Current Concepts of Pharmacotherapy in Hypertension

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Antihypertensive Medications and Anemia

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Antihypertensive medication use can be associated with a reduction in hemoglobin concentration. The magnitude of such a change is generally small, but in certain instances it can be extreme enough to produce a clinically significant degree of anemia. The mechanistic basis for antihypertensive medication–related changes in hemoglobin concentration include hemodilution, hemolytic anemia, and suppression of red blood cell production, as this occurs most commonly with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. A reduction in hemoglobin concentration in a patient who is receiving treatment for hypertension and does not have an obvious source of blood loss should account for potential antihypertensive therapy involvement.
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Although the individual causes of anemia are numerous, 3 major mechanisms are by and large causal: blood loss, inadequate red blood cell (RBC) production, and/or excessive destruction of RBCs. Hemoglobin concentration, however, should always be interpreted in the context of the prevailing volume state: thus, in the instance of excessive diuresis, hemoconcentration may occur. Alternatively, in the case of significant volume retention, there will be hemodilution corresponding to the degree of extracellular fluid volume expansion. Although a number of antihypertensive medications can cause extracellular fluid volume retention, it is generally of an insufficient magnitude to significantly affect hemoglobin concentration; the exception to this would be drugs such as minoxidil and, more recently, endothelin receptor antagonists. In the instance of both of these medications, the observed drop in hemoglobin concentration due to hemodilution can be as much as 10% to 15%.[1,2]

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BLOOD LOSS

Calcium channel blockers (CCBs) are most commonly said to have a relationship with bleeding. Reports from the 1990s suggest an increased hemorrhagic risk associated with CCB therapy; such findings added to the general misgivings and media scare that then surrounded use of these drugs.[3–5] The unease on this issue intensified when Pahor and colleagues[6] published a prospective cohort study involving hypertensive individuals (aged 68 years or older), which suggested that there was a greater risk of gastrointestinal (GI) hemorrhage with CCB compared with β-blocker therapy. A number of other studies offered similar opinions on increased bleeding risk with CCB therapy.[7] The proposed mechanism(s) for a bleeding risk with CCB therapy included inhibition of platelet aggregation and a reduction in the vasoconstrictor response that would ordinarily occur in response to hemorrhage.[8,9] The bleeding risk presumed to occur with CCB therapy also implicated aspirin, in that the combination of a CCB and aspirin was found to increase bleeding beyond what might be seen with either compound alone.[10]

Although a number of studies have seemed to support the concept of an increased bleeding risk

with CCB therapy, they were often methodologically flawed and were matched, if not exceeded, by studies that offered opposing findings. Absent any large outcomes studies, the possible link between CCBs and bleeding was at best uncertain when the totality of evidence was assessed.[7] It took the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[11] to finally show that there was no discernible relationship between CCB use and an excess risk of GI hemorrhage. In ALLHAT, lisinopril was more often associated with an increase in GI bleeding (16% in nonblacks and 28% in blacks) when compared with amlodipine.

HEMOLYTIC ANEMIA

Hemolytic anemia may randomly occur with a number of antihypertensive agents.[12–14] It may also occur as a component of the drug-induced lupus syndrome, as in the case with hydralazine; however, this is a very rare occurrence.[15] Hypersensitivity reactions, including hepatitis and Coombs-positive hemolytic anemia (usually but not always due to the appearance of an antibody with specificity for red cell Rh determinants) can occur with α-methyldopa.[16] Coombs positivity develops in as many as 20% of patients receiving α-methyldopa (≥1 g/d) for several months[17]; hemolytic anemia with α-methyldopa is much less common, occurring in 1% to 5% of patients. Differences in antibody characteristics, including subclass restriction, complement-binding ability, or titer fail to explain why only certain patients who develop an autoantibody undergo hemolysis. Hemolytic anemia has occurred within 2 months of starting therapy, but it more typically occurs after several months of treatment. There is no consistent dose relationship for methyldopa in causing hemolytic anemia, with cases occurring with dosages in the range of 0.125 to 3.0 g/d.[18] In that regard, it is advisable to periodically obtain a Coombs test and/or hemogram in patients receiving long-term therapy with α-methyldopa. α-Methyldopa can be continued in the presence of a positive direct Coombs test result alone; however, if anemia develops, therapy should be stopped. Hemolytic anemia induced by α-methyldopa is typically reversible, with no specific therapy necessary. Anecdotally, if severe anemia is present, it has been suggested that corticosteroid therapy can accelerate recovery.[16] A positive direct Coombs test result may persist for months to years after discontinuation of α-methyldopa.[19]

INADEQUATE RBC PRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are the antihypertensive medications that most commonly affect hemoglobin concentration and do so for the most part in patients with chronic kidney disease (CKD) and/or heart failure (HF).[20] In patients with normal renal function, ACE inhibitor and ARB use does not result in a clinically significant decline in RBC production.[21,22] Two mechanisms exist by which ACE inhibitors can potentially suppress erythropoiesis.[23–25] First, ACE inhibitors reduce circulating insulin-like growth factor 1 and thereby restrict erythropoiesis.[23] Second, ACE inhibitors increase plasma levels of the natural stem cell regulator N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), which prevents the recruitment of pluripotent hematopoietic stem cells.[24,25] The fact that these renin-angiotensin system–blocking agents suppress erythropoiesis is not without some potential benefit. For example, secondary erythropoiesis is not uncommon in a number of situations, including following renal transplantation,[23,24,26–31] prolonged exposure to high altitudes,[32] obesity-hypoventilation,[33] and cystic renal disease.[34] In these settings, ACE inhibitors and ARBs can be used to good effect in suppressing RBC production.

RENAL FAILURE

The relationship between ACE inhibition and anemia became known as early as 1984, when 9 of 12 hypertensive patients on maintenance hemodialysis displayed a decrease in hemoglobin concentration (average, 20.5% decrease), hematocrit level, and RBC cell mass while receiving long-term treatment with captopril.[20] There was no correlation between the dose of captopril given and the degree to which hematologic indices were reduced. After discontinuation of captopril, hematocrit values returned to pretreatment levels.[20] In follow-up studies, it was shown that this phenomenon was coupled with reduced circulating angiotensin II concentrations, which paralleled suppression in erythropoietin production.[35–37] When the antiestrogenic steroid mepitiostane was given together with an ACE inhibitor, anemia was significantly improved but without evidence of changes in circulating erythropoietin concentrations or any indices of renin-angiotensin activity.[37] This observation suggested that there might be an element of erythropoietin resistance to this process.

ACE inhibitor– and ARB-related anemia is a class effect in the CKD population and is independent of dialytic modality, as suggested by findings in both hemodialysis[20–36] and continuous ambulatory peritoneal dialysis patients.[38–40] The exact mechanism(s) of ACE inhibitor–related anemia

in end-stage renal disease (ESRD) is still argued. It was originally postulated that ACE inhibitor administration decreased RBC mass by removing a hypoxic stimulus to erythropoietin release as a result of increasing renal blood flow—a possible mechanism in CKD but one of limited relevance to the ESRD patient. Of note, during chronic ACE inhibition in patients with normal renal function, ACE is reactivated between doses, which explains the lack of major AcSDKP accumulation in such patients.[25] Such is not the case in the presence of even mild degrees of CKD where values of AcSDKP are maintained at higher levels throughout the dose interval.[41] Studies have also suggested that ACE inhibitor–related anemia in ESRD is a product of both decreased erythropoietin concentrations and "erythropoietin resistance,"[35,36] although the latter has yet to be unambiguously shown.[40,42–46]

Whether ACE inhibitors and ARBs differ in their respective ability to affect erythropoiesis remains to be determined. For example, the ARB losartan has been observed to decrease hemoglobin concentration in the setting of posttransplant erythrocytosis. The pattern of response is similar to that observed with ACE inhibitors.[29–31,47] Alternatively, losartan has been variably associated with the development of anemia in ESRD.[48,49] In particular, the carefully performed studies of Schiffl and Lang[49] suggest that the partial resistance to recombinant erythropoietin, observed with captopril, is not seen with losartan. In addition, the studies of Yildiz and associates[50] have demonstrated a greater decrease in hemoglobin concentration with enalapril than with losartan; however, on discontinuation of therapy, relapse occurred more rapidly in those who received enalapril. Unless contraindications to their use exist, ACE inhibitors should remain the preferred compounds for suppression of erythropoiesis when such therapy is warranted.[51]

HEART FAILURE

The clinical relevance of ACE inhibitor–related anemia is difficult to ascertain in the HF patient, although they appear to dose-dependently produce anemia in HF.[52] At the least, it is one of several contributing factors to the low-grade anemia observed in many HF patients. Plasma erythropoietin levels are elevated in HF.[53,54] Elevated erythropoietin levels normalize with ACE inhibitor therapy, a process that parallels the clinical and hemodynamic HF improvement.[53,54] The drop in erythropoietin levels most likely reflects some level of reduction in the renal hypoxia characteristic of untreated HF.[55] This hypothesis is supported by a recent report showing that in patients with HF, renal plasma flow and serum erythropoietin are significantly correlated.[56] The increase in circulating erythropoietin is associated with increased packed RBC volume in patients with severe HF.[54] Plasma volume also increases in HF. Accordingly, the increase in packed RBC volume does not present as an increase in hemoglobin concentration because its presence is masked by hemodilution.[54] Conversely, when ACE inhibitor therapy is started and plasma volume decreases, the anticipated hemoconcentration is not observed since RBC production has decreased in parallel. The exact role of erythropoietin therapy in the HF patient with anemia and, more specifically, anemia based on ACE inhibitor or ARB therapy, remains ill defined[57] as to dose, dose frequency, target hemoglobin, and whether it is even needed since intravenous iron supplementation alone may suffice for correction of anemia in many HF patients.[58]

CONCLUSIONS

Antihypertensive medications can be implicated in a number of organ system–related abnormalities, with some interactions being difficult to detect clinically. Such is the case for the interplay between antihypertensive medications and a reduction in hemoglobin concentration. Whereas serum chemistries are checked with some regularity in the patient with treated hypertension, this is not the case with hemoglobin concentration.

If an antihypertensive medication–related hematologic adverse effect is identified, it is often stumbled on in the course of performing laboratory studies for other reasons. Even with a "newly" reduced hemoglobin concentration, it is not uncommon to look elsewhere and overlook the potential role of antihypertensive medications. The sensible approach to responding to a change in hemoglobin concentration in the treated hypertensive patient is to always consider the potential for a therapy contribution.

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