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Kurzmitteilungen

Comparative absorption of ferrous and heme-iron with meals in normal and iron deficient subjects*

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Vergleich der Resorption von Eisen und Haem-Eisen in Mahlzeiten bei Personen mit und ohne Eisenmangel

Summary: The relative intestinal absorption of heme- and non heme-iron in connection with a standardized test meal was studied in a group of fertile women given 16 mg Fe in the form of $FeSO_4$ and 2 mg Fe in the form of hemoglobin. Both in normal subjects and in women with iron deficiency, the heme-iron was significantly better absorbed (16.13 % ± S.D. 8.0 vs 4.59 ± 3.4, $p < 0.01$ and 22.03 ± 8.9 vs 9.45 ± 7.8, $p < 0.05$). For targeted prophylaxis of iron deficiency with small, side-effect-free doses, heme-iron is thus a valuable component which increases the absorption by about 40 %. Heme-iron does not cause high concentrations in the intestinal lumen of free radical inducing, possibly harmful ferric iron.

Zusammenfassung: Die relative intestinale Resorption von Haem- und Nichthaem-Eisen in Verbindung mit einer standardisierten Testmahlzeit wurde bei fertilen Frauen sowohl bei normalen Versuchspersonen als auch bei Frauen im Eisenmangel gemessen. Im Eisenmangel wurde das Haem-Eisen deutlich besser resorbiert (16.13 % ± S.D. 8.0 gegenüber 4.59 ± 3.4, $p < 0{,}01$ sowie 22.03 ± 8.9 gegenüber 9.45 ± 7.8, $p < 0{,}05$). Für die gezielte Prophylaxe eines Eisenmangels mit kleinen, nebeneffektfreien Dosierungen ist Haem-Eisen daher eine wertvolle Komponente, welche die Resorption um 40 % steigert. Haem-Eisen verursacht keine hohen Konzentrationen freier Radikale im intestinalen Lumen, die möglicherweise schädlich wirkendes zweiwertiges Eisen induziert.

Key words: Iron-absorption – heme-iron

Schlüsselwörter: Eisen-Resorption – Haem-Eisen

Introduction

Iron deficiency is known to be the most common nutrient deficiency among menstruating Scandinavian women. Rybo (1985) claims that latent iron deficiency was, in 1985, still seen in 38 % in a Swedish population of fertile women. Similarly Borch-Iohnsen et al. (1989) in a Norwegian group found a prevalence of 22 %. Even if the clinical relevance of latent deficiency is debatable there may be a need for reducing this widespread deficiency.

Iron deficiency can, in theory, be prevented in one of five different ways, which can also be combined.

1) A diet sufficiently rich in natural iron can be selected. Experience shows that for the at-risk group, young women, such a diet is frequently too rich in energy (Herbertsson, 1985). A diet sufficiently rich in iron without increased energy content is difficult to achieve for many young women.

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2) The diet can be fortified, almost always, with non heme-iron compounds. The disadvantage is that most of the iron will go to groups which are not at risk (Olsson et al., 1983).
3) Iron prophylaxis can be targeted to the risk groups by pharmacological doses of ferrous iron, which, however, usually cause side-effects (Rybo et al., 1971).
4) Iron prophylaxis can be targeted with physiological doses of ferrous iron, which, however, is absorbed poorly or not at all if taken with a meal (Layrisse, 1975).
5) Prophylaxis can be targeted to the risk groups with physiological doses of heme-iron (Borch-Iohnsen et al., 1990).

The aim of the present study was to evaluate the relative absorption of physiological doses of ferrous and heme-iron in conditions under which iron medication is usually taken, namely, together with a meal. However, for the present purpose a meal containing inhibitors of absorption of ionizable iron rather than promoters was used.

Methods

Subjects

The iron was given in the form of a tablet consisting of 8 mg ferrous iron and 1 mg heme-iron. The ferrous iron was $FeSO_4$. The purpose was to see whether a small addition of heme iron could substantially improve absorption.

Two groups of women, matched in age and iron status (Table 1) were randomly given a single dose of two tablets, either labeled for detecting the ferrous or the heme-iron absorption. Both groups were thus given both heme and non-heme iron.

Table 1. Mean values, standard deviations, and range values for age, ferritin in serum and hemoglobin

	N	Age (years)	Ferritin (μg/l)	Hb (g/l)
Ferrous group	13	37.5 ± 3.1 (21 – 54)	32.5 ± 5.4 (9 – 114)	129.8 ± 2.4 (120 – 138)
Heme-iron group	14	38.0 ± 3.0 (20 – 51)	29.4 ± 5.4 (6 – 114)	127.6 ± 3.8 (100 – 146)

In the non-heme iron labeled group, seven apparently healthy women and six with depleted iron stores (Ferritin: 32.5 ± 5.4 μg/l, Hb: 129.8 ± 2.4 g/l) were studied. In the heme-iron labeled group seven healthy women and seven with lowered iron stores (Ferritin: 29.4 ± 5.4 μg/l, Hb: 127.6 ± 3.8 g/l) were studied. Four individuals crossed over and participated in both groups.

Design and diets

To study the absorption of ferrous iron, the ferrous sulfate was labeled with Fe59 according to the method described by Brise and Hallberg (1962). Radioactively labeled hemoglobin was prepared by injecting a pig with Fe59- ferric citrate, collecting heparinized blood, and separating erythrocytes by centrifugation and air drying. The resulting powder was then made into tablets.

The activity used was between 5.4 and 18.0 kBq/tablet. The tablets were given

together with a standardized test meal consisting of tea, whole grain bread, butter, and three slices of sausage.

Iron absorption was measured in a whole body counter, where repeated measurements of activity were made during 14 days, as previously described (Reizenstein, 1973). This method was preferred over the double isotope method (Saylor and Finch, 1953), primarily because it gives quantitative rather than relative values. It is also simpler and causes lower radiation doses.

Statistical methods

For the statistical comparison of the groups, the Mann-Whitny test was used.

Results

The figures demonstrating the absorption rates (% of dosage) of the two forms of iron, are given in Table 2.

Both in normal subjects and in women with iron deficiency, the heme-iron absorption was significantly better than that of ferrous iron.

Table 2. Mean values, standard deviations, and range values for the absorption rates

	Normal (% ± s.d.)	Iron deficiency (% ± s.d.)	Total (% ± s.d.)
Ferrous group	4.59 ± 3.4 (1.0 – 12.4)	9.45 ± 7.8 (0 – 22.9)	6.83 ± 6.4 (0 – 22.9)
Heme-iron group	16.13 ± 8.0** (8.0 – 33.7)	22.03 ± 8.9* (9.7 – 35.5)	19.08 ± 9.0** (8.0 – 35.5)

* $p < 0.05$, ** $p < 0.01$ between ferrous and heme iron groups

Discussion

Iron supplements are traditionally high-dose preparations designed for therapeutic use. High iron doses, however, often cause nausea, constipation or diarrhea (Rybo et al., 1971). High concentrations of one mineral may also interfere with the uptake of other minerals. Thus, high doses (> 50 mg) of iron will disturb the uptake of zinc (Solomons, 1988). During recent years it has also been questioned whether excess ferrous iron could act as an inducer of free radicals (Reizenstein, 1990).

For these reasons, it would be desirable to have effective low-dose iron preparations for prophylactic use. However, earlier methods have not usually studied the realistic situation where there is simultaneous intake of heme and non-heme iron together with a meal. (Layrisse et al., 1972; Heinrich, 1970; Reizenstein, 1975; Hallberg, 1975).

Although most of the absorbed iron was derived from the ionizable iron, this study clearly demonstrated that the addition of heme-iron to physiological doses of ferrous iron in a tablet can increase the amount of iron absorbed by about 40 %. With the standard test meal used here, heme iron shows a significantly better percentage absorption than non heme-iron fraction in such a tablet. However, if a meal had been given containing no inhibitors of the absorption of ionizable iron, but instead promoters like ascorbic acid, the advantage of heme iron would have been reduced. The same is true if the prophylactic iron could be taken on a fasting stomach, but experience shows that medication, particularly prophylactic medication, is frequently forgotten unless it is taken with meals.

A combined ferrous and heme-iron preparation may thus be a rational method for the use of physiological doses of iron as prophylaxis. Such a targeted, absorbable, side-effect-free prophylaxis which could be taken together with meals could also replace general iron fortification, which may accelerate the development of hemochromatosis, perhaps the most prevalent inborn error of metabolism, which in some populations may comprise 0.3 % of the population for homozygous and 10 % for heterozygous subjects. It is only iron in tablet form which can be targeted to sufficiently stringently defined risk groups which clearly are at risk of developing manifest iron deficiency.

In order to increase the absorption from 4.59 % of 16 mg non-heme iron (0.73 mg) to that obtained with the combined tablet, 0.73 mg + 0.32 mg or 1 mg, with non-heme iron alone, the dose would have had to be increased to almost 25 mg non-heme iron.

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