al., 2013).

Leukocytosis is frequently associated with clozapine treatment, with different incidence rates and times of appearance reported (Hummer et al., 1994; Lambertenghi Deliliers, 2000; Lieberman et al., 1989; Popli and Pies, 1995). Transient leucopenia is revealed after clozapine treatment (Hummer et al., 1994; O'Connor et al., 2010; Rajagopal, 2005), as well as neutropenia, although many subjects may present very low absolute neutrophil count (ANC) without evidence of increased susceptibility to infections or to any other adverse effect (Haddy et al., 1999). Neutropenia usually disappears after drug withdrawal, or it causes an abrupt onset of agranulocytosis, with a rapid decline of circulating leukocytes (Alvir and Liberman, 1994; Krupp et al., 1992; Rettenbacher et al., 2010; Stübner et al., 2004). In some cases, neutropenia can be preceded by eosinophilia (Ames et al., 1996; Hummer et al., 1996), which in turn can also appear as an isolated transient benign haematological dysfunction (Banov et al., 1993; Chatterton, 1997; Hummer et al., 1994; Lambertenghi Deliliers, 2000; Popli and Pies, 1995). Transient neutropenia is reported in both Caucasian and Asian first-time clozapine-treated patients (Ahn et al., 2004; Hummer et al., 1994). Atkin et al. (1996) warn that the peak incidence of both neutropenia and agranulocytosis is reached in the first 6–18 weeks of treatment, but it is unclear why some patients develop a transient neutropenia, while others progress to agranulocytosis despite maintenance of clozapine dosage. Neutrophilia occurs in some cases of clozapine overdose, rehabilitation stress and spiking fever in the first 3 weeks of clozapine therapy, together with the onset of respiratory and gastrointestinal symptoms (Roy and Cutten, 1993; Seifritz et al., 1993;

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http://dx.doi.org/10.1016/j.psychres.2017.06.068
Received 13 August 2016; Received in revised form 18 June 2017; Accepted 18 June 2017
Available online 20 June 2017

Trémeau et al., 1997). Ziegenbein et al. (2003) report a case of clozapine-induced aplastic anemia in a patient with Parkinson's disease, while other authors (Lambertenghi Deliliers, 2000; Savithasri Eranti and Chaturvedi, 1998; Tang et al., 2011) outline cases of patients where thrombocytopenia develops during clozapine as monotherapy or politherapy.

All the abovementioned blood dyscrasias are not currently categorized in terms of time of appearance and disappearance, age and gender prevalence of the patients, dose of clozapine, correlation with clinical response, and comparison with other antipsychotics. We examined and compared various blood dyscrasias related to antipsychotic treatment to broaden the existing literature, which has focused exclusively on agranulocytosis so far. Our purpose was to offer practical instructions to prescribers on risks and benefits of the antipsychotic therapy. Furthermore, we provided therapeutical alternatives both in case of treatment continuation and discontinuation, being the latter contemplated in case of appearance of severe blood dyscrasias.

The aim of our retrospective study was to evaluate the incidence, course, and relevance of clozapine-induced blood dyscrasias during the first 18 weeks of treatment, as compared to those induced by other typical and atypical antipsychotics, and to detect possible risk factors.

2. Methods

2.1. Subjects

We retrospectively collected and reviewed full data records of 450 Caucasian patients among whom we selected 285 (147 men and 138 women) who were admitted to the Department of Psychiatry of the University of Naples-SUN from December 1992 to May 2011. We included only patients with basal complete blood count in the normal range of values who completed 18 weeks of antipsychotic treatment. Our ethical committee had reviewed the investigation protocol, established in accordance with the updated version of the Declaration of Helsinki. Each hospitalized patient gave his/her written informed consent, upon full explanation, to the diagnostic and therapeutic procedures chosen by the physician in charge. We used an ad hoc registration form to record demographic, haematological and pharmacological treatment data.

We administered clozapine, typical and other atypical antipsychotics respectively to 135, 75 and 75 patients diagnosed with schizophrenia and bipolar spectrum disorders according to DSM III-R and DSM-IV criteria (Table 1). Clozapine-treated patients with schizophrenia met Kane's criteria for drug-resistance (Kane et al., 1988), while those on typical (TA) and other atypical antipsychotics (AA) did not. All the patients were hospitalized until clinically stable, then were discharged and administered antipsychotics at home by a key relative, who carefully verified patients' compliance during the follow-up. TA and AA groups encompassed a cohort of subjects enrolled in a wider study, yet unpublished, on the correlation between antipsychotic plasma levels and related side effects, including blood dyscrasias. All study participants underwent weekly blood sampling.

In clozapine-treated patients, we performed psychopathological assessment by means of the Expanded Brief Psychiatric Rating Scale (BPRS-E) (Lukoff et al., 1986), both before starting the antipsychotic (baseline) and at the 18th week of treatment. Patients were defined responders when presented a 20% decrease in the BPRS-E total score plus a post-treatment BPRS score of 47 or less.

2.2. Pharmacological treatments

We administered clozapine in 2–3 divided doses, with the last dose of the day given between 8:00 and 9:00 p.m., and dose increments of 25–50 mg every 2 days up to a tolerated and effective dose. We maintained the patients meeting response criteria on the effective dose up to the end of 18th week. We administered atypical antipsychotics other than clozapine to 75 patients (Group AA) once, twice or thrice/day according to drug's half-life; we administered typical antipsychotics in 2–3 divided daily doses to 75 patients (Group TA).

At the end of the 18th week of treatment, among clozapine-treated patients 63 received benzodiazepines, in addition, 33 mood stabilizers and 9 antidepressants; in Group AA, 37 patients were concomitantly treated with benzodiazepines, 19 with mood stabilizers and 16 with antidepressants. Similarly, patients in Group TA received concomitant benzodiazepines ($n=34$), mood stabilizers ($n=17$) and antidepressants ($n=12$).

2.3. Blood samples

We accomplished blood count measurements both before initiating clozapine or other antipsychotic treatments, and weekly up to the 18th week. We collected blood samples for haematological studies between 8:00 and 9:00 a.m. into separate BD vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA) as anticoagulant, and then we sent them to a centralized analysis unit where blood was generally processed by an automated analyzer. We followed this procedure both during patients' hospitalization and after discharge up to the 18th week.

We classified haematological dyscrasias of red blood cells (RBC), white blood cells (WBC) and platelets as deviations from normal reference range values (Table 2), using the criteria adopted by Hummer et al. (1994), Oyesanmi et al. (1999), Lambertenghi Deliliers (2000), and Beutler and Waalen (2006). Specifically, we defined each blood dyscrasias as follows: anemia when the total number of red blood cells (RBC) was $< 4.5\times10^6$/uL and/or a concentration of hemoglobin $<$ 12 g/dL; leukopenia as a total leukocyte count (WBC) $< 3.5\times10^3$/uL, and leukocytosis as a total leukocyte count $> 15.0\times10^3$/uL; neutropenia as an absolute neutrophil count (ANC) of $0.5–1.5\times10^3$/uL; neutrophilia as an ANC $> 7.0\times10^3$/uL; agranulocytosis as a neutrophil count $< 0.5\times10^3$/uL; eosinophilia as a total eosinophil count $> 0.3\times10^3$/uL; eosinophilopenia as an eosinophil count $<$ than 0.1×10^3/uL; thrombocytopenia as a platelet count $< 150\times10^3$/uL, and thrombocytosis as platelets $> 500\times10^3$/uL (Table 2).

We divided all the haematological alterations into transient and persistent, considering their duration. Transient blood dyscrasias were identified as those lasting between one and two weeks after onset, and during which blood cells returned to normal values with continued antipsychotic treatment. Persistent blood dyscrasias were identified as those still present, after onset, at the end of the 18th week of antipsychotic treatment, and in which blood cells did not return to normal values.

2.4. Statistical analysis

We used the SPSS Statistical Package (16.0) to collect and process data; in detail, we calculated descriptive statistics and percentage based on socio-demographic, haematological and clinical variables. We expressed results as mean ± sd or as frequency counts, and we achieved statistical assessment by *t*-test for independent sample or cross-tabulation. We implemented multivariate logistic regression models to identify possible predictors of developing each blood dyscrasia, considered as independent dichotomous outcome. We identified possible predictors according to the relevant literature on this topic and entered them in the model and annexed more data in the Supplementary material. We set level of statistical significance at $p < 0.05$.

3. Results

3.1. Incidence rate and gender prevalence

Demographic and clinical characteristics of antipsychotic-treated patients are shown in Table 1. During the follow-up, blood dyscrasias occurred in 129 patients treated with clozapine (129/135, 95.5%), 66