Oxygen Delivery in the Treatment of Anemia

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THE EVALUATION OF NEW DRUGS DESIGNED TO TREAT SPECIFIC ANEMIAS should include a thorough understanding of underlying pathophysiology, with a focus on enhancing oxygen transport. In this concise review, I discuss the importance of the consideration of oxygen delivery in the treatment of anemia.

PHYSIOLOGY

The red cells in humans, as well as those in most other mammals, are endowed with a level of 2,3-bisphosphoglycerate (2,3-BPG) that is 1000 times as high as the level in all other cells and approximately matches the molar level of hemoglobin tetramer. This metabolic intermediate in the glycolytic pathway binds specifically to deoxyhemoglobin and lowers its affinity for oxygen.[1] Thus, when hemoglobin is exposed to increasing oxygen pressure, the presence of 2,3-BPG lowers the fractional oxygen saturation, and the oxygen-binding curve is shifted to the right (Fig. 1).
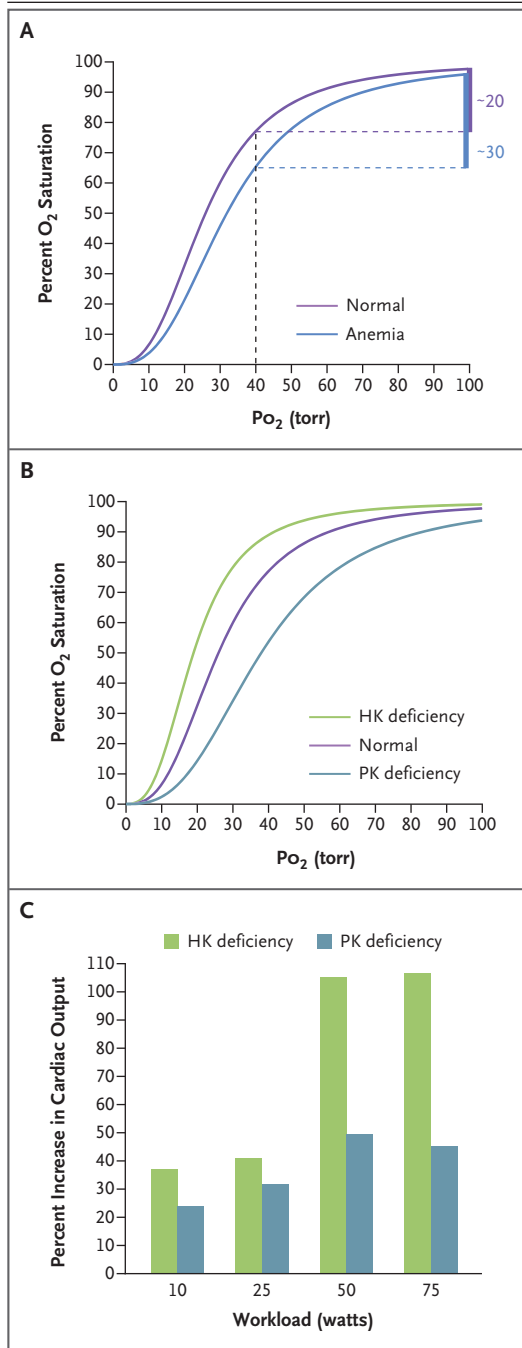
Nearly all patients with anemia, regardless of the cause, have elevated red-cell 2,3-BPG levels. As shown in Figure 1A, this adaptation greatly enhances oxygen delivery. At any given oxygen tension (measured as the partial pressure of oxygen [P_{O_2}]), the oxygen saturation is reduced in a person with anemia. Arterial blood normally has a P_{O_2} of about 95 torr (or 95 mm Hg) and is nearly 100% saturated with oxygen. As red cells pass from an arteriole through its capillary bed to its vein, oxygen is released to respiring cells. At a venous P_{O_2} of 40 torr, the oxygen saturation is about 80%. Thus, approximately 20% of the oxygen in the blood is unloaded. In contrast, in patients with anemia and elevated levels of red-cell 2,3-BPG, the lower oxygen affinity of the blood allows a much higher fraction of the oxygen (about 30%) to be unloaded. This benefit can be shown quantitatively by considering oxygen-carrying capacity rather than hemoglobin levels. In a person with a normal hemoglobin level of 15 g per deciliter, the oxygen-carrying capacity of the blood is 20 ml of oxygen per deciliter. In traversing the arterioles and capillary bed, approximately 20% of this oxygen will be unloaded — that is, approximately 4 ml per deciliter of blood. In contrast, a patient with anemia and a hemoglobin level of 7.5 g per deciliter has an oxygen-binding capacity that is half the normal value (i.e., 10 ml of oxygen per deciliter). If this patient had red cells with normal oxygen affinity, 20% of the oxygen, or approximately 2 ml, would be unloaded per deciliter of blood. However, because the patient's red cells have an elevated level of 2,3-BPG, and thus a lower affinity for oxygen, about 3 ml is released, allowing partial compensation for the deficit in the red-cell mass.

Figure 1. Effect of Oxygen Affinity of Hemoglobin on Oxygen Delivery.

Panel A shows oxygen–hemoglobin dissociation curves for a normal person and a patient with anemia. The percent saturation of hemoglobin with oxygen is plotted against the partial pressure of oxygen (Po_2). The broken lines show that at a Po_2 of 40 torr, approximately 20% of oxygen is unloaded in a person without anemia, whereas approximately 30% of oxygen is unloaded in a person with anemia. Panel B shows oxygen–hemoglobin dissociation curves for a patient with hexokinase (HK) deficiency and a patient with pyruvate kinase (PK) deficiency. The data are from Delivoria-Papadopoulos et al.[2] Panel C shows the change in cardiac output during graded exercise in the patient with HK deficiency and the patient with PK deficiency. The data are from Bunn and Forget.[3]

DIFFERENCES BETWEEN HEXOKINASE AND PYRUVATE KINASE DEFICIENCIES

One of the more gratifying aspects of clinical medicine is the realization that, not infrequently, important insights into pathophysiology emerge from thoughtful observations in small numbers of patients. Some 50 years ago, Frank Oski and his colleagues[2,4] evaluated two adolescents with hemolytic anemia due to inherited defects in red-cell enzymes. One patient had a deficiency of hexokinase, the initial step in the glycolytic pathway mediating the phosphorylation of glucose. As a result, the red cells were deficient in 2,3-BPG (67% of the normal level). As shown in Figure 1B, the red cells had increased oxygen affinity and thus a shift to the left in the oxygen–hemoglobin dissociation curve. The other patient had a deficiency in pyruvate kinase, a downstream enzyme that converts phosphoenolpyruvate to pyruvate. As a result, the red-cell 2,3-BPG level was elevated by a factor of 2.5, which is considerably higher than the level in most other patients with anemia, with a marked shift to the right in the oxygen–hemoglobin dissociation curve. Although the two patients had equivalent degrees of anemia (hemoglobin level, approximately 10 g per deciliter), the patient with hexokinase deficiency had dyspnea and fatigue, whereas the patient with pyruvate kinase deficiency was asymptomatic. This difference in clinical presentation was in accord with measurements of cardiac output during graded exercise on a bicycle ergometer, which showed an increase in the cardiac output by a factor of 2.5 in the patient with hexokinase deficiency, as compared with a much more modest increase in the patient with pyruvate kinase deficiency (Fig. 1C).

DRUGS DESIGNED TO INCREASE HEMOGLOBIN LEVELS

The studies by Oski and colleagues,[2,4] which showed that red-cell oxygen affinity is a major determinant of oxygen delivery, are highly relevant to the evaluation of drugs designed to increase hemoglobin levels in patients with anemia. Recently, two drugs have been introduced to increase hemoglobin levels in patients with two types of hemoglobinopathy: sickle cell disease and thalassemia.

In 2019, voxelotor (Oxbryta) was approved by the Food and Drug Administration (FDA) for the treatment of sickle cell disease, the first drug to receive such approval since hydroxyurea was approved 21 years ago. Hydroxyurea became a standard of care because of its efficacy in reducing the frequency of vaso-occlusive crises and in ameliorating anemia. Although voxelotor is effective in increasing hemoglobin levels in patients with sickle cell disease, double-blind phase 3 trials have revealed no significant effect on the frequency or severity of vaso-occlusive events.[5,6] The drug binds covalently to the N-terminal of α-globin in oxyhemoglobin S (and F), resulting in stabilization of a conformation of hemoglobin that cannot polymerize, as well as in a marked increase in overall oxygen affinity. In vitro studies showed that the drug is a potent inhibitor of red-cell sickling,[7] which depends on the deoxygenation of hemoglobin to form the polymerizing T conformation. The lack of efficacy of voxelotor in ameliorating vaso-occlusion is probably caused by impaired unloading of oxygen in the microcirculation of the organs and tissues due to increased oxygen affinity.[8] A recent in vitro modeling study based on rigorous assessment of the effect of drugs on the kinetics of sickling under flow conditions in the microcirculation showed that hydroxyurea enhanced oxygen delivery, whereas voxelotor did not.[9]

In 2022, mitapivat (Pyrukynd) won FDA approval for the treatment of patients with hemolytic anemia due to pyruvate kinase deficiency.[10,11] The drug, which binds to and stabilizes the mutant enzyme, induces an increase in hemoglobin and decreases hemolysis in these patients primarily as a result of an approximately 40% increase in red-cell ATP. In addition, the drug causes an approximately 35% decrease in red-cell

2,3-BPG both in these patients and in normal volunteers.[12] These results prompted a recent open-label phase 2 trial involving patients with either β-thalassemia or α-thalassemia who had anemia but were not dependent on transfusions, with the rationale that the ineffective erythropoiesis and hemolysis might also be mitigated by an increase in red-cell ATP.[13] All five patients with α-thalassemia, along with 11 of the 15 patients with β-thalassemia, had an increase in the hemoglobin level of more than 1 g per deciliter. There was no mention in the report of changes in the red-cell 2,3-BPG level, but the drug almost certainly caused a marked decrease, as previously observed in unaffected persons.[12]

In a recent phase 1 clinical trial involving 16 patients, Xu et al.[14] evaluated the use of mitapivat for the treatment of sickle cell disease. At the highest dose of the drug, more than half the patients had a hemoglobin response, defined as an increase in hemoglobin of at least 1 g per deciliter. In addition, a dose-dependent decrease in red-cell 2,3-BPG levels was observed.

The increase in red-cell oxygen affinity in patients treated with either voxelotor or mitapivat would induce a hypoxic drive sufficient to cause the observed modest increase in hemoglobin levels, which is similar to the hemoglobin elevation in persons who have inherited a mutant hemoglobin that increases oxygen affinity.

CONCLUSIONS

These scenarios about treatment with voxelotor or mitapivat should alert physicians to be aware that at a given hemoglobin level, drug-induced alterations in the oxygen-binding curve can have an impressive effect on oxygen delivery, similar to that observed by Oski and his colleagues[2,4] in the two adolescents with red-cell enzyme deficiencies. Medical students are properly taught that the signs and symptoms of anemia are due to an insufficient supply of oxygen to organs and tissues. Practicing physicians use the blood hemoglobin level as a readily measured and accurate assessment of the severity of anemia and its response to therapy. However, in evaluating the effect of drugs designed to alleviate anemia, therapy-induced increases in the hemoglobin level may be misleading, even illusory. It is important to be aware that the drug may have an

adverse effect on oxygen delivery that offsets its enhancement of oxygen-carrying capacity.

The development of new drugs imposes a large financial burden on our health care system and arouses hope on the part of the patients for whom they are prescribed. An accurate assessment of the efficacy and value of a drug often depends on a firm understanding of the underlying physiology.

REFERENCES

1. Benesch R, Benesch RE. Intracellular organic phosphates as regulators of oxygen release by haemoglobin. Nature 1969; 221:618-22.

2. Delivoria-Papadopoulos M, Oski FA, Gottlieb AJ. Oxygen-hemoglobulin dissociation curves: effect of inherited enzyme defects of the red cell. Science 1969;165: 601-2.

3. Oxygen and carbon dioxide transport. In Bunn HF, Forget BG. Hemoglobin: molecular, genetic, and clinical aspects. Philadelphia: W.B. Saunders, 1986:117.

4. Oski FA, Marshall BE, Cohen PJ, Sugerman HJ, Miller LD. The role of the left-shifted or right-shifted oxygen-hemoglobin equilibrium curve. Ann Intern Med 1971;74:44-6.

5. Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. N Engl J Med 2019;381:509-19.

6. Howard J, Ataga KI, Brown RC, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol 2021;8(5): e323-e333.

7. Oksenberg D, Dufu K, Patel MP, et al. GBT440 increases haemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease. Br J Haematol 2016;175:141-53.

8. Hebbel RP, Hedlund BE. Sickle hemoglobin oxygen affinity-shifting strategies have unequal cerebrovascular risks. Am J Hematol 2018;93:321-5.

9. Henry ER, Metaferia B, Li Q, et al. Treatment of sickle cell disease by increasing oxygen affinity of hemoglobin. Blood 2021;138:1172-81.

10. Kung C, Hixon J, Kosinski PA, et al. AG-348 enhances pyruvate kinase activity in red blood cells from patients with pyruvate kinase deficiency. Blood 2017; 130:1347-56.

11. Grace RF, Rose C, Layton DM, et al. Safety and efficacy of mitapivat in pyruvate kinase deficiency. N Engl J Med 2019; 381:933-44.

12. Yang H, Merica E, Chen Y, et al. Phase 1 single- and multiple-ascending-dose randomized studies of the safety, pharmacokinetics, and pharmacodynamics of AG-348, a first-in-class allosteric activator of pyruvate kinase R, in healthy volunteers. Clin Pharmacol Drug Dev 2019;8:246-59.

13. Kuo KHM, Layton DM, Lal A, et al. Safety and efficacy of mitapivat, an oral pyruvate kinase activator, in adults with non-transfusion dependent α-thalassaemia or β-thalassaemia: an open-label, multicentre, phase 2 study. Lancet 2022; 400:493-501.

14. Xu JZ, Conrey AK, Frey IC, et al. A phase 1 dose escalation study of the pyruvate kinase activator mitapivat (AG-348) in sickle cell disease. Blood 2022;140:2053-62.