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INADEQUATE TREATMENT OF EXCESSIVE ERYTHROCYTOSIS[1]

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SUMMARY. Patients with Chronic Mountain Sickness or Excessive Erythrocytosis (EE) are permanent residents of high altitude 3600 m, and have red blood cell counts (RBC) above 6.5 x 10^6 and appear cyanotic. This causes aesthetic and psychological problems in their life. Occasionally, observers may believe they are alcoholics. When RBC are increased, they search for a miraculous cure. According to several previously evolved concepts of EE, treatments have included: leeches, marrow radiotherapy by administration of radioactive substances like phosphorous, and more recently, phlebotomies, tea infusions, garlic tablets and most dangerously, administration of a previously prohibited cytotoxic agent, phenylhydrazine. One concept of providing treatment for EE patients is to permanently destroy their RBCs. However, the effect of phenylhydrazine usage is toxic for the bone marrow, the liver and other tissues, changing the color of the skin from cyanotic to yellow, with jaundice. The conjunctivae of the eyes become icteric and the urine becomes dark brown. Once started on treatment, patients are tested periodically and their RBC count indeed diminishes, and they may feel satisfied. However this toxic medication may have a fatal outcome. By reducing the number of RBCs, the arterial oxygen content (CaO_2) of the blood is diminished. We have found the majority of patients with EE to have abnormal chest x-rays. Ergometric testing of these patients may produce severe oxygen debt. In one of the patients, on the 4th stage of the Bruce Protocol, intense pain in both legs gradually became intolerable and he required post-exercise oxygen. Following interruption of the phenylhydrazine, CaO_2 returned to normal in approximately 60 days, with a rise of RBCs slightly above previous levels. The patient experienced no symptoms of illness. This case and multiple other cases have lead us to believe that EE is a compensating mechanism for lung disease at high altitude and that the RBC mass should not be decreased.

Key words: Excessive erythrocytosis, Phenylhydrazine, treatment.

RESUMEN. Los pacientes con el mal de montaña crónico o eritrocitosis excesiva (EE) son residentes de la altura (3600 m) con ≥ 6.5 x 10^6 glóbulos rojos (GR) que presentan cianosis. Esto ocasiona problemas estéticos y psicológicos en su vida ya que las demás personas creen que son alcohólicos. Cuando hay aumento de los GR, ellos buscan una cura milagrosa. De acuerdo a los conceptos evolutivos de la EE, los tratamientos han incluído: sanguijuelas, radioterapia de la médula ósea mediante administración de substancias radioactivas como el fósforo, y más recientemente, flebotomías, infusiones de té, tabletas de ajo y la más peligrosa la administración de la fenilhidrazina, agente citotóxico prohibido. Encontramos que la mayoría de los pacientes con EE tienen placas radiográficas de tórax anormales. El concepto de los tratamientos es el de disminuir los GR. Sin embargo, la fenilhidrazina es tóxica para la médula ósea, el hígado y otros tejidos, cambiando el color de la piel de cianótica a ictérica. Las conjuntivas se tornan ictéricas y la orina café oscura. Una vez iniciado el tratamiento, la sangre de los pacientes es analizada periódicamente y el recuento de GR disminuye, con lo que quedan satisfechos. Sin embargo, este medicamento tóxico puede producir la muerte. Al reducir los GR, el contenido arterial de oxígeno (CaO_2) en la sangre disminuye. Las pruebas ergométricas en estos pacientes durante el tratamiento producen gran débito de oxígeno. En el paciente descrito, en el 4to nivel del protocolo de Bruce, el dolor intenso de ambas pantorrillas se hizo intolerable y requirió oxígeno post ejercicio. Al interrumpirse la fenilhidrazina, el CaO_2 retorna a niveles normales en aproximadamente 60 días, con una elevación de los GR por encima de los valores iniciales, y mejoría de la capacidad de ejercicio. Este y muchos otros casos nos llevan a creer que la EE es un mecanismo de compensación de la enfermedad pulmonar en la altura y que la cantidad de GR no debe ser disminuída.

Palabras claves: Eritrocitosis excesiva, tratamiento, fenilhidrazina.

INTRODUCTION

Since Monge (Monge, 1928; 1929; 1943) described chronic mountain sickness (CMS), the treatment of these patients has been controversial. These high altitude inhabitants suffer from an increased number of red blood cells and are cyanotic. They usually are diagnosed with Excessive Erythrocytosis because they consult a physician due to their cyanosis or headaches, or simply because a routine blood test reveals an increased hematocrit. Frequently they are told that their high hematocrit is very dangerous and so their understood objective is to find a doctor to be treated to reduce the number of red blood cells. Unfortunately, they may fall

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easily into the hands of unscrupulous physicians. Hence they receive multiple panaceas or see physicians who propose phlebotomies. However some physicians have given these patients, phenylhydrazine, a hemolytic agent long abandoned because of its toxicity (Litter M. 1984). In the past, we have seen several cases treated with this medication.

We present a case report in order to illustrate the toxic effects of this drug in a patient with EE. He was initially seen by us, before being given the treatment and later while he took the drug.

METHODS

Patient FG was first seen in consultation because of cyanosis, headaches and fatigue. He was a non-smoker, drank alcoholic beverages occasionally, had minor digestion problems. His father died of lung cancer and his mother had a cardiac pacemaker. Five brothers were healthy. A complete physical examination was performed on this 44 year old subject. Weight was 74.3 Kg, height 163 cm, blood pressure 120/90 mm Hg and his pulse was 90 per minute. The electrocardiogram revealed elevation of S-T segments in V-2 and V-3. On laboratory examination, the hematocrit was 67%, hemoglobin 22.3 gm%, 7.5 million red blood cells per mm^3, and 8700 white blood cells per mm^3 and a 70 % neutrophil differential count. The urine analysis was normal.

Pulmonary function studies found a diminished forced vital capacity (FVC), 79% of predicted, FEV.1, 77% predicted and FEF 25-75, 59% of predicted. A flow-volume curve was compatible with chronic bronchial obstruction. The Nitrogen Washout test revealed a diminished Total Lung Capacity (87% predicted), and residual volume (72% of predicted), with no signs of uneven ventilation. Radial artery blood gases at rest found a $PaCO_2$ of 39 mm Hg, PaO_2 39 mm Hg and pH of 7.38, a compensated respiratory acidosis. His chest x-rays, showed enlarged hila, nodular images distributed in both lungs, a 2 cm in diameter calcified nodule, and an enlarged heart.

A hyperoxic test breathing 100 % oxygen showed significant pulmonary shunt reaching a PaO_2 of only 104 mm Hg (normal above 200 mm Hg). He was diagnosed as having chronic obstructive pulmonary disease, cor pulmonale, myocardial ischaemia and pulmonary shunting with compensatory excessive erythrocytosis. He was given antibiotics, mucolitics, bronchodilators, and a weight loss diet. On the second visit, two months later, he felt much better, his hematocrit increased to 73 % and blood gases improved (Fig. 1). He naturally thought he was getting worse. He was lost to follow-up, but reappeared confidently 6 months later with a hematocrit of 53% and leukocytosis of 10300. In the interim he had received phenylhydrazine, two tablets a day prescribed by a hematologist. He was pale yellow with jaundice readily evident in his sclerae.

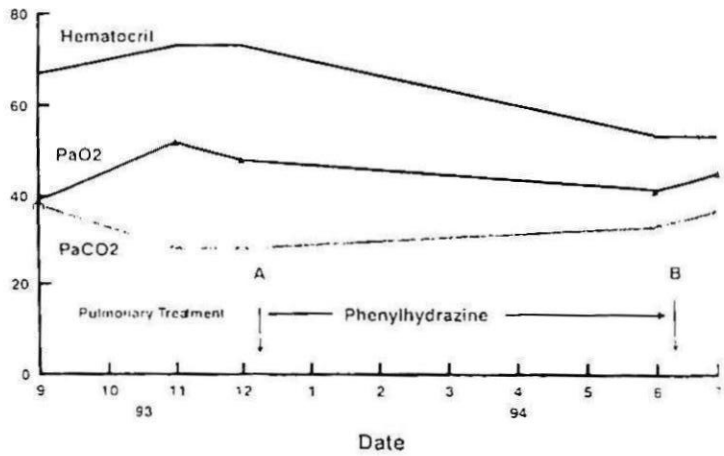

Fig. 1. Effect of Phenylhydrazine in a patient with Excessive Erythrocytosis who was in pulmonary treatment until line A, when he consulted elsewhere and was started on phenylhydrazine, to be later rechecked by us in line B.

The urine analysis showed a dark brown color, ketones +, nitrites +, bilirrubin +++, Urobilinogen +++, protein ++ and hemoglobin ++++. The blood smear showed target cells along with poikilocytes and anisocytosis (Fig. 2).

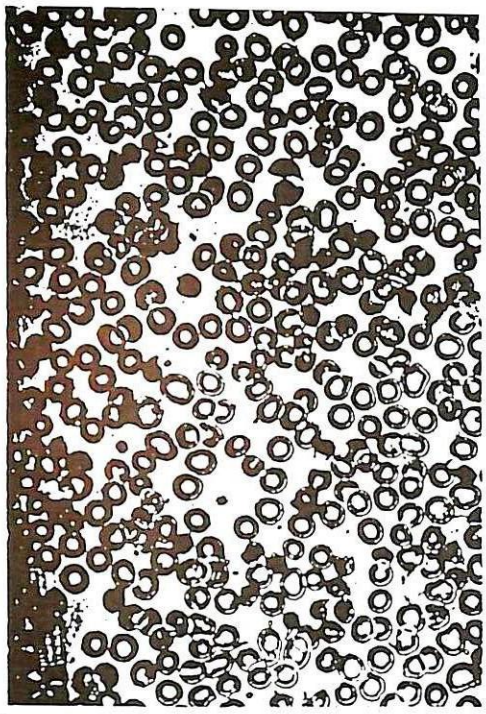

Fig. 2. Red cell smear with Wright stain in the same patient while receiving Phenylhydrazine at line B of fig 1.

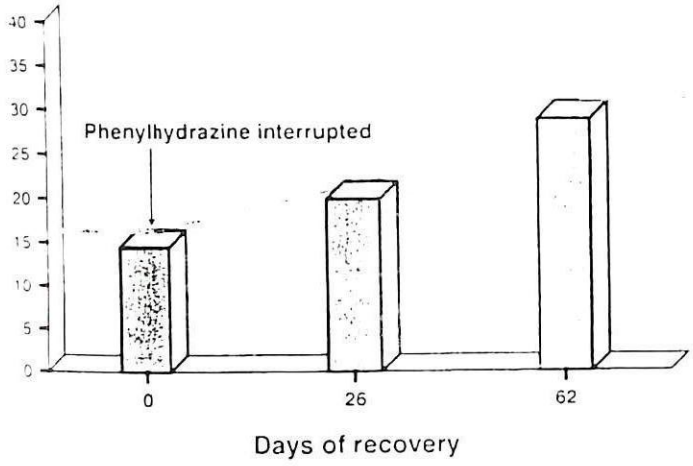

Fig. 3. Once Phenylhydrazine is interrupted the oxygen content rises in 3 months as observed in another patient.

On a treadmill exercise test with the Bruce Protocol, he made an effort to reach 5 levels. Upon stopping, he was extremely cyanotic, could hardly talk, was very dyspneic and complained of intense pain in both calves. He was given oxygen because we had never seen so severe oxygen debt post exercise.

DISCUSSION

This is another case of the previously reported iatrogeny (Zubieta-Calleja and Zubieta-Castillo, 1989). This patient was diagnosed as having EE secondary to long term cardio-pulmonary disease at high altitude (3600 m). When he was originally treated by us, we focused the treatment on improving the pulmonary function and his hematocrit increased, but so did his PaO_2 (52 mm Hg). While receiving Phenylhydrazine his oxygen content was reduced dramatically and due to the large shunt, his PaO_2 was 41 mm Hg although he looked less cyanotic (actually yellow). The exercise test found him capable of achieving the 5th level (normal, for a sedentary healthy person at 3600 m) but at great oxygen debt. This was a patient with a large intra-pulmonary shunt whose compensating EE was significantly reduced. Therefore the oxygen content of his blood was reduced along with his work capacity. In another patient, the arterial oxygen content gradually increased in 62 days, upon interruption of Phenylhydrazine and it was observed that there was a significant improvement on uphill walking the steep streets of La Paz, something he had been unable to do while on the drug (Fig. 3).

In the first patient, blood and urine analysis showed intense hemolysis, characteristic of the use of phenylhydrazine. This can be extremely dangerous leading to renal insufficiency, hepatotoxicity and bone marrow toxicity. The pulmonary shunt could not be improved by decreasing the red blood cell mass. Unfortunately we did not perform an exercise test before receipt of the drug.

Our previous experience in patients with EE found no one with the intense post-exercise cyanosis and oxygen debt that this patient experienced. Although unable to reach level 5, their recovery is usually uneventful. We strongly recommend that patients with EE and pulmonary disease, not be treated with this drug, nor should they have their RBC mass reduced. To our knowledge there is no safe drug treatment for reduction of EE. Treatments should be directed at the etiology of the pulmonary lesions that cause EE at high altitude, not at the secondary increased red cell mass.

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