EDITORIAL

Iron Preparations: New and Old

By Ernest Beutler

THERE ARE few responses to treatment in medicine as gratifying as that of the iron-deficient patient to iron. Treatment with large doses of inorganic ferrous salts is inexpensive, convenient and very effective. Occasionally, patients do not appear to tolerate the large doses of inorganic iron usually prescribed in the therapy of iron-deficiency anemia. As a result, a great many new iron preparations, all allegedly less irritating than ferrous sulfate in the usual doses, have been made available during the past few years. The practitioner is understandably bewildered by the large number of claims and counterclaims for the superiority of one iron preparation over another. In view of this, the excellent “double-blind” studies carried out recently by Kerr and Davidsohn1 are of particular interest. One hundred volunteers were given 6 packets of pills and asked to take them in the dosage prescribed (35 mg. of elemental iron, 3 times daily after meals) from Monday through Friday for 6 successive weeks. Included were ferrous sulfate, ferrous gluconate, ferrous succinate, ferrous calcium citrate, and 2 lactose placebos. One of these was a “known” placebo, since the patients were told that it was given merely to test the coating on the other pills; the other placebo was thought by the patients to be an iron preparation. Of the 93 subjects who completed the trial, 19 to 23 complained of significant, untoward symptoms with each of the iron preparations. Twenty complained of symptoms with the “unknown” placebo, but only 2 with the “known” placebo. Closely comparable results were obtained by the same authors in a group of pregnant women given ferrous sulfate, ferrous gluconate, ferrous gluconate plus ascorbic acid, or a lactose placebo.2 These very interesting findings suggest, first of all, that the need for a substitute for ferrous sulfate may not be as great as is commonly supposed. Secondly, they call for a searching re-examination of the evidence upon which the claims of superiority of the new iron preparations are based.

In order to possess a significant advantage over ferrous sulphate tablets, which may be considered to be the standard of therapy in the United States, a new iron preparation must be shown to be better tolerated than ferrous sulfate and must be at least as effective in the treatment of iron-deficiency anemia. Examination of published reports regarding the most widely promoted newer iron preparations shows that neither of these criteria has been fulfilled.

Thus, the only published information regarding one new preparation containing relatively minute amounts of iron in combination with an emulsifying agent consists of a report in which the new drug was given to 26 patients.3 Only a few of these were apparently iron-deficient; included were patients

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with diagnoses such as “arthritis,” “cancer (pancreas),” “gallbladder disease,” “glomerulonephritis,” and “hypoproteinemia.” In the iron-deficient patients and the others, very mediocre rises of hemoglobin were obtained, but no comparison with standard doses of ferrous sulfate is possible because no adequate controls receiving standard therapy were studied. Six patients had received a variety of other iron preparations earlier, but only 1, or at the most 2, of these patients were iron-deficient. Because of the lack of controls, it is impossible to evaluate the claim that this drug is better-tolerated than standard doses of ferrous sulfate.

Similarly, a second preparation recently released to physicians consists of ferrous sulfate given in a sustained release-type of preparation recommended in doses considerably smaller than usual ferrous sulfate therapy. Again, what is the evidence for the superiority of the new medication? In one published clinical study,4 20 patients were given the dosage recommended by the manufacturer. Only 10 of these patients appeared to be suffering from iron-deficiency anemia. The other 10 were vaguely classified as nutritional anemia, miscellaneous anemia and, in 2 cases, pernicious anemia. No controls receiving standard iron therapy were included. Thus, it is impossible to evaluate either the efficacy of the new drug or its claimed lack of irritating qualities. In addition, the fact that it is claimed that the new iron preparation may be used for “maintenance therapy for patients with pernicious anemia” suggests a certain lack of familiarity on the part of the investigators with some of the basic precepts of the treatment of anemias. Experimental studies of this same new sustained-release preparation are equally unconvincing. It is claimed that it will correct anemia induced in healthy males by repeated phlebotomy.5 However, the data presented failed to bear out this contention. Not only the hemoglobin, red cell count and hematocrit of the patients remained at subnormal levels, but even the plasma iron deficit remained uncorrected. Perhaps better results would not have been achieved with standard iron therapy with ferrous sulfate, but, alas, no controls were studied.

Other studies of new iron preparations, published in the past few years, are similarly unsatisfactory. They are, in general, essentially uncontrolled investigations, the new preparations usually being given to patients who at some time in the past thought they were intolerant of iron. The facts that most of these new preparations are compounds with molecular weights greater than that of ferrous sulfate and that a 300 mg. tablet contains considerably less iron than a comparable ferrous sulfate tablet are usually conveniently forgotten. Furthermore, the response of the anemic patients has not been compared with suitable controls receiving ferrous sulfate therapy. Rather, the response has been compared to vaguely stated responses in textbooks based on a different dosage of iron or has been based on estimates of absorption based on iron tolerance curves. The reliability of the latter in estimating iron absorption is open to question. The level to which the plasma iron rises after an oral dose depends not only on the amount absorbed but also on the rate of absorption and the rate of clearance. It is interesting that claims of superiority of new iron preparations have been based on the fact that both high and low iron tolerance curves are obtained.6,7
The studies of Kerr and Davidsohn suggest that 35 mg. of elemental iron given 3 times daily rarely, if ever, produces untoward side effects. Larger doses of iron may well occasionally cause gastrointestinal disturbances in patients, and it is entirely possible that one or more of the new iron preparations which have been presented to the profession in the past 2 years may have advantages over ferrous sulfate therapy. If this is indeed true, it should be possible to demonstrate such superiority in well conceived, well controlled studies. In the meanwhile, it would appear that ferrous sulfate, USP is the initial treatment of choice for iron-deficient patients. The drug industry should make a critical evaluation of the evidence before presenting new preparations of iron to the medical profession. Physicians must examine with care the evidence upon which claims of superiority of new iron preparations are based.

REFERENCES
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