Safety of Intravenous Iron During Infections

Given the unanswered questions regarding intravenous iron and infection, is it okay to continue a course of iron in patients who develop an infection? Is there reason to think it may impair a patient's immune response and recovery?

My answer is no, I do not believe that intravenous iron treatment should be continued when the patient develops an infection. This answer is based on the low likelihood that iron treatment would be effective during an acute infection, and on the risk for worsening the infection. There is very little in the way of published data to support this opinion; rather my view is based on theoretical considerations.

Most microorganisms require iron to survive, and obtain this iron from the infected host. As a result, the human body "locks away" iron during an infection, trading a temporary decrease in hemoglobin (this phenomenon has been poorly named the anemia of chronic disease) for the survival benefit of limiting the infecting organism's access to iron. A key question is whether treatment with intravenous iron would provide a new source of iron to the infecting microorganism. Again, there are no published data that allow us to critically answer this question. Experimental evidence suggests that iron salts such as ferrous sulfate may exacerbate an infection. For example, a mild infection in animals may be converted into a severe one when free iron is administered (1, 2). In humans, certain infections may occur when iron-overloaded patients are treated with desferrioxamine (3). It is likely that this agent binds iron in a manner that allows bacteria to gain access to the molecule. But is the same true of intravenous iron? Since there is no adequate source of published data to help answer this question. I believe we must err on the side of caution. I would avoid the use of intravenous iron (and probably oral iron as well) during episodes of acute infection.

Steven Fishbane
Mineola, NY

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Bone Mineral Density Measurements in Dialysis Patients

Measuring bone mineral density is increasingly used in the general population. One would think it might be of value in dialysis patients, though I haven't seen recommendations or guidelines for interpretation in this population (not to mention what to do with the data therapeutically). Can you provide some guidance?

Osteoporosis and secondary fractures have an enormous public health impact. Osteoporosis is defined as low bone mass and microdeterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk (1). The clinical significance of osteoporosis is in the increased risk for fracture that accompanies reductions in bone mineral density (BMD) (2). Approximately 1.3 million fractures that occur annually in the United States in people over the age of 45 years are thought to be secondary to osteoporosis (3). The risk of fractures increases progressively as BMD declines (4, 5). Fracture risk increases 1.4- to 3-fold for each standard deviation decrease in BMD. In the general population, hip fracture has been associated with an increased risk of death (6). In the general population, increasing bone mass or reducing bone loss is thought to be important in the prevention of osteoporotic fractures and may reduce the associated morbidity and mortality.

The prevalence of low BMD and risk of fracture are increased among patients with end-stage renal disease (ESRD) (7–10). Overall the risk of hip fracture is more than four-fold higher than the general population (8). While the age-specific relative risk of hip fracture is highest in the youngest age groups, the added risk of hip fracture associated with ESRD increases steadily with increasing age and increases as time since first dialysis

increases. Factors that predict hip fracture among ESRD patients include increasing age, female gender, Caucasian race, low body mass index, and the presence of peripheral vascular disease (11). Men and women are equally affected (8). In studies assessing BMD, cortical BMD tends to be lower than in age- and sex-matched controls and is thought to contribute to the increased risk of fracture (9). Although postulated mechanisms for bone loss include age, diabetes, aluminum toxicity, hyperparathyroidism, and acidosis (12, 13), risk factors for bone loss are not well defined.

There are no separate guidelines for interpretation of BMD for ESRD patients. BMD is most commonly measured using dual energy X-ray absorptiometry (DEXA). BMD is measured in grams per square centimeter and reported as a *T* score [standard deviation (SD) from the mean of peak bone mass] and a *Z* score (SD from the mean bone mass of age-, gender-, and race-matched controls). Osteopenia and osteoporosis are defined as they are in the general population. These definitions are based on the World Health Organization Study Group recommendations which suggest that BMD more than 1 SD below the mean of peak bone mass ($T < -1$) defines osteopenia and more than 2.5 SD below the mean of peak bone mass ($T < -2.5$) defines osteoporosis (14).

There are no reports assessing the impact of screening ESRD patients for BMD on bone loss or fracture. However, by screening ESRD patients that are at particular risk for low bone mass, physicians may identify and treat patients that are at high risk for fracture and may potentially reduce the risk of fracture and death. This may be particularly important for those patients who will eventually receive a kidney transplant, since the posttransplant period has been associated with significant bone loss (15). Screening with DEXA should not be performed more frequently than yearly. Unfortunately there are few data regarding the effectiveness or safety of interventions for bone loss among ESRD patients. Possible interventions to increase BMD include optimizing calcium balance, hormonal therapy (estrogen, testosterone), bisphosphonates, calcitonin, posture training, and exercise. Patients who are treated should be monitored yearly with DEXA.

Catherine Stehman-Breen
Seattle, WA

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New Vitamin D Analogs

Two new vitamin D analogs, doxercalciferol (Hectorol) and paricalcitrol (Zemplar) have recently become available. How do they differ from each other (and from calcitriol)? Are there any clear-cut indications for one or another of these two agents over calcitriol?

The ideal therapeutic agent for vitamin D. hormone replacement should manage parathyroid hormone (PTH), calcium, and phosphate simultaneously. The first priority must be to control (or prevent) the cascade of events that leads to secondary hyperparathyroidism (SHPT). In practical terms, this means that a suitable vitamin D analog would effectively suppress PTH without raising the serum levels of calcium and phosphate.

Calcitriol

Calcitriol is the active form of vitamin D_3 (1,25-dihydroxyvitamin D_3). It has, for many years, been the most prescribed therapy for chronic kidney disease (CKD) patients with vitamin D deficiency. Available both as an oral supplement and intravenous injection, synthetic calcitriol is biologically equivalent to calcitriol that is normally produced in the kidney from its precursor, α-hydroxyvitamin D_3. Calcitriol has demonstrated effectiveness in treating the classic disorders caused by vitamin D deficiency: renal osteodystrophy and SHPT.

However, the effective therapeutic doses of calcitriol required to treat SHPT can stimulate release of calcium and phosphorus from bone via osteoclast stimulation and

increase their absorption in the intestine. This process can lead to both hypercalcemia and hyperphosphatemia, and increased calcium and phosphorus product.

Paricalcitrol

Paricalcitrol is a vitamin D analog currently marketed under the trade name Zemplar (paricalcitrol injection). This compound (also called 19-nor-D_2 or 19-nor-1,25-dihydroxyvitamin D_2) differs from calcitriol in that it is structurally similar to vitamin D_2 and not to vitamin D_3. Paricalcitrol was found to decrease serum PTH levels in rats with little or no hypercalcemia (1). Animal studies also showed that paricalcitrol was much less active than calcitriol in mobilizing calcium and phosphate from bone (2). Clinical studies in CKD patients confirmed that paricalcitrol can effectively control SHPT with minimal hypercalcemic and hyperphosphatemic effects (3). However, paricalcitrol has not been directly compared to calcitriol to assess differences in efficacy and safety.

Doxercalciferol

Doxercalciferol, like paricalcitrol, is an analog of vitamin D_2. This compound, also known as 1α-hydroxyvitamin D_2, is marketed under the trade name Hectorol, and is available in oral formulation as well as intravenous injection. Like alfacalcidol, doxercalciferol is an out of sequence precursor of active D_2 hormone. It is already hydroxylated at the 1α-position (normally the second activation step for D_2), and requires only hydroxylation at the 25 position (normally the first activation step for D_2), which is done in the liver. The result is 1,25-dihydroxyvitamin D_2 (vitamin D_2 hormone). By avoiding the need for activation in the kidney, doxercalciferol can be used in patients with little or no kidney function (4). Oral administration of doxercalciferol was shown to be safe and highly effective for the treatment of SHPT in hemodialysis patients with minimal hypercalcemia and hyperphosphatemia (5, 6).

Comparison of Treatment Alternatives

Current forms of vitamin D replacement therapy suffer from several limitations. Although calcitriol and its analogs have been effective in decreasing the percentage of patients with severely elevated PTH levels, many patients still experience poor PTH control and an increased risk of adynamic bone disease. Calcitriol has a low therapeutic index and leads to hypercalcemia and hyperphosphatemia, sometimes limiting the treatment options for patients with SHPT (7). While calcitriol may be indicated to treat hypocalcemia, its use for vitamin D replacement is associated with the complications described above. These limitations have focused attention on analogs of vitamin D_2 such as paricalcitrol and doxercalciferol.

Therapeutic Implications

The deficiency in active vitamin D accompanying kidney failure leads to a broad range of complications, from secondary hyperparathyroidism to cardiovascular disease. Early initiation of vitamin D replacement therapy in patients with renal insufficiency should be considered for many patients; such therapy may improve outcomes and minimize the risk of developing complications. Conventional vitamin D therapy suffers from the limitations of hypercalcemia and hyperphosphatemia as well as resulting in nonphysiologic concentrations of D hormone. Evidence suggests that alternatives to conventional vitamin D offer potential advantages.

Jill S. Lindberg
New Orleans, LA

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Hepatitis B Surface Antigen-Positive but DNA-Negative Patients

It is highly recommended that hepatis B surface antigen (HB_SAg)-positive patients be dialyzed in a separate room in order to prevent the transfer of hepatitis B virus (HBV). However, some HB_SAg-positve patients have a negative polymerase chain reaction (PCR) test for HBV DNA, indicating that there is no active replication. Should these patients still be isolted from the group? Should HB_SAg testing be replaced by HBV PCR testing?

The presence of hepatitis B surface antigen (HB_sAg) should be considered indicative of ongoing hepatitis B virus (HBV) infection and potential infectiousness, re-

gardless of the patient's HBV DNA status. All HB_sAg-positive patients should receive dialysis in a room separate from HBV-susceptible patients using separate machines, equipment, instruments, and supplies. Staff members caring for HB_sAg-positive patients should not care for HBV-susceptible patients at the same time (e.g., during the same shift or during patient changeover).

Both qualitative and quantitative tests for detection of HBV DNA are available. However, these tests are not U.S. Food and Drug Administration approved, and substantial variation in results has been reported. Furthermore, the infectious status of patients positive for HBsAg but negative for HBV DNA is not known. These tests are most commonly used in patients being managed with antiviral therapy and should not be used for purposes of routine screening.

Miriam J. Alter
Atlanta, GA