ERYTHROPOIETIN AND THE POLYCYTHEMIA OF HIGH-ALTITUDE DWELLERS

Nicholas Dainiak, Hilde Spielvogel, Sandra Sorba, Leon Cudkowicz

Departments of Medicine and Laboratory Medicine, University of Connecticut Health Center, and Connecticut Region Red Cross, Farmington, CT, USA

Department of Internal Medicine, University of Cincinnati, Cincinnati, OH, USA

Instituto Boliviano de Biologia de Altura, La Paz, Bolivia

INTRODUCTION

High-altitude natives residing at similar altitudes exhibit varying degrees of erythrocytosis, depending in part upon their geographical location[1-3]. A recent report by Winslow et al[3] suggests that hematocrit and hemoglobin levels correlate with circulating erythropoietin levels in such individuals. These authors contend that individuals with elevated erythropoietin levels may be functionally anemic even though the hematocrit and hemoglobin values are elevated.

An unusual disorder characterized by profound erythrocytosis and hyperviscosity was first described by Carlos Monge Medrano in 1925[4]. This disorder, known as Monge's disease, chronic mountain sickness or "erythemic syndrome of altitude", characteristically leads to cardio-pulmonary failure and premature death[5]. Provocatively, descent to sea level results in normalization of the hematologic values, suggesting that erythropoiesis in such individuals remains subject to normal physiological control mechanisms[6]. It has been hypothesized that over-response to physiologic stimuli might be the primary cause of chronic mountain sickness[6]. We have previously suggested that a similar mechanism is responsible for erythrocytosis in young individuals wherein the drive to produce erythropoietin in response to phlebotomy is exaggerated[7,8]. In this report, we have measured erythropoietin levels in patients with Monge's disease and healthy high-altitude dwellers. Our results suggest that chronic mountain sickness may be a heterogeneous disorder that is sometimes characterized by excessive erythropoietin production in the face of profound erythrocytosis.

MATERIALS AND METHODS

Subjects

Experimental subjects in Bolivia were recruited from local healthy

Molecular Biology of Erythropoiesis
Edited by J. L. Ascensao *et al.*
Plenum Press, New York

residents and by referral to the Instituto Bolivio Biologica de Altura (IBBA) in La Paz (3600 meters). They included 11 healthy volunteers (nine females and two males) with a mean hemoglobin of 17.1 g/dl (range of 15.2 to 20.5 g/dl) and a mean hematocrit of 49.5% (range of 46 to 58%); and eight patients with chronic mountain sickness (two females and six males) with a mean hemoglobin of 23.6 (range of 20.6 to 27.0 g/dl) and a mean hematocrit of 71.8% (range of 64 to 81%). The ages of healthy residents and patients were similar. None of the subjects visited lower altitudes or underwent phlebotomy in the several months preceeding study.

Erythropoietin Assays

Serum was separated from whole blood immediately following phlebotomy and frozen thereafter. Prior to assay, serum samples were thawed and tested in a minimum of two (and in most cases three) different erythropoietin assays. The hypertransfused, polycythemic mouse erythropoietin bioassay was used in all cases. Four days following induction of polycythemia in CF_1 female mice by hypertransfusion, 1.00 ml of serum was subcutaneously injected into each of five animals. ^{59}Fe was injected into the tail veins 24 hours later, and its incorporation into erythrocytes after 24 hours was determined and compared to incorporation induced by concurrently tested normal saline and erythropoietin standards, as previously described[9]. In each case, an additional erythropoietin assay was performed, as follows.

An in vitro bioassay in splenocytes of C57BL/6J x C3H/HEJ mice which were previously injected with phenylhydrazine HCl was employed, according to methods previously described[10]. In addition, the erythropoietin radioimmunoassay of Sherwood and Goldwasser[11] was performed at the University of Chicago in a double-blind fashion. Human plasma obtained from hematologically normal residents at sea level contains less than 50 mu/ml, less than 25 mu/ml and less than 10 mu/ml for the in vivo bioassay, in vitro bioassay and radioimmunoassay, respectively.

Statistical Methods

Values were compared among groups by calculation of the geometric means and analysis of variance followed by the Newman-Keuls multible comparison test[12]. Correlation coefficients (r) were determined for results obtained in different erythropoietin assays, using standard methods. Differences were considered significant when $p < 0.05$.

RESULTS

Circulating erythropoietin levels ranged from 10 to 2,000 mu/ml in all assays for all subjects tested. In general, levels obtained in the three erythropoietin assays were comparable, although the best correlation of values was between those obtained by the in vivo bioassay in hypertransfused mice and those obtained by radioimmunoassay (see Figure 1). Values obtained with the in vivo bioassay were higher than those obtained with the radioimmunoassay, and in no case was a radioimmunoassay value higher than the corresponding in vivo bioassay value for a given sample.

Table 1 summarizes the erythropoietin levels obtained in healthy individuals and patients with chronic mountain sickness. Whereas values were higher relative to hematocrit in healthy La Paz residents compared to those obtained in residents at sea level in the United States, there was no apparent correlation between hemoglobin or hematocrit level and erythropoietin level. Erythropoietin values in patients with Monge's disease could be easily separated into two distinct groups: group I with