Testing the Mettle of Iron Prescribing: Optimizing Oral Iron Therapy

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ABSTRACT

Although iron is an essential mineral in the homeostasis and functioning of multiple organ systems, its use as a therapeutic entity should be reserved for people with bona fide iron-deficiency anemia. Especially when it is added onto pre-existing polypharmacy in older adults, iron can subject patients to a plethora of dose-related side effects and drug interactions. Judicious use of laboratory studies, such as the serum ferritin assessment, may help to minimize superfluous use of oral ferrous sulfate.

INTRODUCTION

Iron-deficiency anemia (IDA) is a relatively commonplace medical problem that health care practitioners encounter in both ambulatory and inpatient settings. Causes can include increased iron demands, impaired gastrointestinal (GI) absorption, blood loss, and poor nutritional intake. Because of the mineral’s abundance in many foods, inadequate dietary intake is rarely the sole contributor to a clinical deficiency syndrome; however, it can accelerate the appearance of iron deficiency in the presence of other causes.

The recommended dietary allowances (RDAs) for iron can usually be met through dietary sources such as meats, spinach, eggs, and soybean products. Consequently, the therapeutic use of iron supplements is truly necessary only in a relatively small percentage of patients. It is estimated that IDA occurs in about 10% of adult women and in 1% of adult men.1

This article offers guidelines to help practitioners carefully select patients for oral iron supplementation and to help them maximize their patients’ therapeutic response and tolerance to oral iron therapy.2

TOO MUCH IRON?

The literature supports the contention that iron therapy is often overprescribed. For instance, in a retrospective study of prescribing patterns of internal medicine house officers, 64% of patients who had been prescribed iron therapy had not completed the appropriate diagnostic testing. Upon further review of the medical records, it was determined that 43% of the patients did not meet the criteria for iron deficiency. On the basis of our anecdotal experience, as well as on our findings in the literature, the superfluous use of iron is also quite prevalent in extended-care facilities.3,4

Iron therapy is associated with several potential shortcomings and complications:

1. Iron can exacerbate symptoms of gastroesophageal reflux disease (GERD). Therapeutic doses of oral iron preparations sometimes cause significant adverse GI effects in up to 20% of patients.5 Iron can have a corrosive effect on the GI mucosa, resulting in constipation, nausea, diarrhea, abdominal pain, and dark stools.

2. In worst-case scenarios, excessive iron ingestion can also lead to iatrogenic hemochromatosis, with subsequent multiple-organ damage and increased vulnerability to a wide array of infections.

3. Iron chelates many drugs in the GI tract, thus interfering with their systemic absorption. Some agents that are sequestered by iron include the quinolones, the tetracyclines, and levotirothryione. Conversely, antacids and aluminum-containing drugs can decrease iron absorption.6,7,8

Pharmaceutical manufacturers have attempted to reduce iron’s adverse GI effects by formulating extended-release preparations. Unfortunately, the reduction of adverse events with these products generally corresponds to a reduction in iron that is actually absorbed.1,9 Although iron absorption is reduced by about half when the mineral is given with food, compared with when it is taken on an empty stomach, some believe that the tradeoff of improved GI tolerance with food offsets the loss of iron’s bioavailability. Furthermore, the bioavailability of iron is thought to be driven by “body need.” The bioavailability can range from 5% to 10% in healthy patients to 20% in patients with severe iron deficiency.1

Vitamin C (ascorbic acid) 500 mg to 1 g, taken with each dose of iron, improves absorption by only another 10% from the baseline value. Thus, adding ascorbic acid to iron is usually not practical; this endeavor can contribute to ascorbic acid–related side effects, including the precipitation of calcium oxalate kidney stones in predisposed patients. Vitamin C also contributes to the problems inherent in any polypharmaceutical situation.10,11

Given this proclivity for the overuse of iron and some of its impending risks,3,4 it is important to understand the therapeutic nuances of appropriate iron prescribing. Of course, this effort begins with getting the correct diagnosis.

DIAGNOSIS

Clinical manifestations of IDA are often vague and non-specific. Symptoms may include fatigue, weakness, shortness of breath, and headache. The common “gold standard” for the diagnosis of iron deficiency in clinical practice involves the invasive act of obtaining a staining of a bone marrow aspirate. In lieu of obtaining a bone marrow sample, appropriate interpretation of laboratory tests may suffice. This process is germane to the optimal prescribing of iron products. Classic laboratory values in patients with IDA usually reveal microcytic, hypochromic anemia with low serum iron levels, high total iron-binding capacity (TIBC), low transferrin saturation, and low serum ferritin levels.1,7

Many prescribers unintentionally overlook other important factors and look only at serum iron levels in anemic patients. Because serum levels are also low in anemia of chronic disease
Iron Therapy

(ACD), for which iron would not be beneficial, they should consider other indices (Table 1). One secondary check involves the TIBC, which tends to be higher in iron-deficiency states and lower in patients with ACD. As a result of this finding and because of the interrelationship between these two parameters, IDA tends to yield transferrin saturation levels of less than 15%.

The serum ferritin, however, is thought to be the most sensitive and specific single noninvasive test for assessing true iron stores. A ferritin level range of 12 to 30 ng/ml or lower is thought to be a reasonably good diagnostic measure of true IDA. Because ferritin is an acute-phase reactant, however, upward skewing can occur in both acute and chronic inflammatory conditions. This means, of course, that “false-negative” ferritin results are possible with these patients.

Chronic disease states, such as renal or liver failure, human immunodeficiency virus (HIV) infection, sickle cell disease, conditions necessitating repeated blood transfusions, malignancies, and chronic inflammatory disorders, may elevate measured values up to 45 to 100 ng/ml or even as high as 160 ng/ml in iron-deficient patients. In fact, in a study done by Coenen et al., six of 40 patients with chronic inflammatory disorders had ferritin levels above 160 ng/ml, which might be falsely elevated. Again, if the ferritin result does not correlate well with other clinical and laboratory findings, a bone marrow aspirate can then be considered.9,12

Given these limitations, and because iron deficiency is a chronic disorder that is treated with long-term therapy, assessment of iron deficiency and subsequent iron repletion needs is best done when patients are not in the throes of an acute medical event. In fact, several studies show a reasonable correlation between the erythrocyte sedimentation rate (ESR) and ferritin levels. Thus, in both acute and chronic inflammatory states, an elevated ESR suggests that serum ferritin levels might be falsely elevated. Again, if the ferritin result does not correlate well with other clinical and laboratory findings, a bone marrow aspirate can then be considered.9,12

When iron therapy is used empirically in patients with less classic “borderline” or “mixed” diagnoses, practitioners can check the reticulocyte count for an early assessment of clinical response. Good responses, which would justify continued therapy, elicit an elevation in the reticulocyte count from a baseline value of less than 2%–3% to 4%–6% during the peak period of one to two weeks after initiation of treatment. In terms of hemoglobin response, an increase of at least 2 g/dl after about three to four weeks is a desirable outcome.

In general, unless patients have an occult blood loss, such as GI microbleeding resulting from nonsteroidal anti-inflammatory drugs (NSAIDs) or diverticula, iron supplementation should not be considered a lifelong necessity. In most patients without a continued underlying blood loss, chronic malabsorption, or extremely poor dietary status, iron stores should be replete after three to six months of therapy. Ferritin levels reaching at least 50 ng/ml with normalized Wintrobe indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration) should imply full iron storage repletion and, therefore, an appropriate endpoint for iron supplementation.1

**STRATEGIES FOR SUPPLEMENTATION**

Ferrous sulfate tablets are the most commonly used formulation for oral iron supplementation. Contrary to popular belief, the therapeutic dose of ferrous sulfate might not be a one-size-fits-all 325 mg three times daily. Small-scale studies in young women with moderate anemia have shown that hemoglobin values can be significantly raised with ferrous sulfate 200 mg when given as infrequently as once per week.10 In addition, most sources suggest a starting dose of ferrous sulfate, from 300 to 325 mg once daily, to be increased slowly according to the patient’s GI tolerance. A slow titration not only allows for acclimation of the GI tract but also can help practitioners determine a minimum therapeutic dose.

Many patients may demonstrate hematological improvement, with less likelihood of intolerance and noncompliance, when they are taking once-daily or twice-daily iron. Administering iron less frequently can have beneficial effects on adherence and tolerance to therapy and might also reduce problems with drug–drug interactions.

Ideally, oral iron should be taken separately from potentially chelating medications by two to three hours. For example, patients receiving twice-daily ciprofloxacin (Cipro®, Bayer) and ferrous sulfate three times a day would need to take iron five times each day. This schedule reduces the likelihood of these medications being taken properly.

**CONCLUSION**

The next time that readers are considering prescribing ferrous sulfate 325 mg three times a day, it is of the utmost importance to remember the three tenets of iron supplementation:

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**Table 1**

<table>
<thead>
<tr>
<th>Anemia</th>
<th>MCV/MCH/MCHC</th>
<th>RDW</th>
<th>Serum Fe</th>
<th>TIBC</th>
<th>Transferrin Sat.</th>
<th>Ferritin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency anemia</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High*</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>WNL to slightly low</td>
<td>WNL</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>WNL to high</td>
</tr>
</tbody>
</table>

*The TIBC may be low if patients also have underlying chronic disease and/or malnutrition.
Pressure Ulcers: What to Think When Giving Zinc

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ABSTRACT

Good nutrition is vital to the healing of pressure ulcers, and zinc appears to play a major role in facilitating this process. To date, five randomized, placebo-controlled trials have been conducted to evaluate the benefit of zinc supplementation in the healing of these wounds. Generally, these studies have shown a trend toward improved healing only among patients who are deficient in zinc. When used superfluously, zinc may become one more unnecessary drug that can actually hinder the healing process, with the potential to become detrimental to treated patients.

INTRODUCTION

Pressure ulcers are common in older adults, especially those confined to a bed or a wheelchair. After these wounds have formed, they become difficult to treat. Good nutrition is vital for healing. Vitamins A, B, C, and E and the minerals copper, selenium, and zinc all appear to play a major role in facilitating the healing process.1 Zinc serves as a cofactor for several enzymes that are important for cellular growth and replication. A deficiency of this mineral appears to decrease protein and collagen synthesis, resulting in impairment of wound healing.2 Interestingly, patients with chronic pressure ulcers, when compared with control subjects, tend to be mildly deficient in zinc.1

EFFICACY

The efficacy of zinc in improving rates of wound healing remains unclear. Five randomized, placebo-controlled trials and a meta-analysis have been conducted to evaluate the efficacy of zinc supplementation in patients with chronic leg ulcers.3–8 With one exception, these trials did not demonstrate a statistically significant benefit of zinc for all patients with pressure ulcers. Although statistically significant results were not achieved in some subgroups, a potential improvement in wound healing was noted in each of the five trials.3–7

In addition, two of these studies compared the efficacy of zinc therapy in zinc-deficient patients with that of patients with normal zinc serum concentrations. The patients with low baseline zinc concentrations demonstrated a statistically significant improvement in wound healing, whereas patients who were not considered to be deficient in zinc attained no such benefit.3,4

ZINC SUPPLEMENTATION

Zinc therapy, although relatively safe when used appropriately, may produce some bothersome adverse effects. Orally
administered zinc can directly irritate the gastrointestinal tract, sometimes causing vomiting and diarrhea, especially when high doses are used. Excessive zinc supplementation also has the potential for adverse effects on wound healing. This paradoxical finding is thought to be the result of two separate mechanisms:

- The negative effect on tissue repair may be secondary to an impairment of neutrophil and lymphocyte function.9
- Excess zinc may compromise the ability of copper and calcium—two other important minerals in the wound-healing process—to access the wound.10

Zinc is implicated in contributing to several drug–drug interactions. When given within two to four hours of fluoroquinolones or tetracyclines, concomitant zinc administration results in the chelation or binding of these antibiotics within the gastrointestinal tract.11–14 Absorption of the antibiotic can be significantly decreased, with total drug exposure subsequently diminished. As a result, therapy may fail and the risk of acquired antibiotic resistance may increase.15,16

As mentioned earlier, zinc supplementation in patients with leg ulcerations has not demonstrated improved wound healing unless patients were zinc-deficient.3–7 “Normal” plasma zinc concentrations are generally within the range of 70 to 130 mcg/dl.17 Although serum levels do not necessarily reflect total body stores, conventional wisdom suggests that zinc therapy might be recommended in patients with baseline serum levels below 100 mcg/dl. It is believed that serum concentrations below this value are associated with impaired wound healing.18

Supplementation with 220 mg of zinc sulfate (50 mg of elemental zinc) orally, dosed once to three times daily, is recommended.2 Because of the impending risks of dose-related side effects, drug–drug interactions, and the difficulties inherent in multiple daily doses, we favor the empirical use of once-daily dosing for periods of two to three months. After this time, total body stores of zinc should be at or close to repletion. After zinc stores are replete, the mineral’s biological half-life of 250 days should help to negate the occurrence of acute-onset deficiency.19

One reasonable algorithm to employ is to check zinc levels before the initiation of therapy and to begin treatment only when the levels are approximately 100 mcg/dl or lower. If the wound is not adequately healed after six to 12 weeks of zinc supplementation, zinc levels should be checked again. An assessment of zinc levels can cost an institution approximately $20.00 to $25.00 and can cost the patient or third-party payer nearly $80.00 (T. Morrow, personal communication, February 2003).

A more cost-effective approach might be to treat patients empirically for six to eight weeks without regard to baseline zinc values and to check zinc levels only in the event of poor wound healing. If zinc concentrations have normalized in the presence of a nonhealing wound, other cofactors and conditions are probably the culprits. In such cases, treatment with zinc should be discontinued. If the ulcer has healed, zinc therapy can be stopped without the need for a post-treatment level assessment.

CONCLUSION

Zinc appears to play a major role in facilitating the healing process. To date, zinc supplementation has benefited patients with pressure ulcers only when zinc deficiency was present. When used inappropriately, zinc can hinder the healing process. In addition, zinc can become one more unnecessary drug that increases the complexity of patients’ drug regimens and that enhances the probability of iatrogenic drug-related effects. Practitioners should prescribe zinc with caution so that supplementation with this mineral does not become an impediment to the optimal treatment of patients.

REFERENCES

Emerging Palliative Treatment Options for Fibromyalgia

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INTRODUCTION
Fibromyalgia is a chronic condition that affects about 2% of the U.S. population. Most patients are women. The initial presentation of this painful condition occurs between approximately 30 and 40 years of age, but the distribution is variable between the age of onset and diagnosis because most patients tend to cope with the pain rather than pursue the necessary medical attention.

Fibromyalgia is characterized by a variety of nonspecific symptoms, such as diffuse soft-tissue pain, fatigue, morning stiffness, and nonrestorative sleep (when a person awakens without feeling refreshed). Less common symptoms include migraine headache, irritable bowel syndrome, subjective swelling, and major depression. All of these symptoms are usually determined by various circumstances, including stress, physical activity, sleep abnormalities, and the weather.1-3

With no established laboratory tests to diagnose fibromyalgia, the diagnosis usually is based on standards of exclusion. Palpation of specific sites ("tender points") during a physical assessment aids in guiding practitioners in arriving at the diagnosis. These 18 diagnostic points produce a considerable amount of generally localized pain that does not radiate when pressure is applied. The sites are as follows:4

- occiput: both sides, at suboccipital muscle insertions
- low cervical vertebra: both sides, at anterior aspects of intertransverse spaces at C5–C7
- trapezius: both sides, at midpoint of upper border
- supraspinatus: both sides, at origins, above scapular spine near medial border
- second rib: both sides, at second costochondral junctions, just lateral to junctions on upper surfaces
- lateral epicondyle: both sides, 2 cm distal to epicondyles
- gluteal area: both sides, in upper outer quadrants of buttocks in anterior fold of muscle
- greater trochanter: both sides, posterior to trochanteric prominence
- knee: both sides, at medial fat pad proximal to joint line

For a diagnosis of fibromyalgia to be confirmed, certain criteria established by the American College of Rheumatology must be met.5 Fibromyalgia is defined as pain and tenderness existing for at least three months and manifested in 11 of 18 tender points upon palpation after a force of 4 kg is applied. The pain must be located on bilateral sites of the body, above and below the midsection, and within the axial skeleton. Patients describe the pain as being more severe than that experienced with rheumatoid arthritis and osteoarthritis. Muscle cramping, aching, and stiffness limit everyday functions as well as the sleep patterns of affected individuals.2,4

The pathophysiology of fibromyalgia remains a mystery, but many speculations and hypotheses abound in the literature. Many agree that a viral infection, toxin exposure, or some type of trauma might be a cause. Impaired functioning of the hypothalamic-pituitary axis and changes in certain neurotransmitters, such as serotonin, epinephrine, substance P, and N-methyl-D-aspartate, correlate with pathophysiological hypotheses.1

Serotonin, a key neurotransmitter, is implicated in the origin of fibromyalgia because it is responsible for part of the sleep cycle, pain thresholds, depression, anxiety, and other psychiatric disorders. Decreased serum concentrations of serotonin and an increased density of serotonin receptors, located on circulating platelets, are characteristic.2,3 These factors have been associated with the common symptoms of the condition. For example, low serum concentrations of serotonin have been associated with a decreased pain threshold because serotonin regulates pain perception in both the central nervous system and the periphery and modulates the function of substance P (which is involved primarily in pain transmission).

Fibromyalgia also produces sleep abnormalities caused by impaired serotonergic neurotransmission within the brain and spinal cord. Sleep abnormalities have also been associated with restless legs syndrome and nocturnal muscle spasms. As the quality of sleep is affected, patients are more prone to experiencing the symptoms of fatigue and irritability. These neurotransmitter mechanisms play a role in the increased pain, poor quality of sleep, and possibly even mood disorders in affected patients.1,2

POTENTIAL BENEFITS OF ANTIDEPRESSANT THERAPY
Fibromyalgia is a chronic condition for which no cure currently exists. The first approach to treatment is the use of palliative nonpharmacological therapy. Various approaches include massage therapy, hypnotherapy, behavioral therapy, acupuncture, and aerobic exercises (e.g., swimming) that do not place added stress on affected areas. These therapeutic modalities offer only limited benefit and should be combined with pharmacological agents that are aimed at reducing pain and other bothersome symptoms.1

Diet may also play a role in stimulating or worsening patients’ symptoms. Many health care professionals agree that certain fatty, fried, or sugary foods might act as possible triggers of pain. It is recommended that patients eat whole foods such as vegetables, whole grains, fruits, and protein. Caffeine should be avoided, because even small amounts can lead to sleep disturbances.5,6

Possible therapeutic agents that have been used to relieve the symptoms of fibromyalgia include:

- antidepressants.
- nonsteroidal anti-inflammatory drugs (NSAIDs).
- benzodiazepines, such as clonazepam (Klonopin®,
Fibromyalgia

Roche), 0.5–1.5 mg, and alprazolam (Xanax®, Pharmacia & Upjohn).
- analgesics, such as tramadol (Ultram®, Ortho-McNeil).
- cyclobenzaprine (Flexeril®, Alza (2.5–10 mg).

Because fibromyalgia is not necessarily associated with important inflammatory processes, the following NSAIDs provide minimal to modest benefit:
- ibuprofen
- naproxen (e.g., Naprosyn®, Anaprox®, Roche)
- etodolac (Lodine®, Wyeth-Ayerst)
- ketoprofen (e.g., Orudis®, Oruvail®, Wyeth-Ayerst)

Benzodiazepines such as diazepam (Valium®, Roche) have been used to aid sleep and muscle relaxation to alleviate restless legs syndrome. However, these agents are not used very often because of their possible potential to be addictive.

Tramadol, a central-acting analgesic, has the additional action of inhibiting norepinephrine and serotonin reuptake; therefore, it may be used as a possible alternative treatment.

Cyclobenzaprine is structurally related to the tricyclic antidepressants (TCAs) and has effects similar to those of amitriptyline (see later).

Certain antidepressants, such as citalopram (CelexaTM, Forest), sertraline (Zoloft®, Pfizer), and venlafaxine (Effexor®, Wyeth-Ayerst), have been evaluated in the treatment of fibromyalgia, and preliminary studies involving selective serotonin reuptake inhibitors (SSRIs) are beginning to emerge in the literature.2

One agent that has been evaluated in clinical studies is the TCA amitriptyline (e.g., Elavil®, AstraZeneca; Endep®, Roche). Amitriptyline acts by inhibiting serotonin and norepinephrine reuptake and therefore increases serum concentrations of these two neurotransmitters. Through randomized placebo-controlled studies, amitriptyline has been shown to be effective at lower doses than in the treatment of depression (i.e., 10 mg at bedtime).1 The sedative effects of amitriptyline have proved beneficial to patients because it allows a more peaceful sleep.

One major disadvantage of amitriptyline is the incidence of extensive anticholinergic side effects (dry mouth, blurred vision, constipation, and urinary retention). Clinical data have confirmed that amitriptyline provides short-term improvement outcomes, but long-term efficacy has not been established because of the placebo effect. Other TCAs have not been extensively studied.1

SSRIs have also been considered as a potential therapeutic regimen in the treatment of fibromyalgia. As a result of their high selectivity for blocking serotonin receptors, some specialists hypothesize that there might be a potential benefit.1 SSRIs are also better tolerated than TCAs.1

Fluoxetine (Prozac®, Eli Lilly) has been evaluated in double-blind clinical trials to determine its efficacy. The drug has proved to exhibit pain-reduction capabilities according to various pain measures and questionnaires, and further study is warranted.8 One study showed more improvement when fluoxetine was combined with a TCA.9 Patients who took citalopram and sertraline have also shown improvement.1 However, these studies were limited in various ways, and the results have not been properly validated.

General weaknesses that characterize the studies involving SSRIs include a sample size that was too small, short follow-up with drug therapy, and high dropout rates. Because of their favorable safety profiles, it is possible that these agents will prompt future studies. In addition, because depression can be associated with fibromyalgia, the two conditions might be treated with one therapeutic agent.1

CONCLUSION

Fibromyalgia is a continuous burden on the lifestyle of affected individuals. It is commonly associated with pain at various tender points. On the basis of the current wisdom regarding the pathophysiology of the disorder, drug therapy is currently targeted at correcting various neurotransmitter abnormalities. Serotonin has been singled out in particular because of its implications regarding the pathophysiology of fibromyalgia in the production of pain. Antidepressants have been evaluated in clinical trials to determine their effectiveness in the treatment of fibromyalgia. Amitriptyline has proved beneficial, but its long-term efficacy has not been established. SSRIs also show promising beneficial effects, but further studies are required to validate the results. Longer-term and more extensive studies of at least 500 or more patients should be conducted for at least one year to confirm the results of these preliminary studies.

REFERENCES