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Iron Absorption following a Single Oral Dose of Ferrous Sulfate or Ferric Gluconate in Patients with Gastrectomy

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Key Words
Ferrous sulfate · Ferric gluconate · Iron deficiency anemia · Gastrectomized patients

Abstract
Background: Iron deficiency anemia frequently occurs in gastrectomized patients. ***Methods:*** Serum iron levels following the ingestion of a single oral dose of 105 mg elemental iron, taken as ferrous sulfate (FeS) or ferric gluconate (FeG), have been evaluated in 20 gastrectomized patients (and 20 controls). All subjects participated on 2 different test days, 1 month apart: they took a single dose of 105 mg elemental iron as FeS or FeG after a night of fasting. Serum iron concentrations at baseline, 30, 60, 120 and 180 min after the oral dose administration were measured. ***Results:*** In patients and controls receiving FeG, serum iron levels did not significantly change. After oral ingestion of FeS, patients' serum iron levels gradually increased. The increase in serum iron levels was 148 and 168% at 120 and 180 min in patients ($p < 0.0001$ for both evaluations), whilst in controls, it was 216% at 120 min and 234% at 180 min, i.e. significantly higher than in gastrectomized patients ($p < 0.001$ for both evaluations). ***Conclusions:*** In gastrectomized patients, a single oral dose of FeS shows a significant increase in iron serum concentration, albeit lower than in controls. Further studies on a larger sample of patients will be necessary to confirm these results.

Introduction

Iron deficiency anemia in totally gastrectomized patients has been described with a prevalence ranging between 15 and 54% according to patient selection, type of surgery, time after gastrectomy and presence of anemia before surgery [1].

Due to the removal of both the gastric antrum and duodenum, and to frequent alkaline reflux, total gastrectomy can cause an irreversible modification of oral iron absorptive capabilities [2].

Oral iron absorption may also be affected by the type of pharmaceutical preparation, in particular by the ionic state of iron salts administered. Iron, to be absorbed, must be in its ferrous form. Under normal conditions, a ferric reductase enzyme on the enterocyte brush border reduces ferric (Fe^{3+}) to ferrous (Fe^{2+}) iron; then, a protein called 'divalent metal transporter 1' transports iron across the enterocyte cell membrane into the cell. The alkaline environment, due to the reduced production of chloride acid and the absence of the duodenum – believed to be the primary site of iron absorption – could negatively influence the conversion from the trivalent to the bivalent form and therefore impair iron absorption [3].

On the other hand, oral iron intake can be burdened by gastrointestinal side effects such as diarrhea, heartburn, abdominal pain, nausea and vomiting [4].

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For these reasons, in case of iron deficiency anemia, intravenous iron administration is often the preferred route for prompt iron storage replacement. Unfortunately, intravenous iron administration has been described related to the onset of possible hypersensitivity and allergic reactions (with a rate of 0.8%) such as cutaneous rush, hives, generalized itch, headache, myalgia and serious anaphylactic reactions (with a rate of 0.04%) [5].

It could be useful, in our opinion, to evaluate the residual oral iron absorptive capability of different pharmaceutical formulations in gastrectomized patients, also in order to tweak a simple and reliable test to identify potential candidates for oral iron administration.

For the purpose of this study, FeS and FeG have been chosen because these are the oral iron formulations most frequently prescribed in Italy. In the scientific literature, FeS has been described as the best iron salt formulation recommended for oral administration, but it is available as tablets only. FeG is the second most frequently prescribed iron salt formulation in Italy and is present as a solution for both oral and intravenous administration. FeG is widely used in its liquid form in patients with swallowing difficulties.

It was the aim of the study to compare the acute effects of two commercially available oral iron preparations of FeS and FeG on iron serum levels after a single dose in gastrectomized patients and controls.

Patients and Methods

This single blind randomized controlled study has been conducted in 20 patients (11 males, 9 females, aged 49.7 ± 12.4 years) followed up after total gastrectomy at the Clinical Nutrition Unit of Federico II University Hospital in Naples and in 20 control subjects.

All patients had received a Roux-en-Y gastrectomy (the median time after surgery was 28 months, range 8–120) due to gastric cancer (16 cases), gastric lymphomas (2 cases), caustic ingestion (1 case) and gastric volvulus (1 case).

All patients were considered disease free at the time of the study, in particular, those with anamnesis of oncological disease at the last follow-up performed 1–3 months before this study.

Patients have been consecutively recruited during a routine follow-up visit. None of them had received blood transfusions or intravenous iron during the 6 months prior to the study. In all patients, the presence of other conditions promoting anemia has been ruled out.

The 20 healthy, age- and sex-matched controls have been recruited among patients' relatives or staff volunteers.

All patients and controls gave their informed consent for participation in the study, and the study protocol was approved by the local ethical committee.

Patients' clinical, anthropometric and demographic data are presented in table 1.

Methods

All subjects participated on 2 test days 1 month apart, according to a randomized protocol; they took a single dose of 105 mg elemental iron given as FeS (1 tablet) or FeG (7.5 ml in a vial) in the morning, after 12-hour overnight fasting.

Blood samples were collected for serum iron concentration dosing at baseline and 30, 60, 120 and 180 min after taking the oral dose.

Clinical and Laboratory Evaluation

Anthropometric measurements have been performed, and the body mass index was calculated as body weight (kg) divided by squared height (m^2).

After 12-hour overnight fasting, before subjects ingested the iron dose, blood samples were collected for the determination of the following parameters: hemoglobin, mean corpuscular volume, serum iron, ferritin, transferrin, and total iron-binding capacity.

All subjects took their oral dose at 9.00 a.m. in the experimental unit and continued to fast for 3 h; blood samples were collected at 30, 60, 120 and 180 min after administration for serum iron dosing.

The blood samples taken at 30, 60, 120 and 180 min after iron ingestion were collected from an antecubital vein into sterile tubes through an indwelling catheter. Samples for hemoglobin determination were collected in EDTA tubes, whilst samples for serum iron, transferrin and ferritin dosages were collected in serum separator tubes. All samples were sent to the laboratory for analysis. For hemoglobin analysis, a hematologic analyzer (ADVIA 2120, Siemens) was used; serum iron and ferritin levels were determined by spectrophotometry (Modular, Hitachi); in particular, for ferritin dosage, an immunoenzymatic assay was used. Finally, for transferrin and total iron-binding capacity, a nephelometric method was used.

Statistical Analysis

Data were digitized and analyzed with the SPSS 15 program. Means, standard deviations and frequencies were used as descriptive statistics. Comparisons between groups were performed with the simple t test. Percent concentration change was calculated. Bivariate correlations were analyzed with the Pearson correlation test. Differences were considered significant with p values <0.05.

Results

All patients had received total Roux-en-Y gastrectomy (fig. 1). Baseline hematochemistry results are reported in table 1.

Two patients (10%) had baseline hemoglobin <12 g/dl and hematocrit <35%. Three patients (15%) had serum iron levels <60 μg/dl and 3 showed a mean corpuscular volume of <80 fl. Three patients had serum ferritin <20 ng/ml, 5 patients between 20 and 50 ng/ml and 6 patients between 50 and 100 ng/ml.

Baseline mean serum iron levels in patients and controls were not significantly different (table 1).

Table 1. General characteristics and hematobiochemical data of patients and controls

	Patients	Controls	p	Normal range
Males/females	11/9	10/10	n.s.	
Age, years	49.7±12.4	50.8±11.9	n.s.	
Time for surgery, months	42±27	–	n.s.	
BMI, kg/m^2	20.5±3.2	20.3±3.3	n.s.	18.5–25
WBC, n/μl	6,215±1,671	6,297±1,775	n.s.	4.8–10.8
RBC, ×10^6/μl	4,532±508	4,485±1,775	n.s.	4.0–5.6
Hemoglobin, g/dl	13.4±1.4	13.9±0.9	n.s.	12–16
Hematocrit, %	39.7±3.7	40.7±2.6	n.s.	35–48
MCV, fl	87.5±9.2	87.6±6.8	n.s.	80–97
Lymph, n/μl	2,005±919	1,885±956	n.s.	1.0–4.8
Platelets, ×10^3/μl	250±103	253±102	n.s.	130–400
Iron, μg/dl	89.9±29.6	92.4±26.5	n.s.	60–110
Ferritin, ng/ml	105.0±73.9	119.7±112.12	n.s.	5–150
Transferrin, g/l	2.7±0.5	2.6±0.4	n.s.	2.0–3.6
Transferrin saturation, %	25.1±8.4	27.2±7.9	n.s.	20–50
Protein, g/dl	7.2±0.5	7.3±0.6	n.s.	6.5–8.2
Albumin, g/dl	4.4±0.2	4.5±0.3	n.s.	3.6–5.2
Prealbumin, g/dl	0.2±0.3	0.2±0.2	n.s.	0.2–0.4
Cholesterol, g/dl	185±26	192±32	n.s.	<190
Pseudocholinesterase, U/l	7,619±1,938	8,912±2,123	n.s.	5,400–13,200
B_{12} vitamin, pg/ml	904±518	679±231	n.s.	190–866
Folate, ng/ml	15.86±4.9	12.3±3.7	n.s.	3.0–16.0

n.s. = Not significant; BMI = body mass index; WBC = white blood cells; RBC = red blood cells; MCV = mean corpuscular volume; Lymph = lymphocyte count.

Administration of FeG

In patients receiving FeG, basal iron serum levels were 97.5 ± 35.6 μg/dl and did not significantly change at 30 (93.0 ± 34.9 μg/dl), 60 (93.8 ± 35.1 μg/dl), 120 (97.3 ± 35.2 μg/dl) and 180 min (99.4 ± 37.3 μg/dl) after oral ingestion of 105 mg oral iron.

Similarly, in controls receiving FeG, basal iron serum levels were 91.5 ± 25.9 μg/dl and did not significantly change at 30 (91.1 ± 27.9 μg/dl), 60 (96.9 ± 29.5 μg/dl), 120 (100.9 ± 34.5 μg/dl) and 180 min (112.8 ± 41.5 μg/dl).

Administration of FeS

Baseline serum levels of iron in patients receiving FeS were 92.4 ± 16.5 μg/dl and gradually increased to 98.3 ± 15.2 μg/dl at 30 min ($p < 0.0001$), 110.4 ± 16.9 μg/dl at 60 min ($p < 0.0001$), 137.2 ± 28.6 μg/dl at 120 min ($p < 0.0001$) and 155.6 ± 37.0 μg/dl at 180 min ($p < 0.0001$). The increase in serum iron levels (ΔFe) was 148 and 168% at 120 and 180 min, respectively ($p < 0.0001$ for both evaluations).

In controls receiving FeS, basal levels (96.1 ± 37.1 μg/dl) gradually increased at 30, (115.1 ± 45.4 μg/dl; $p <$

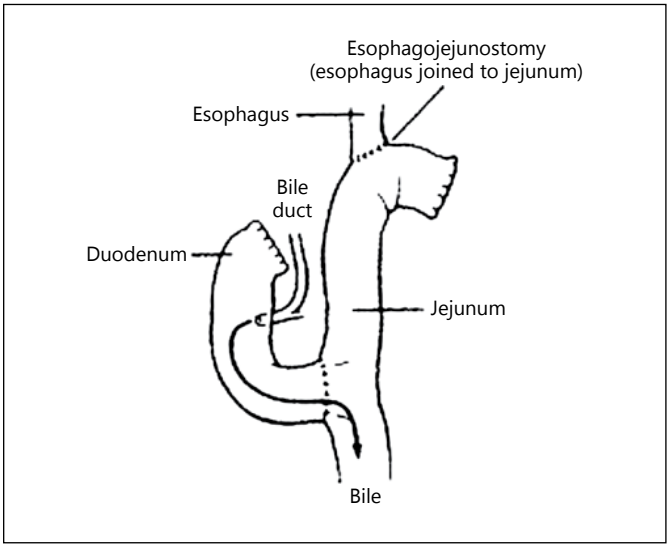

Fig. 1. Roux-en-Y reconstruction. After removal of the stomach and closure of the duodenal stump, end-to-side esophagojejunostomy is performed. The second jejunal loop is divided: the aboral end is pulled up to the esophagus, while the oral end is sewn into the pulled-up limb, 50 cm distal to the esophagojejunal anastomosis as an end-to-side jejunojejunostomy.

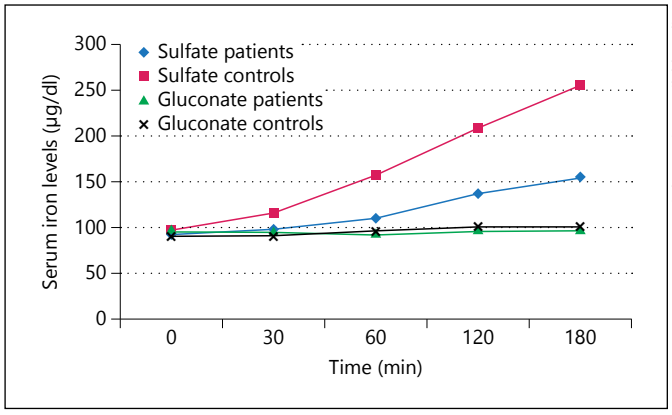

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Fig. 2. Mean serum iron levels following a single oral dose of 105 mg elemental iron as FeS or FeG in patients and controls. Samples have been collected at 0, 30, 60, 120 and 180 min. Patients receiving FeS: $p < 0.0001$ at all time points. Controls receiving FeS: $p < 0.0001$ at all time points. Patients receiving FeG: p ns at all time points. Controls receiving FeG: p ns at all time points.

0.0001), 60 (157.2 ± 70.2 µg/dl; $p < 0.0001$), 120 (208.7 ± 78.9 µg/dl; $p < 0.0001$) and 180 min (255.5 ± 67.9 µg/dl; $p < 0.0001$). ΔFe in controls was 216% at 120 min and 234% at 180 min, i.e. significantly higher than in gastrectomized patients, both at 120 and 180 min ($p < 0.0001$ for both evaluations) (fig. 2).

There was no correlation between ΔFe at 120 and 180 min and hemoglobin levels, as well as serum iron, transferrin and ferritin levels, both in patients and in controls.

In conclusion, following the 3-hour test, both in patients and controls taking oral FeG, there were no significant differences in serum iron concentration at all time points, whilst iron serum levels were significantly increased following the administration of FeS.

None of the gastrectomized patients or controls experienced gastrointestinal and other side effects during the oral test.

Discussion

Patients with gastrectomy may experience progressive blood hemoglobin decrease due to reduced iron absorption. Considering the impairment of oral absorption, intravenous iron formulations are prescribed worldwide in case of iron depletion, with some risks of serious complications [6].

On the other hand, different iron intravenous preparations are available in different countries, in particular, iron sucrose is mainly prescribed in the USA, whilst in our country, the only intravenous formulation available is FeG, which is also administered orally.

Our study evaluated the presence of residual intestinal iron absorption capacity in patients with total gastrectomy; for this purpose, the technique of serum iron monitoring after the administration of a single oral dose of different pharmaceutical iron preparations may result as a simple and reliable method [7]. To avoid the effects of previous administrations and of cross-interferences of iron compounds, a 1-month washout interval between the testing days was observed.

Patients have been compared with controls in order to evaluate residual iron absorption after gastrectomy but also to directly compare iron absorption of two different types of iron pharmaceutical preparations: FeS and FeG.

In the present study, we decided to test the two most commonly prescribed oral iron formulations in Italy, FeS (as tablets or capsules) and FeG (in liquid form).

In the scientific literature, FeS has been described as the best iron salt formulation recommended for oral administration, but it is available as tablets only.

FeG is the second most frequently prescribed iron salt formulation in Italy and is present as a solution for both oral and intravenous administration. FeG is widely used for its liquid form in patients with swallowing difficulties. We had hypothesized that due to its liquid form, FeG could be more promptly absorbed than FeS tablets, as the latter require to be first broken up and then dissolved in gastroenteric juices; however, the findings of our study proved this hypothesis to be incorrect.

A single oral dose of FeS shows a more favorable acute ΔFe than FeG in both gastrectomized patients and controls.

This finding can probably be explained by the different ionic form of the two compounds: in particular, FeS is a ferrous bivalent ion whilst FeG is a ferric trivalent form.

Non-heme iron is known to be absorbed by enterocytes only in a bivalent form; consequently, trivalent iron requires reduction in the bivalent status before absorption.

However, the present results confirm the findings of previous studies that showed that FeS, when compared with other compounds, leads to higher serum iron levels (i.e. better iron absorption) both in animals and humans [8, 9].

To the best of our knowledge, there are no studies on FeG oral absorption other than those on intravenous administration. Some studies on the oral absorption of FeG [10–12] report a similar absorption to FeS. Unfortunately, FeG is not available in Italy.

Our data strongly evidence the different acute response of the two tested iron preparations, both in controls and gastrectomized patients.

In gastrectomized patients, the lack of gastric acid secretion could influence the reduction of Fe^{3+} to absorbable Fe^{2+}, thus impairing the absorption of iron gluconate. Still, this is not the only reason, because iron gluconate does not appear absorbed in normal healthy controls either.

Another study has compared oral absorption of iron sulfate with iron glycinate in gastrectomized patients, demonstrating a greater absorption of iron sulfate [13].

FeG is an iron amino acid chelate and, in earlier studies, it has been demonstrated to be more bioavailable than FeS orally [14].

In order to exclude possible factors potentiating the absorption, all consecutive gastrectomized patients have been recruited, irrespective of the presence or absence of anemia; moreover, we have administered the same dose for both products to compare the effects of the two compounds.

The presence of an acute iron serum concentration increase after oral iron administration in gastrectomized patients could allow us to find a predictive test to identify patients responsive to oral iron supplementation.

These data show the presence of acute absorption of FeS in totally gastrectomized patients, even though at a lower level than in control subjects. This finding, if confirmed on chronic dosing, could allow us to prescribe oral FeS compounds in gastrectomized patients, thus avoiding intravenous iron administration.

In conclusion, gastrectomized patients seem to have residual oral acute iron absorption capacity, in particular when iron tablets are given as ferrous bivalent ion. Therefore, the oral route could be considered to prevent or treat iron deficiency anemia early in these patients. Further studies on a larger scale and for longer periods of observation following oral iron administration are required to confirm the efficacy of long-term oral iron administration in gastrectomized patients.

Disclosure Statement

No conflict of interests to declare.

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