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Probable ticlopidine-induced severe aplastic anemia and cholestatic hepatitis

Sir,

Ticlopidine is a thienopyridine derivative with platelet-inhibitor capability used to reduce the risk of stroke. The most common adverse effects are mild and transitory: diarrhea, nausea, dyspepsia and rashes. More serious side effects are less frequent; they include: neutropenia, thrombocytopenia, purpura and cholestatic hepatitis, whose pathogenesis is not fully un-
derstood.1-4

A 67-year-old man with no history of liver or hematological disease was admitted to the hospital on February 12, 1996. He had been suffering for ten days from acholia, choloria, fever, weakness and painless jaundice. His medical antecedents included chronic auricular fibrillation, hiatal hernia and duodenal ulcer with gastrointestinal bleeding. Treatment on ad-
mission consisted of digoxin, ciprofl oxacine (for the last 3 days), occasionally acetaminophen and ticlopidine (250 mg po bid) for 69 days. The patient was markedly icteric, with 39°C fever and crepitation at both pulmonary bases. He had no abdominal tenderness and no palpable gallbladder or lymph nodes. The urine was dark brown and the stool was light. On admission, WBC count was 0.6×10^9/L (90% lymphocytes), hemoglobin 13 g/dL, platelets 79×10^9/L, reticulocytes 0%, ALAT 24 iu/L (S-40), γGT 321 iu/L (S-53), alkaline phosphatase 512 iu/L, bilirubin 18 mg/dL (conjugated 10 mg/dL) and abdominal ultrasound showed hepatomegaly, but no evidence of biliary obstruction. Coagulation tests, renal functions, immunoglobu-
in level, complement, autoantibodies and sucrose hemolytic tests were normal; viral screening was negative for AHV, BHV, CHV, HIV, CMV, and EBV; the bacterial blood cultures and par-
astigic investigation were negative as well. A chest x-ray displayed a minor cardiomegaly. The trephine biopsy showed a pattern of severe aplastic anemia with very hypoplastic cellularity and an absence of granulocyte, erythrocyte and megakaryocytic cells, pre-
senting mainly mononuclear cells. On day 3 his blood cell counts were: 0.3×10^9/L (0% neutrophils), 9.4 g/dL hemoglo-
bin, platelets 16×10^9/L and 0% reticulocytes. Our diagnosis was very severe aplastic anemia and intrahepatic cholestasis, probably due to ticlopidine. We suspended ticlopidine and began with empirical broad-spectrum iv antibiotic, antifungal agents, G-CSF (Linograstin®), Chugai-Rhone-Poulenc, 150 mg/m^2, isolation, transfusion and hydration. On the fifth day we started immunosuppressive therapy with ATG (Atgam® Upjohn, 15 mg/kg iv daily for 8 days). The clinical evolution was excellent: on the twelfth day WCB count was 5.7×10^9/L, platelets were 93×10^9/L, hemoglobin 9 g/dL, reticulocytes 32×10^9/L, bilirubin 3.7 mg/dL, alkaline phosphatase 402 iu/L and γGT 268 iv/ L. All the analyses were normal after three weeks and on the fourteenth day, the patient was discharged. Sixty days later his tests were clinically and biologically normal.

In our study, we describe one of the first cases of the associa-
tion of ticlopidine and severe aplastic anemia in addition to intrahepatic cholestasis. We believe the combination of general supportive and specific therapy probably determined the posi-
tive clinical evolution, as spontaneous normalization is usually observed within three to five weeks after suppression of ticlo-
pi dine.1-4 We conclude that patients receiving ticlopidine should

References

Desferrioxamine in the treatment of myelodysplastic syndromes

Sir,

For many patients with myelodysplastic syndrome (MDS) refractory anemia is the main clinical problem. Unfortunately, only some patients benefit from treatment with hematopoietic growth factors.1-4 Unresponsive individuals often have a high transfusion requirement and need iron chelation treatment. In some of these patients, desferrioxamine (DFO) has been report-
ed to be effective not only as an iron-chelating agent but also in reducing the transfusion requirement.1-4 In the last few years, we have treated three MDS patients with DFO. All three patients presented isolated anemia (see Table 1). All patients received 30 mg/kg of DFO three days per week, by subcutaneous infu-
sion over a 12-hour period via a disposable infusion. No other medication was given. On each transfusion day, transfusion (of red cell concentrate, RCC) was given if Hb was below 9 g/dL; the transfusion requirement was estimated using the following formula:2-4

\[
\frac{(A \times BV + B \times 75) - (C \times BV)}{D}
\]

where A = pre-transfusional Hb (g/dL) at start of a transfusion 
episode; B = number of RCCs supplied on that day; C = pre-transfusion Hb at a subsequent transfusion episode; BV = blood volume; 75 = mean Hb content (g) in one RCC; D = num-
ber of days between A and C; and 31 = 31 days/month. The results for patients #1 and #2 show a reduction in transfusion requirement following DFO treatment, in accordance with previous reports.1-4 These authors observed that the reduc-
tion in transfusion requirement correlated with the efficacy of iron chelation (as indicated by the reduction in the hepatic iron concentration), but not with the degree of attainment of nor-
mal iron stores.4 In our patients, improvement was observed

despite the fact that serum ferritin levels did not decrease, although it must be noted that ferritin level alone is a poor guide to the extent of iron overload. Thus, the effects observed on the transfusion requirement may be independent of the normalization of iron stores, and depend only on the chelant properties of DFO. It would be of interest for future studies to investigate these possibilities.

Table 1. Results of DFO treatment in three MDS patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/age</th>
<th>FAB subtype</th>
<th>Hb pre (g/dL)</th>
<th>Req pre (g/month)</th>
<th>F pre (µg/L)</th>
<th>Treatment period (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/71</td>
<td>RA</td>
<td>7.8</td>
<td>141</td>
<td>1581</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>M/25</td>
<td>RARS</td>
<td>8.5</td>
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<td>2430</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>M/70</td>
<td>RARS</td>
<td>8.1</td>
<td>143</td>
<td>2778</td>
<td>20</td>
</tr>
</tbody>
</table>

Hb: pre-transfusional Hb. Req: transfusion requirements. F: ferritin. pre and post: means for the three months before and after the treatment period.

In conclusion, we consider DFO treatment to be an attractive option for MDS sufferers who require regular transfusion. As has been reported previously, long periods of treatment seem to be necessary before any improvement is observed. In our opinion, DFO is most suitable for non-elderly patients who can easily manage self-administration of the drug.

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References


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