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RESEARCH ARTICLE

Antipsychotic Drugs Induced Iron Deficiency Anemia in Schizophrenic Patients

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Abstract

Background: Psychiatric manifestations and its association with the antipsychotic drugs induced IDA is still controversial. Iron deficiency is the most evident risk factor for developing neuroleptic-induced extra pyramidal symptoms (EPSs), on the basis of emerging evidences; here we report the iron deficiency anemia observed in the on antipsychotic drug treated schizophrenic patients.

Methods: The hematological and absolute indices, morphological and serum iron indices assessment was focused on 120 Pakistani schizophrenic patients, who were on the chronic treatment of antipsychotic drug particularly haloperidol for more than 12 weeks of clinical practice, and 44 normal controls.

Results: Marked decrease ($p<0.0001$) was observed in the hematological indices such as hemoglobin, RBCs count and packed cell volume while marked but insignificant decrease was observed in the level of mean cell volume(MCV) in the schizophrenic patients. The morphological assessment shows significant alterations on the peripheral blood smear of the schizophrenic patients with hypochromic (>10%) and microcytic cells as compared to normocytic –normochromic controls. The serum ferritin and iron levels in these patients were within the normal range. However, significant ($p<0.0001$) inverse correlation was observed in the level of serum iron and ferritin with increased TIBC level in the schizophrenic patients as compared to the normal individuals.

Conclusion: The present study clearly delineates on the basis of sequential analysis, morphological and biochemical assessment that the type of microcytic-hypochromic anemia is iron deficiency anemia. Moreover, the clinical manifestation of iron deficiency anemia are varied and related to its severity and duration.

Introduction

In recent years, the involvement of iron in neurological disease has received increased attention particularly with reference to the Alzheimer's and Parkinson's disease, in which brain iron content has been increased (1). However, Iron deficiency and iron deficiency anemia has also been documented with the use of classical antipsychotic drugs, as they are responsible to change normal iron metabolism and increase iron uptake to the brain. Apathy, irritability, lethargy, lack of concentration, hypoactivity, increased anxiety and decreased cognition and attention are the symptoms associated with iron deficiency reported in adults and children's (2). Some evidence suggests a role of

iron deficiency in tardive dyskinesia and akathisia, a common extrapyramidal side effects of classical antipsychotic drugs particularly haloperidol (3-4).

The hyperdopaminergic state in the limbic system is associated with the positive symptoms of schizophrenia in patients treated with haloperidol; a high affinity d2 receptor antagonist. In long-term use high striatal d2 occupancy by haloperidol lead to the appearance of EPS such as tardive dyskinesia, Parkinsonism and akathisia however iron deficiency has been reported in the patients of restless legs syndrome (akathisia). Iron is essential for proper CNS metabolism, the heterogeneity of uneven distribution of iron in human and rat's brain suggested that iron may play a functional role in regions richly innervated by dopaminergic and GABAergic neurons. However, the neurobiological mechanism behind iron's role in behavior and cognition remains elusive (5).

A long period of negative iron balance, culminating in exhaustion of the body's iron stores result in IDA; the successive stages of iron deficiency are iron stores depletion, iron deficient erythropoiesis and iron deficiency anemia. In early ID (iron depletion), the concentration of serum iron is occasionally below normal values and storage iron is markedly depleted, however, this stage is usually not accompanied by any abnormalities in blood. As the iron deficiency progresses, morphological changes in blood appears leading to the development of anemia, although serum iron concentration is usually low at this stage while some cells may be smaller and paler than normal. Moreover, classic changes of hypochromic, microcytic, hypoferremic anemia become manifested with advanced iron depletion**.** Diagnosis and correction of underlying causes have important implications for the recognition of iron deficiency anemia, prompted by histological features and aided by specific clinical and laboratory data (6-7).

The clinical manifestations of iron deficiency and iron deficiency anemia are varied and related to its severity and duration. When Iron deficiency anemia (IDA) develops, it may be mild (Hb 9.5-11g/dl), moderate (8-9.5g/dl), or severe (<8g/dl). However, Hematological manifestations for IDA is typically characterized by mean cell volume (MCV) and mean cell hemoglobin (MCH) concentrations of <80fl and <26pg, respectively (12). Though no definite research has so far emerged to clarify and confirm the clinical significance, it is possible that the interaction between serum iron and antipsychotic drug affected the iron absorption and binding affinity (8-9).

The present study aims to evaluate the interaction between IDA, EPS, in response to the long-term haloperidol and clozapine medication, in schizophrenia patients. The preliminary experimental verification suggests that this approach might be promising in providing useful insight on the development of iron deficiency anemia in schizophrenic patients chronically treated with different antipsychotic drugs.

METHODS

The blood samples of the schizophrenic patients (n=120) were collected, after obtaining written informed consent from different psychiatric hospital allover Karachi. All patients met the criteria for the diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders IV and were on haloperidol and clozapine treatment according to the normal clinical practice for more than 12 weeks. The control group comprised of healthy subjects (n=44) with no previous history of any psychiatric disorder or any other common disease such as diabetes etc.

Criteria for the DSM-IV diagnosis were established by a group of psychiatrist who reviewed the medical record data and where necessary, interviewed the patients. The records of the schizophrenic patients were also used to determine the gender, age of the patients, age at the first onset of illness, duration of illness, duration of antipsychotic treatment, current daily antipsychotic drug dosage, %age of positive and negative symptoms and PANSS score. Additionally we have collected the dietary information of these patients; they all have taken normal routine diet, which is not supposed to be iron deficient.

Hematological parameters including hemoglobin, hematocrit, RBC and differential counts, absolute indices, Red cell Distribution Width (RDW) and morphological features of RBCs by peripheral blood smear were performed standard laboratory methods using automated chemistry analyzer. Additionally Serum Iron Concentration (SIC), Total Iron Binding Capacity (TIBC) (Roche Ltd.) and the serum ferritin level (Randox Ltd.) were also determined in the schizophrenic patients and control group. All statistical analysis (student's t-test & correlation) was carried out by using SPSS and statistica-V software.

RESULTS

The present study focuses on the antipsychotic drug induced blood dyscrasias in the schizophrenic patients. The socio-demographic and clinical features of 120 schizophrenic patients chronically treated with haloperidol (n=92) and clozapine (n=28) was summarized in **Table 1**. No significant difference was observed in the two treatment groups on age, age at 1st onset of illness, duration of treatment and dosage of antipsychotic drug treatment. The assessment of extra pyramidal (EPS) side effects of the typical antipsychotic drug haloperidol was evaluated as per

reported in the patient history profile on different stages during treatment. Significant differences were observed in the side effect profile of haloperidol and clozapine at their clinically effective dosage (**Table 2).** Extra pyramidal syndrome (EPS) like Dystonia, Parkinsonism, Akathisia and Tardive dyskinesia were significantly more common in patient treated with haloperidol. In contrast, Agranulocytosis was significantly more common in the clozapine treated patients.

Table 1 Demographic and clinical features of Schizophrenic patients treated with haloperidol (n=92) and clozapine (n=28).

Variables	Schizophrenic patients (Haloperidol)	Schizophrenic patients (Clozapine)
Age (Years)	29.07±9.05	27.0±7.10
Age at Ist onset of illness (years)	24.07±7.48	21.09±3.71
Duration of receiving treatment (years)	3.66±3.03	3.53±4.01
Dosage of AP drugs(mg/day)	22.30±8.39	22.4±36.2
Positive symptoms (%PS)	40.47±9.77	39.36±11.05
Negative symptoms (%NS)	56.37±8.26	69.31±11.92
PANSS (%)*	48.41±6.74	55.71±10.79

- Values are Mean± S.D.
- PANSS- Positive and Negative Symptoms Scale (total %age)*.

Table 2 Comparison of the side effects profile associated with typical (haloperidol) and atypical (clozapine) antipsychotic drugs.

Adverse affects	Haloperidol	Clozapine
EPS (Dystonia,Parkinsonism, Akathesia,Tardive- Dyskinesia	+++++	+
Sedation	++	+++++
Hypotension	+	+++++
Agranulocytosis	-	+++++

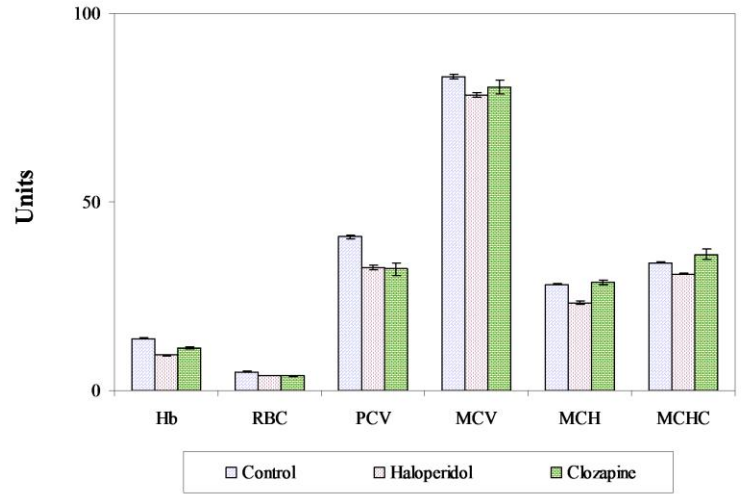
- Haloperidol (Dose= 2-200mg/day)
- Clozapine (Dose= 5-60 mg/day)
- The + sign represents the severity of side effects.

Table 3 Calculations used for interpreting erythrocyte indices in order to discriminate two types of microcytic anemia: thalassemia minor and iron deficiency.

Calculations	Iron Deficiency	Thal. Minor	Our Results
MCV- (5xHb) - RBC-3.4	>0	<0	16.21
MCV/RBC	>13	<13	18.68
MCH/ RBC	>3.8	<3.8	6.22
Red blood cell (RBC)	<5.0	>0.5	4.19
MCH x (MCV) ^{2}/100	>1530	<1530	1599

The hematological indices including hemoglobin concentration, complete blood cell count and absolute indices (PCV, MCV, MCH and MCHC) are the measures that provided information about the severity of anemia (10). The schizophrenic patients chronically treated with haloperidol (n=84) showed significant ($p<0.0001$) decrease in hemoglobin concentration (9.36±1.29) and the RBC counts (3.9±0.191) with a slight decrease in PCV (32.61±3.02), MCV (79.09±4.44), and MCH (23.27±2.52) level indicating anemia (**Figure 1**). While MCHC level (28.59±1.96) is significantly ($p<0.0001$) increased in these patients as compared to their respective controls. In contrast, the hematological profile of the schizophrenic patients treated with clozapine (n=28) shows slight decrease in hemoglobin concentration (11.26±1.85), RBCs counts (3.9±0.61), PCV (32.16±7.95) and MCV (80.50±8.72) except slight increase in MCH (28.63±3.16) and MCHC values (36.1±6.66) do not attributed to anemia (**Figure 1**). We also considered some calculations for the initial screening of microcytic anemia using erythrocyte indices in order to discriminate IDA with thalassemia minor (**Table 3**).

Figure 1 Comparison of Hematological indices (Mean±SEM) in haloperidol and clozapine treated schizophrenic patients.

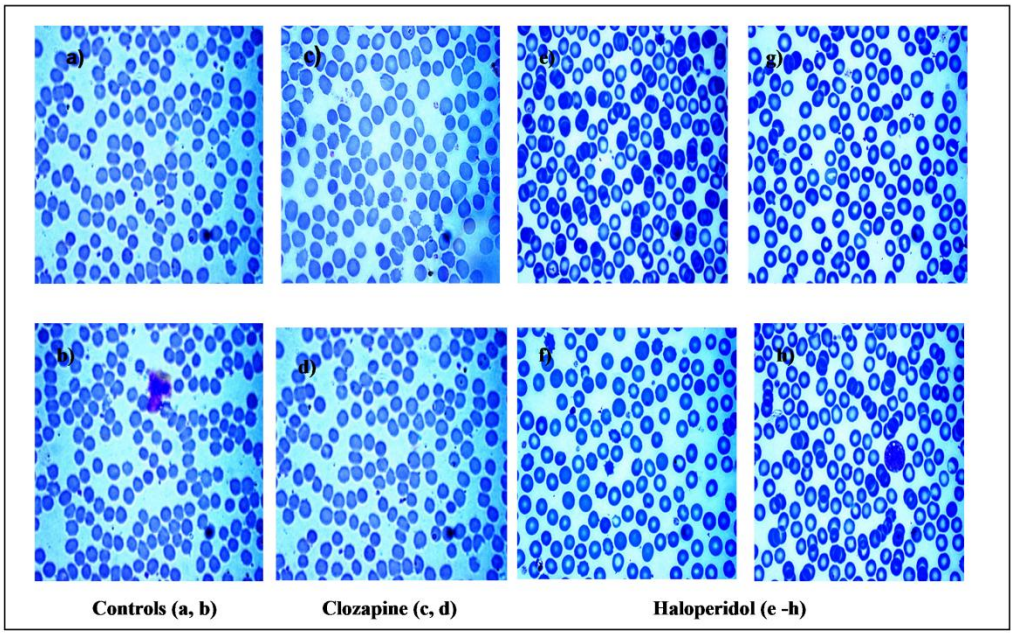


Hb- hemoglobin (g/dl), RBC- Red blood cell concentration (Cu.mm), PCV-Packed cell volume (%), MCV-Mean cell volume (fl), MCH-Mean cell hemoglobin (pg), MCHC- mean cell hemoglobin concentration (%), RDW-Red cell distribution width (%).

Analysis of peripheral blood smear allows interpretation of multiple visible characteristics of the red blood cells (RBC), including shape, size and pigmentation. The characteristic changes in the size and the hemoglobin content of the red cells revealed the presence of anemia although the degree of anisocytosis is correlated with the severity of IDA.

In addition to the clinical assessment, the differential diagnosis based on morphologic examination of blood smear was carried out. The peripheral blood smear of the schizophrenic patients show characteristic changes in the morphology of RBC. The appearance of the hypochromic cell (>10%) with microcytic cells may suggest iron deficiency anemia when compared with normocytic-normochromic controls. However, no characteristic change in RBC morphology was observed subsequent to clozapine treatment in the schizophrenic patients (**Figure 2**).

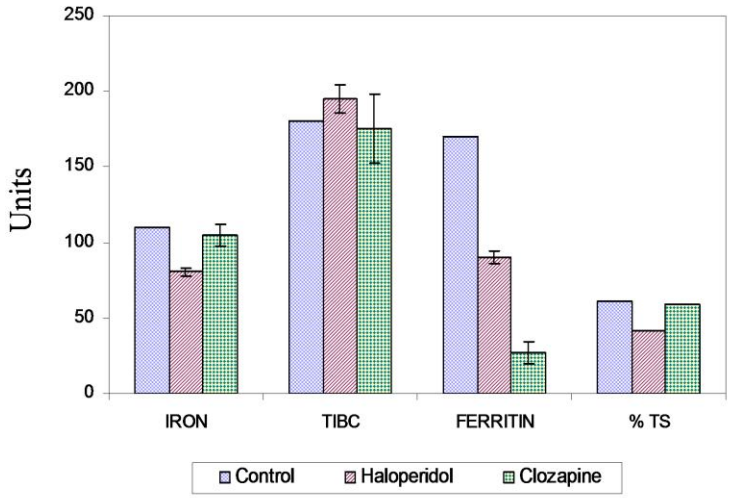
Figure 2 Light microscopy of Leishman's stained slides of peripheral blood smear of antipsychotic drug treated schizophrenic patients.



The peripheral blood smear of the control (a & b), and clozapine treated patients (c-d) individual, show Normocytic and Normochromic morphology of RBC while (e-h) represent the hypochromic–microcytic cells following chronic haloperidol treatment.

Iron profile is a useful biochemical marker to confirm iron deficiency when other findings are inconclusive. Significant changes ($p<0.0001$) were observed in the iron profile, serum iron (80.42±20.79) and ferritin (90.12±38.01) level was decrease with increased level of TIBC (195.1±82.73), in the schizophrenic patients treated with haloperidol as compare to the normal controls suggesting iron deficiency **(Figure 3).** A decrease in the blood level of iron was previously reported (9) with the haloperidol treatment, which was further assessed by some biochemical parameters to confirm the presence of IDA. Additionally it was confirmed that the patients were taken normal diet, which is not supposed to be iron deficient. On contrary, in case of schizophrenic patients treated with clozapine, No significant changes were observed in the iron profile except marked decrease in Ferritin (27.12±22.71) level (**Figure 3**).

Figure 3 Comparison of Iron profile ((Mean±SEM) of schizophrenic patients chronically treated with haloperidol and clozapine.



Iron (µg/dl), TIBC-Total iron binding Capacity (µg/dl), Ferritin (ng/dl), %age TS-Transferrin saturation (%).

Discussion

The present study on the basis of sequential analysis, morphological and biochemical assessment clearly delineates the presence of iron deficiency anemia in schizophrenic patients treated with antipsychotic drugs (haloperidol/clozapine). Iron studies cannot be accurately assessed on the basis of serum ferritin, serum iron and RBC features alone, but is dependent on each other and hence a strong association can be identified on this basis.

In our results, it is alarming to note that almost 75% of schizophrenic patients on long-term haloperidol treatment showed >10% hypochromic and microcytic cells when compared to normocytic-normochromic cells observed in clozapine. The appearance of characteristic changes in the morphological features of RBC particularly the presence of hypochromic-microcytic cells (>10%), reinforces the detection of type of microcytic anemia-IDA (iron deficiency anemia). Further validations by other parameters, in response to the chronic treatment of haloperidol in schizophrenic patients, indicated that it is a side effect of a drug rather than a disease state in schizophrenia. Additionally, we confirmed that the patients were not taken an iron deficient diet.

The iron profiles of schizophrenia patients after long-term haloperidol treatment may be explained by the following two hypotheses; Firstly, long-term administration of haloperidol may modulate the iron level in schizophrenia. Secondly, the iron levels observed in schizophrenia may be affected by antipsychotic drug treatment. The later possibility appears more likely, since a number of studies performed in schizophrenic patients, on blood (8, 13-14) and brain with long-term antipsychotic drug treatment shows the same (9).

There is evidence that long term haloperidol treatment can negatively impact iron status in individuals due to its chelation abilities. Because there are links between abnormal brain iron levels and neurological dysfunction (e.g., high iron is linked with neurodegeneration and low iron is linked with altered dopamine biology (3, 9). Alteration in iron metabolism has been associated with the antipsychotic drugs although an association between peripheral and brain iron level is difficult to assess. Restless-legs syndrome (akathisia) an EPS, related with haloperidol demonstrates a high prevalence of iron deficiency. The most likely mechanism of iron deficiency in the schizophrenic patients is the interaction of neuroleptic drugs and the dopamine D2 receptor, as it affects iron deposition in caudate nucleus (11) perhaps due to the iron chelating property of haloperidol. Accordingly, iron stores are more dynamic and may be more susceptible to chelation by neuroleptics at the onset of iron deficiency (9). Once iron deficiency has been induced, iron stores are depleted and therefore are not available any further for interaction with antipsychotics. Furthermore, alterations of DRD2 receptor number was suggested to be associated with body iron status particularly during iron deficiency after chronic haloperidol treatment. Consequently, this

decrease iron may augment the availability of free haloperidol for the dopamine D2 receptor. There are also other factors that may further complicate the evaluation of iron deficiency in patients. Changes in the serum iron level, in schizophrenic patients reported here and that of decrease iron in brain regions (9) support the notion that dopaminergic pathway is sensitive to iron deficiency (15-19).

Variability in clozapine and haloperidol induced blood disorders in patient do not support any association between low serum iron and DRD2 gene polymorphism, whereas dopamine trafficking is affected and possibly related to known dopamine system alterations in iron deficiency (20). It has been suggested that dopamine D2 receptor is an iron-containing protein and low serum iron level results in hypo function of D2 receptors which predisposes patients on antipsychotic medication vulnerable to akathisia / IDA. The correlation between iron status and haloperidol induced changes suggests the overall contribution of drug in the development of iron deficiency, if any, cannot be overlooked as it was found with clozapine medication.

In conclusion, our study strongly supports the role of typical antipsychotic in development of iron deficiency anemia in schizophrenic patients, this decrease in serum iron and ferretin levels along with increase TIBC also relates to akathisia in these patients. Furthermore, the iron levels affected by two drugs types are not identical and may represent the adverse effects of drug response reported for the first time in Pakistani schizophrenic patients and the knowledge utilized to support possible monitoring strategies to reduce blood disorders from antipsychotic drug treatment.

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