Original Article

HALOPERIDOL INDUCED VARIATIONS IN HEMATOLOGICAL INDICES

Wasti A¹, Ghani R², Manji MA³ & Siddiqui NA⁴

ABSTRACT
It is essential for the effective management of drug action to understand the underlying pathogenesis of hematological dyscrasias. Hematological side effects of neuroleptic drugs occur infrequently but remain a potential cause of serious toxicity. The risk of butyrophenone induced blood dyscrasias seems to be underestimated in the literature, therefore we decided to report this as an animal model evaluation.
The present work was undertaken to investigate the effect of typical antipsychotic drug (Haloperidol- 0.2mg/Kg), both as purified and commercially available form administered to rats (n=15), on hematological indices.
Data of the present study suggests that the chronic administration of haloperidol may cause iron deficiency anemia. Although the morphological changes were more obvious in case of purified haloperidol treated rats as compared to the commercially available injections.

KEY WORDS: Typical antipsychotic drug, Haloperidol (Serenace), Hematological side effects, IDA - Iron deficiency anemia.

INTRODUCTION
Hematological side effects of neuroleptic drugs occur infrequently but remain a potential cause of serious toxicity¹. An understand-
ing of the pathogenesis of hematological dyscrasias is essential for their effective management². The side effect profile of traditional or typical neuroleptic agents has been a highly limiting factor during acute and chronic treatment but hematological effects are rare³. Although the risk from most drugs is very small but it may affect peripheral blood cells and bone marrow. Neutropenia, leukocytosis and anemia are the common side effects⁴. Anemias are disorders characterized by decreased hemoglobin, which is frequently accompanied by decreased red cell count. The diagnostic hypothesis of microcytic anemia is based on complete blood cell count (CBC) results. Discordant properties of the red blood cell (RBC) have been exploited to differentiate the two most common types of microcytic anemia, iron deficiency anemia and heterozygous thalassemia. Deficiency of iron is probably the most common cause of microcytic anemia through out the world⁵-⁹.

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Iron deficiency anemia (IDA) has been documented to be caused by the administration of various antipsychotic drugs. However, to date no definite research has emerged to clarify and confirm the clinical significance of the interaction between haloperidol and iron\textsuperscript{10}.

The focus of the present study is haloperidol (a butyrophenone) induced hematological dyscrasias, associated with chronic treatment of drug both purified form and commercially available injections on animal model, most commonly used for the treatment of schizophrenia and other psychotic disorders.

SUBJECTS AND METHODS

The Albino Sprague Dawley rats (n=15) with an average weight of 180g were divided into three groups. First group (n=5) was administered intramuscular haloperidol (0.2 mg/Kg) of purified form (Sigma) while the second group (n=5) was treated with (0.2 mg/Kg) commercially available haloperidol injection (Searle) and the controls (n=5) were subjected to saline treatment, for 21 consecutive days. The rats were decapitated 18 hours after the last injection. Whole blood and serum samples were collected separately and analyzed.

Numbers of preparations were made in duplicate (n=10 for each group). The hematological parameters including hemoglobin, RBC and differential counts, absolute indices including hematocrit (packed cell volume, PCV), Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW) and morphological features of RBCs via peripheral blood smear were performed by standard laboratory methods. Serum iron concentration (SIC), total iron binding capacity (TIBC) (Roche Ltd.) and the serum ferritin level (Randox Ltd.) were determined. The percentage transferrin saturation was also calculated\textsuperscript{11-13}. All statistical analysis was performed using graph pad prism and statistica software.

RESULTS

Iron deficiency anemia (IDA) has been documented to be caused by the administration of various antipsychotic drugs. However, to date
no definite research has emerged to clarify and confirm the clinical significance of the interaction between haloperidol and iron.

The hematological indices including hemoglobin concentration, complete blood cell count and absolute indices (PCV, MCV, MCH and MCHC) are the measures that give information about the severity of anemia. Our results showed the hemoglobin concentration and the RBC count in both the experimental groups to be significantly decreased (p < 0.05) respectively. A significant decrease (p < 0.05) in PCV, MCV, and MCH level with high RDW value indicating anemia was observed while MCHC level did not show any significant change in both the experimental groups as compared to their respective controls (Table-I).

**DISCUSSION**

The peripheral blood smear has been reported to reveal characteristic changes in the size and the hemoglobin content of the red cells, observed in some types 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 rats treated with haloperidol injection showed anisocytosis and hypochromic cells while the rats treated with purified form of haloperidol showed in addition to anisocytosis and hypo-chromic cells, microcytic cells when compared to their respective normocytic-normochromic control rats (Fig. 1) suggesting that the type of anemia may be microcytic-hypochromic.

A decrease in the blood level of iron was previously reported with the haloperidol treatment, which were further confirmed by some biochemical parameters to confirm the presence of IDA. A significant decrease (p<0.05) in serum iron level as compared to serum ferritin level and transferrin saturation (%) with concurrent increase (p<0.05) in serum TIBC was shown in both the experimental groups as compared to their respective controls (Table-II) indicating that IDA is caused by the chronic treatment of haloperidol in an animal model.

**CONCLUSION**

Unfortunately the side effect profile of traditional neuroleptic drugs has been the highly limiting factors. Our study however, does imply the hematological effects related with the chronic treatment of haloperidol (both as com-

**TABLE - I: Comparison of Hematological indices following chronic haloperidol (both purified and injection form) treatment in rats (* p<0.05)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Haloperidol Injection (n=10)</th>
<th>Haloperidol Purified Form (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% age increase ↑ or decrease ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>3.64 ↓</td>
<td>19.38* ↓</td>
</tr>
<tr>
<td>RBC</td>
<td>2.40 ↓</td>
<td>13.30* ↓</td>
</tr>
<tr>
<td>PCV</td>
<td>5.25 ↓</td>
<td>34.71* ↓</td>
</tr>
<tr>
<td>MCV</td>
<td>4.62 ↓</td>
<td>15.50 * ↓</td>
</tr>
<tr>
<td>MCH</td>
<td>0.91 ↓</td>
<td>07.70 ↓</td>
</tr>
<tr>
<td>MCHC</td>
<td>0.92 ↑</td>
<td>0.01 ↑</td>
</tr>
<tr>
<td>RDW</td>
<td>20.48 ↑</td>
<td>39.75*↑</td>
</tr>
</tbody>
</table>

Hb= hemoglobin g/dl, RBC= red cell count cu/mm, PCV= packed cell volume %, MCV= mean corpuscular volume fl, MCH= mean corpuscular hemoglobin pg, MCHC= mean corpuscular hemoglobin concentration g/dl, RDW= red cell distribution width %

**TABLE - II: Comparison of Iron profile following chronic haloperidol (both purified & injection form) treatment in rats (*p<0.05)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=10)</th>
<th>Haloperidol injection (n=10)</th>
<th>Haloperidol purified Form (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>197.20±7.820</td>
<td>134.80±18.450*</td>
<td>82.50±9.980*</td>
</tr>
<tr>
<td>TIBC</td>
<td>937.80±35.67</td>
<td>1163.60±33.72*</td>
<td>1590.0±203.5*</td>
</tr>
<tr>
<td>%T. Saturation</td>
<td>21.04±1.676</td>
<td>11.560±1.942 *</td>
<td>5.425±1.367*</td>
</tr>
</tbody>
</table>

Iron ug/dl, TIBC= total iron binding capacity ug/dl, % transferrin saturation
mercially available form and purified form) in an animal model. The sequential analysis based on the morphological and biochemical assessment suggests that the type of microcytic-hypochromic anemia is IDA. Because iron studies cannot be accurately assessed on the basis of serum ferritin, serum iron or RBCs features alone. These parameters appear to be dependent on each other and a strong association can be identified. The severity of iron deficiency anemia is more obvious in the purified powder as compared to commercially available injection treatment. However, the mechanism of the interaction of haloperidol and iron is yet to be investigated.

REFERENCES