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FROM THE FAMILY PRACTICE INQUIRIES NETWORK

Are any oral iron formulations better tolerated than ferrous sulfate?

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EVIDENCE-BASED ANSWER

Ferrous salt preparations (ferrous sulfate, ferrous gluconate, and ferrous fumarate) are equally tolerable. (Grade of recommendation: A, based on randomized controlled trial.) Controlled-release iron preparations cause less nausea and epigastric pain than conventional ferrous sulfate (grade of recommendation: A, based on randomized controlled trials), although the discontinuation rates between the 2 iron formulations were similar. Ferrous sulfate remains the standard first-line treatment of iron-deficiency anemia given its general tolerability, effectiveness, and low cost.

EVIDENCE SUMMARY

A randomized, double-blinded, placebo-controlled study in 1496 subjects examined side-effect rates of 3 iron salt formulations using equal dosages of elemental iron (**Table**).[1] Gastrointestinal (GI) side-effect rates were not significantly different. The side-effect rate in the ferrous sulfate group (23%) was significantly different from that of the placebo group (14%); thus, for every 11 patients treated with ferrous sulfate, 1 patient would have GI side effects attributable to the iron salt (number needed to harm [NNH] = 11).

Two formulations—controlled-release iron preparations and polysaccharide–iron complexes—decrease the amount of iron presented to the proximal GI tract. Three large randomized trials assessed tolerability of controlled-release iron preparations compared with ferrous sulfate.[2–4] The only double-blinded study found a lower rate of nausea and epigastric pain in the controlled-release iron formulation among 1376 blood donors receiving 200 mg/day elemental iron (3.3% vs 6.4%, $P < .05$, NNH = ~32).[2] A nonblinded randomized trial of 543 non-anemic adult patients taking 50 mg/day elemental iron also found a lower rate of stomach-related side effects in the controlled-release group (12.2% vs 27.2%, $P < .001$, NNH = ~7).[3] However, none of the 3 studies showed a difference in the discontinuation rates between the 2 iron formulations. Comparative constipation rates among the trials were conflicting.

Two small, nonblinded, randomized trials of polysaccharide–iron complexes reported conflicting results. A study of 159 subjects found fewer subjects discontinuing the polysaccharide–iron complex taken with meals than ferrous sulfate taken on an empty stomach.[5] A study of 60 subjects taking both preparations on an empty stomach found no difference in side-effect rates.[6] Two small, randomized, blinded studies found no difference in rates of GI side effects between carbonyl iron and ferrous sulfate.[7,8]

Representative average wholesale prices* for various iron supplement formulations

Iron supplement group	Generic or brand name	Dosage	Cost of 1-month course
Ferrous salts	Ferrous sulfate (generic)	Tablet: 325 mg po tid	$0.63 to $5.11 (90 tabs)
	Ferrous fumarate (generic)	Tablet: 300 mg (99 mg iron) po bid	$1.80 (60 tabs)
	Ferrous gluconate (generic)	Tablet: 325 mg (36 mg iron) po tid	$2.70 to $5.00 (90 tabs)
Controlled-release	Slow FE (Novartis)	Tablet: 160 mg (50 mg iron) po tid	$18.92 (90 tabs)
	Ferro-Grad-500 (Abbott)	Tablet: 105 mg iron po bid	$31.84 (60 tabs)
Polysaccharide–iron complex	Niferex-150 (Schwarz Pharma)	Capsule: 150 mg iron po qd	$10.50 (30 caps)
Carbonyl iron	Feosol (SmithKline Beecham)	Tablet: 50 mg iron po tid	$18.38 (90 tabs)

*2001 Drug Topics, Red Book. Daily dosages given here deliver 150 to 210 mg of elemental iron and are for comparison of average costs. Actual dosage should be adjusted according to the calculated need for iron replacement and the results of laboratory monitoring.

RECOMMENDATIONS FROM OTHERS

Wintrobe's Clinical Hematology[9] and *Williams Hematology*[10] recommend ferrous sulfate as the standard oral iron preparation, and assert that claims of improved tolerability of one oral iron preparation over another have not been substantiated.

Clinical Commentary by Andrea Gordon, MD, at **http://www.fpin.org**.

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