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# Decreased Treatment Failure Rates following Duodenal Release Ferrous Glycine Sulfate in Iron Deficiency Anemia Associated with Autoimmune Gastritis and *Helicobacter pylori* Gastritis

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**Key Words**
Autoimmune gastritis · Ferrous glycine sulfate · *Helicobacter pylori* · Iron deficiency

**Abstract**
***Background and Objectives:*** Since gastric acidity and ascorbate play a critical role in the solubilization and reduction of iron for subsequent absorption, the achlorhydria associated with autoimmune and *Helicobacter pylori* gastritis may explain the poor response of such patients to oral iron treatment. In order to circumvent this problem, we explored the therapeutic potential of a duodenal formulation of ferrous glycine sulfate consisting of micropellets that do not dissolve at the acid environment of the stomach but, owing to their solubility at a higher pH, discharge their content directly into the duodenum. ***Design and Methods:*** In a case-control study, the treatment results of 39 patients with iron deficiency anemia receiving a duodenal formulation of ferrous glycine sulfate (group A) were compared with the results of 39 patients receiving other oral iron compounds (group B). Autoimmune gastritis, *H. pylori* gastritis or both were present in over 75% of patients in each group. ***Results:*** After 1 and 3 months of treatment, mean hemoglobin in group A increased from 9.5 ± 1.2 to 11.2 ± 1.3 and 12.8 ± 1.3 g/dl, respectively. By comparison, in group B, the corresponding values increased from 9.3 ± 1.3 to 10.2 ± 1.5 ($p = 0.019$) and 11.1 ± 1.7 g/dl ($p = 0.022$). A favorable response, defined as a more than 2 g/dl increase in basal hemoglobin or hemoglobin exceeding 12 g/dl, was obtained in 33 of 39 patients in group A compared with only 18 of 39 in group B ($p = 0.009$). Because of treatment failure, 14 patients in group B were subsequently referred for intravenous ferric sucrose therapy versus only 3 in group A ($p < 0.0001$). Conversely, of 5 patients in group A managed by intravenous iron prior to referral, 4 became independent of parenteral iron after starting the duodenal formulation of ferrous glycine sulfate. ***Interpretation and Conclusions:*** In patients with iron deficiency anemia associated with autoimmune and *H. pylori* gastritis with a high rate of refractoriness to oral iron treatment, satisfactory response to a duodenal formulation of ferrous glycine sulfate can be elicited in the vast majority of cases, obviating the need for expensive, inconvenient and occasionally risky intravenous iron administration.



## Introduction

Following initial diagnostic workup in patients presenting with iron deficiency anemia (IDA), treatment is implemented to correct anemia and prevent relapse. In

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the majority of patients, oral iron treatment should be satisfactory [1, 2]. It has long been established that the bioavailablity of ferrous iron is far better than ferric iron [3] and that slow release formulations may interfere with absorption [4, 5]. Despite these clearly defined principles, treatment failure remains a significant problem. Poor compliance and poor choice of oral medications may explain some of these failures [2]. However, impaired iron absorption associated with asymptomatic celiac disease [6–9], autoimmune atrophic gastritis and *Helicobacter pylori* gastritis [10–19] are increasingly recognized as conditions responsible for obscure IDA refractory to oral iron treatment.

Both autoimmune and *H. pylori* gastritis interfere with the normal gastric secretion of hydrochloric acid and ascorbate [20, 21]. Since gastric acidity and ascorbate play a critical role in the solubilization and reduction of iron for subsequent duodenal and upper jejunal absorption, the achlorhydria associated with autoimmune and *H. pylori* gastritis may explain not only the circumstances aggravating IDA but also the poor response of such patients to oral iron treatment [22–23]. In order to circumvent this problem, we have decided to explore the therapeutic potential of a duodenal formulation of ferrous glycine sulfate (ferro sanol® duodenal, Sanol GmbH, Monheim, Germany) consisting of ferrous glycine sulfate micropellets that do not dissolve at the acid environment of the stomach but, owing to their high surface area and solubility at higher pH, discharge their content into the duodenum [4, 24]. These features make it independent of normal gastric acidity.

In the present report, we describe the therapeutic effects of the duodenal formulation of ferrous glycine sulfate as compared with other oral iron compounds in common use in a population of patients with IDA associated with a very high prevalence of autoimmune gastritis and *H. pylori* infection.

## Methods

*Target Population*

The population studied was part of a long-term prospective study consisting of all patients referred for consultation for IDA by family physicians to a community hematology clinic between 1 September 2001 and 31 August 2006. Inclusion criteria were a hemoglobin level at referral of <11.5 g/dl in females and <13.0 g/dl in males and the following criteria for IDA: mean corpuscular volume <80 fl, transferrin saturation <15% and serum ferritin <12 μg/l. The prospective study was approved by the Institutional Helsinki Committee of the Shaare Zedek Medical Center. As described previously [16, 19], within the above period, 261 patients were referred for investigation of IDA. There were 83% females and 17% males. Anemia was most commonly attributed to menorrhagia (32%), followed by autoimmune gastritis (25%). In 19% of patients, *H. pylori* infection was the only positive finding. Gastrointestinal (GI) anatomic lesions were identified in 13% and celiac disease in 5% of cases. All 17 patients (6%) in whom no underlying disease could be identified were fertile females.

*Laboratory Methods*

Complete blood counts were performed by a Sysmex SE-9000 automated analyzer (Kobe, Japan) calibrated daily with standards provided by the manufacturer. Routine biochemical measurements including serum iron (normal range 59–158 μg/dl), total iron binding capacity (normal range 226–338 μg/dl) and serum ferritin (normal ranges in males 40–340 and in females 14–150 μg/l) were performed by a Hitachi 747 automated analyzer with quality control assurance by Ukneqas (Birmingham, UK). Fasting serum $B_{12}$ levels were determined by the Advia Centaur VB12 assay which is an automated competitive immunoassay using direct chemiluminescent technology. The lower limit of normal was defined as <181 ng/l. Fasting serum gastrin levels were determined by GammaDab® Gastrin $^{125}$I RIA kit (DiaSorin, Stillwater, Minn., USA) and expressed in picograms/milliliter (normal limit <107 pg/ml). For the detection of IgG antibodies to *H. pylori* in human serum, the Immulite® 2000 *H. pylori* IgG, a solid-phase chemiluminescent immunometric assay (DPC Diagnostics, Los Angeles, Calif., USA), was used, with an analytical sensitivity limit of 0.4 U/ml, with <1.0 U/ml considered to be negative. Anti-parietal cell antibodies directed against $H^+$,$K^+$-ATPase were measured by Varelisa enzyme immunoassay (Sweden Diagnostics GmbH, Freiburg, Germany). Intrinsic factor antibodies were assayed by enzyme-linked immunoassay (Alphadia®, Waver, Belgium) detecting type I and type II antibodies. Results exceeding 1.1 were considered positive. Anti-endomysial IgG and IgA antibodies were determined by an indirect immunofluorescence antibody test for semiquantitative detection of antibodies using the ImmuGlo™ Anti-Endomysial Antibody Test System (Immco® Diagnostics, Buffalo, N.Y., USA). Results were considered positive if ≥1:40 dilution. Antigliadin antibodies were measured by an indirect assay using peroxidase-labeled rabbit anti-human IgG and IgA antibodies employing the Bindazyme™ Human Anti-Gliadin IgG and IgA kits (The Binding Site Ltd., Birmingham, UK). Results were considered positive if ≥10 U/ml for IgG and 5 U/ml for IgA antibodies.

The $^{13}$C-urease breath test was performed as described by Gal et al. [25]. Briefly, patients were given 75 mg urea labeled with $^{13}$C in 200 ml orange juice, and breath samples were collected before (T0) and 30 min after $^{13}$C intake. Results were expressed as the difference between the two scores (Δ over baseline). The cutoff $^{13}C/^{12}C$ of T30′ – T0′ was 3.5%. Patients were instructed to discontinue treatment with $H_2$ antagonists, proton pump inhibitors or any antibiotics 1 week before the test. Repeat tests for validation of *H. pylori* eradication were performed after at least 1 month of completing triple therapy.

*Diagnostic Workup*

For each patient, a questionnaire has been completed including the following details:

*Medical history:* symptoms, blood donation, a history of epistaxis or GI blood loss, use of aspirin or other nonsteroidal anti-

inflammatory drugs, a family history of GI disease including cancer, cold intolerance or increased hair loss, dysphagia and brittle nails; excessive menstrual bleeding was defined as more than 2 days of heavy bleeding and the presence of formed clots; details of iron therapy prior to referral were recorded; electronic records of blood counts and iron measurements were reviewed for the 12 months preceding referral.

*Physical examination:* brittle or flat nails, pallor, abdominal mass, splenomegaly, mucosal or cutaneous telangiectasiae.

*Laboratory tests:* complete blood count, serum iron, total iron binding capacity, serum ferritin, serum $B_{12}$, folate, sedimentation rate, fibrinogen and C-reactive protein; routine biochemistry including serum albumin and cholesterol; celiac serology including anti-endomysial and antigliadin antibodies; *Helicobacter pylori* IgG antibodies; antiparietal cell antibodies and serum gastrin; intrinsic factor antibodies were assayed in patients who were antiparietal cell antibody positive.

*GI Studies*

Males and postmenopausal females had full endoscopic investigation including colonoscopy and upper GI endoscopy. Young females with GI symptoms or a cancer family history had the same GI workup. All patients with positive endomysial antibodies were referred for upper GI workup for suspected intestinal malabsorption, including duodenal biopsies. Young females with a history of menorrhagia, with no GI complaints and a negative family history had 5 occult blood tests each (Hemoccult II) and, if all were negative, no initial GI workup was required. All patients with abnormal titers of *H. pylori* IgG antibodies were referred for urease breath test for confirmation of *H. pylori* infection [18]. The urease breath test was repeated after 1 month of completing triple therapy.

*Treatment*

Oral iron treatment of the ferrous glycine sulfate group (group A) consisted of ferro sanol duodenal (Sanol GmbH, Monheim, Germany) containing 100 mg elemental iron taken on an empty stomach once daily. Prior to referral, and in the case-control group consisting of patients presenting before 1 January 2005 (group B), the following iron medications have been used: ferric polymaltose (Ferrifol® iron III hydroxide polymaltose complex 100 mg iron/tablet; CTI, Yokneam, Israel), exsiccated ferrous sulfate (Slow-Fe® 50 mg elemental iron/tablet; Novartis, Basel, Switzerland), exsiccated ferrous sulfate (Ferrograd® 105 mg elemental iron/tablet; Abbott, Chicago, Ill., USA), ferrous fumarate (Foric® 100 mg elemental iron/tablet; Sam-On, Bat-Yam, Israel), ferrous calcium citrate (Ferrocal® 50 mg elemental iron/tablet; Rekah, Holon, Israel), and ferrous serine sulfate (Aktiferrin® 34 mg elemental iron/tablet; Merckle GmbH, Ulm, Germany). The daily dosage of oral iron was equal to 100 mg elemental iron with all preparations used. Patients referred for intravenous therapy received ferric iron sucrose (Venofer® 100 mg elemental iron/5 ml; Vifor, St. Gallen, Switzerland) in repeat infusions of 100–200 mg calculated to correct anemia and replenish 500–1,000 mg iron stores.

Follow-up visits including relevant repeat laboratory tests were performed at 1-month intervals for the first 3 months and at 2- to 6-month intervals thereafter. Triple therapy for *H. pylori* eradication consisted of omeprazole 20 mg × 2/day, amoxycillin 1 g × 2/day and clarithromycin 500 mg × 2/day for 7 days.

*Statistical Analysis*

Data of all 261 patients were tabulated in the order of presentation and listed in chronologic order according to diagnostic categories. For the selection of case controls, the 39 patients receiving ferrous glycine sulfate (group A) were matched with 39 patients treated with other oral iron compounds (group B) in retrograde order of presentation, starting on 31 December 2004, i.e. prior to the introduction of ferro sanol duodenal, with identical numbers of consecutive patients within each diagnostic category.

We employed the Student t test for continuous variables and the $\chi^2$ test for categorical variables. All tests were two-tailed. For all the analyses we used the SPSS 10.0 for Windows.

## Results

Starting on 1 January 2005, ferrous glycine sulfate capsules became available for use in Israel and were offered to the majority of the 65 new patients presenting between January 2005 and August 2006.

Of the 65 new patients, 39 (60%) were prescribed treatment with ferrous glycine sulfate (group A). All but 2 were females and their age was 43 ± 13 years (mean ± 1 SD). The underlying conditions associated with IDA are listed in table 1. Also listed in table 1 is a second group of 39 additional patients intended to serve as case controls. These patients receiving other oral iron preparations (group B) were randomly selected by including identical numbers of patients referred between January 2003 and December 2004, i.e. immediately prior to the introduction of ferrous glycine sulfate, presenting with the same categories of underlying conditions. As shown in table 1, the disease categories of the 2 groups (patients receiving ferrous glycine sulfate vs. those receiving other medications) were near identical. Likewise, the high proportion of females in each group and the age of patients was very similar.

All 39 patients in group A received ferrous glycine sulfate representing 100 mg/day elemental iron. The 39 case-control patients in group B received the same amount of elemental iron, at a period when ferrous glycine sulfate was not yet available, in the form of ferrous fumarate (17 patients), slow-release ferrous sulfate (9 patients), ferrous serine sulfate (8 patients), ferric polymaltose (3 patients), or ferrous calcium citrate (2 patients).

Response to oral iron treatment as assessed by hemoglobin levels is described in table 2 and figures 1 and 2. In the group of patients treated with ferrous glycine sulfate (group A), an increase in mean hemoglobin was sharpest in the first month of treatment (from 9.5 ± 1.2 to 11.2 ± 1.3 g/dl) and reached a plateau (12.8 ± 1.3 g/dl) at 3 months (fig. 1, table 2). By comparison, in the

**Table 1.** Demographic and clinical features of oral iron treatment groups

| | Group A (ferrous glycine sulfate) | Group B (other oral preparations) |
|---|---|---|
| Patients | 39 | 39 |
| Males/females | 2/37 | 3/36 |
| Age, years | 43 ± 13 | 39 ± 13 |
| *Underlying conditions, n* | | |
| Autoimmune gastritis | 4 | 5 |
| Autoimmune gastritis and *H. pylori* | 10 | 9 |
| *H. pylori* | 3 | 2 |
| *H. pylori* and menorrhagia | 13 | 13 |
| Menorrhagia | 6 | 7 |
| Gastrointestinal anatomic lesion | 3[a] | 3[b] |

[a] Colon cancer (n = 1), bleeding polyp of colon (n = 1), bleeding hemorrhoids (n = 1).
[b] Hiatus hernia (n = 1), bleeding dysplastic polyp of the duodenum (n = 1), reflux esophagitis (n = 1).

**Table 2.** Hemoglobin response to oral iron treatment (g/dl)

| | Time | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | –3 months | –2 months | –1 month | 0 months | 1 month | 2 months | 3 months | 4 months |
| Group A (n = 39) | 9.3 ± 1.3 | 9.7 ± 0.8 | 9.3 ± 1.2 | 9.5 ± 1.2 | 11.2 ± 1.3 | 11.9 ± 1.0 | 12.8 ± 1.3 | 12.9 ± 1.0 |
| Group B | | | | | | | | |
| All (n = 39) | 9.8 ± 1.2 | 9.5 ± 1.1 | 9.5 ± 0.9 | 9.3 ± 1.3 | 10.2 ± 1.5<br>p = 0.019 | 10.9 ± 1.4<br>p = 0.019 | 11.1 ± 1.7<br>p = 0.022 | 11.0 ± 2.2<br>p = 0.023 |
| Standard (n = 27) | 10.4 ± 1.2 | 9.7 ± 1.1 | 9.4 ± 1.0 | 9.3 ± 1.4 | 10.2 ± 1.7<br>p = 0.037 | 11.2 ± 1.5<br>p = 0.179 | 10.9 ± 1.6<br>p = 0.008 | 10.8 ± 2.1<br>p = 0.050 |
| Slow release (n = 12) | 9.1 ± 0.8 | 9.1 ± 0.8 | 9.7 ± 0.9 | 9.3 ± 1.1 | 10.2 ± 1.1 | 10.6 ± 1.2 | 11.4 ± 2.6 | 11.7 ± 2.6 |

Data do not include 4 patients who never started treatment. p values reflect comparisons with group A.

group of patients receiving other oral iron medications (group B), an increase in mean hemoglobin levels was significantly lower (p = 0.02) at all time points, plateauing at 3 months with a mean hemoglobin level of 11.1 ± 1.7 g/dl. Because of the heterogeneity of oral iron medications in group B, we have reanalyzed the data according to 2 subcategories: standard oral medications (27 patients) and oral medications with potential limitations in absorbability (12 patients) such as slow-release formulations of ferrous sulfate (Slow-Fe and Ferrograd, 9 patients) and ferric polymaltose (3 patients). As shown in the last 2 rows of table 2, the significant difference in response between groups A and B was still maintained when analysis was confined to the 27 patients receiving standard iron medications. Conversely, the hemoglobin response within the 2 subgroups of group B was indistinguishable.

Analysis of response rates (table 3) indicates that in group A, treated with ferrous glycine sulfate, 33 of 39 patients had a favorable response to oral iron treatment. There were 6 failures: 4 patients never started ferrous glycine sulfate and 2 of them elected to receive intravenous iron treatment. One additional noncompliant patient discontinued treatment early on, and the last one had gross GI bleeding managed by intravenous iron and was subsequently cured by resection of a newly discovered colon cancer. On the other hand, 4 of 5 patients previously managed by long-term intravenous iron became independent of parenteral iron treatment after switching to ferrous glycine sulfate.

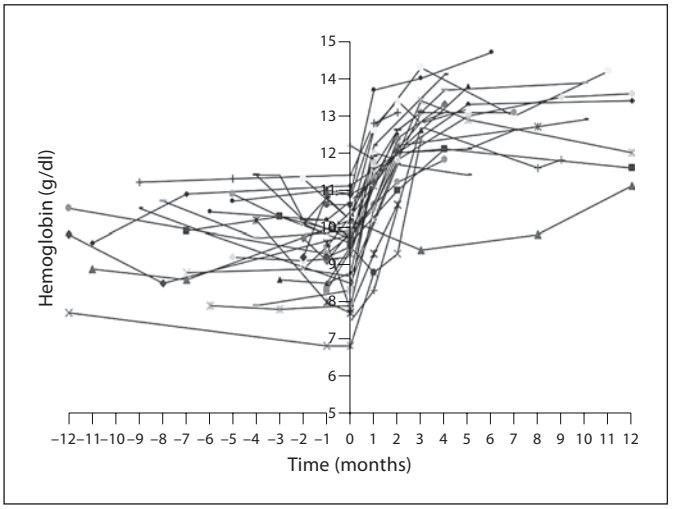


**Fig. 1.** Hemoglobin levels before and after referral in patients receiving duodenal release ferrous glycine sulfate (group A). Time 0 indicates the start of treatment.

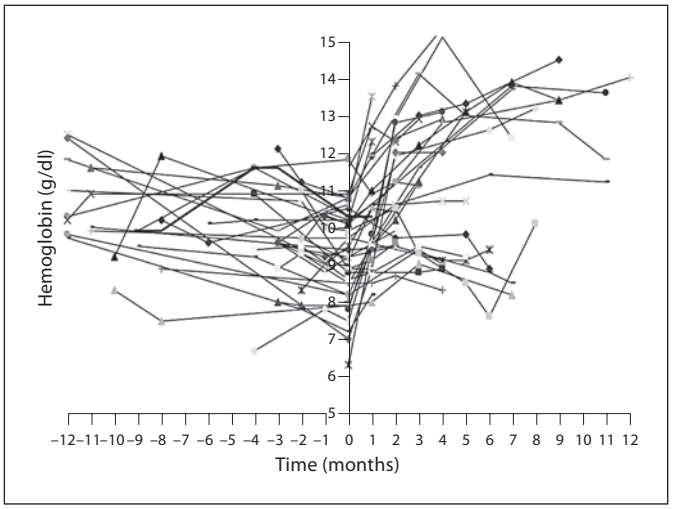


**Fig. 2.** Hemoglobin levels before and after referral in patients receiving other oral iron medications (group B). Time 0 indicates the start of treatment.

By comparison, among the 39 patients treated by other oral iron preparations (group B), only 18 had a favorable response (18 of 39 vs. 33 of 39; p = 0.009) and 21 patients (54%) failed to respond. Failure rates in the 2 group B subgroups were 14 of 27 for patients on standard oral iron medications (52%) and 7 of 12 for patients on slow release and ferric polymaltose medications (58%). The most common cause of treatment failure in group B was refractoriness to oral iron despite apparently good compliance (16 patients). Other, less common causes of treatment failure were intolerance to oral iron [3], poor compliance in 1 and gross GI bleeding caused by a dysplastic duodenal polyp in another patient. Because of the high rate of treatment failures, 14 patients were referred for intravenous iron treatment compared with only 3 in the ferrous glycine sulfate group (14 of 39 vs. 3 of 39; $p < 0.0001$). Of the remaining 7 treatment failures, 1 patient responded favorably to subsequent *H. pylori* eradication treatment, 1 was cured by resection of a bleeding polyp and 5 did not continue follow-up visits.

A closer look at figure 2 reveals that assessing responses by mean hemoglobin values may obscure the fact that some patients in group B had a satisfactory response to treatment whereas others failed to respond altogether. Indeed, if the total group of 39 group B patients is separated into responders (18 subjects) and nonresponders (21 subjects), the 18 responders achieved hemoglobin levels indistinguishable from group A (12.0 ± 1.1 and 12.8 ± 1.4 g/dl at 2 and 4 months, respectively). Conversely, the 21 nonresponders represent absolute failures with no increase in mean hemoglobin levels at all (10.0 ± 0.7 and 9.2 ± 0.9 at 2 and 4 months).

**Table 3.** Response to oral iron by treatment group

| | Group A (ferrous glycine sulfate) | Group B (other oral preparations) |
|---|---|---|
| Total patients | 39 | 39 |
| Responsive[a] | 33 | 18 |
| Failure | 6 | 21 |
| Intolerance | 0 | 3 |
| Gross bleeding | 1 | 1 |
| Poor compliance | 1 | 1 |
| Never started medication | 4 | 0 |
| Refractory despite good compliance | 0 | 16 |
| Referred for intravenous ferric sucrose (Venofer) | 3[b] | 14 |

[a] Responsive defined as increase in hemoglobin >2 g/dl or hemoglobin exceeding 12 g/dl.

[b] Because of patient's choice (n = 2), persistent gross GI bleeding (n = 1).

A possible confounding factor in the evaluation of response to treatment was the management of *H. pylori* infection. Of the 39 patients in group A receiving ferrous glycine sulfate, 21 were *H. pylori* positive and 7 received triple therapy for *H. pylori* eradication. All 7 had a favor-

able response to oral ferrous glycine sulfate treatment prior to *H. pylori* eradication, and therefore, this treatment did not have a measurable effect on response to iron therapy. By comparison, among the 39 patients in group B treated by other oral iron preparations, 21 were *H. pylori* positive and 11 received eradication treatment. Of the 11 patients receiving triple therapy, 6 had a favorable response to oral iron prior to *H. pylori* eradication, 2 did not improve despite *H. pylori* eradication, 1 patient failed eradication, and 2 were inevaluable because of premature implementation of intravenous iron in 1 patient and failure of follow-up in the other. Thus, *H. pylori* eradication did not result in a measurable modification of early response to iron therapy in either 1 of the 2 treatment groups.

## Discussion

The rules of iron treatment are well established. Following diagnostic workup to determine the cause of iron deficiency, treatment is implemented to correct iron deficiency and to prevent relapse. In the majority of cases, oral iron treatment should be satisfactory and parenteral treatment is reserved for specific indications [1, 2]. Ferrous sulfate is an inexpensive and effective form of oral iron, and despite a large variety of alternative compounds available for use, there is little evidence for claims of superiority. Ferrous iron is 3–7 times better absorbed than ferric iron at doses ranging from 30 to 200 mg without significant difference between the absorption of ferrous sulfate, fumarate, glycine sulfate or gluconate [3]. Absorption from a 100-mg dose of ferrous sulfate is about 15–20% at the beginning of treatment and drops to 5–10% after 1 month [26]. No difference in side effects of iron from simple ferrous sulfate tablets or slow release preparations such as Slow-Fe or Ferrograd has been shown in well-controlled studies [27]. Iron absorption takes place in the duodenum and upper jejunum and is enhanced by acid environment and ascorbate.

Despite these well-defined principles of iron therapy, treatment failures remain a significant problem. In a proportion of cases, this may be explained by poor compliance or impaired iron absorption [2]. In addition to celiac disease [6–9], autoimmune gastritis and *H. pylori* infection are increasingly recognized as important causes of unexplained IDA [10–19] and a failure to respond to oral iron treatment. However, the choice of oral iron medications may also play a significant role in determining the outcome of therapy.

The 78 IDA patients described in the present report are representative of the total number of 261 consecutive IDA patients studied at our clinic since 1 September 2001, as reported earlier [16, 19]. The vast majority of these patients were females of reproductive age and many of them had autoimmune and *H. pylori* gastritis with or without the simultaneous presence of menorrhagia. We and others have previously shown that the failure to respond to oral iron therapy is a common problem in this population of IDA patients [11, 15, 16, 19]. Both autoimmune and *H. pylori* gastritis interfere with the normal secretion of hydrochloric acid and ascorbate by gastric parietal cells [20, 21]. Since gastric acidity and ascorbate play a critical role in the solubilization and reduction of iron for subsequent duodenal and upper jejunal absorption, and since without the protection of normal gastric secretions iron is liable to be precipitated as insoluble ferric hydroxide [1], the achlorhydria associated with autoimmune and *H. pylori* gastritis may explain not only the underlying conditions aggravating IDA but also the poor response to oral iron treatment [20–23].

Ferrous glycine sulfate has been in use for over 40 years as an oral iron medication. Early studies have shown that its relative effectiveness equals that of ferrous sulfate [3, 5, 28]. An important feature of ferrous glycine sulfate as currently marketed is its formulation promoting duodenal absorption (duodenal formulation of ferrous glycine sulfate). Its capsule shell dissolves in the stomach, releasing hundreds of micropellets. These micropellets do not dissolve at the acid gastric environment but, owing to their high surface area and solubility at higher pH, rapidly discharge their content into the duodenum [4, 24]. These features make it independent of normal gastric acidity. Detailed clinical studies have shown that the duodenal formulation of ferrous glycine sulfate has a bioavailability equaling 95% of aqueous ferrous ascorbate in iron-deficient subjects, a mean daily absorption of 11 mg from a single dose of 100 mg iron, and the ratio of its cost per amount of iron absorbed is very favorable [4]. It was shown to be effective in preventing anemia in blood donors [29], and its efficacy in the treatment of anemia in inflammatory bowel disease was equal to that of intravenous iron sucrose [30]. At present, the duodenal formulation of ferrous glycine sulfate is not registered for general use in Israel, but is available by limited permit through application to the District Health Authorities.

Based on previous evidence indicating abnormal gastric acid secretion in autoimmune and *H. pylori* gastritis [20–22] interfering with iron absorption, we anticipated that an iron formulation offering optimal duodenal ab-

sorption independent of gastric acidity may result in improved therapeutic response. These expectations were fully confirmed by results of the present study. The 2 experimental groups of 39 subjects were near identical in age, gender and underlying clinical conditions with a very high proportion of autoimmune and *H. pylori* gastritis. They were very similar in demographic background and treated by the same medical team. Nevertheless, the results of treatment were markedly different. All but 6 of the patients prescribed ferrous glycine sulfate (group A) had a satisfactory response, with an increase in mean hemoglobin from 9.5 to 12.8 g/dl within 3 months, a response similar to that observed in a recent study by Nielsen et al. [31]. Because this was an intent-to-treat analysis, we insisted on including among the 6 failures 4 who never took the prescribed ferrous glycine sulfate. By contrast, in the control group (group B), 21 of 39 patients failed to show a satisfactory response to oral treatment, and consequently, 14 were referred for intravenous iron treatment. Only 1 patient on ferrous glycine sulfate was referred for intravenous iron treatment for medical indications, i.e. massive bleeding from colon cancer. Two other patients elected to receive intravenous iron by their own decision. Remarkably, of 5 patients in group A managed by intravenous iron prior to referral, 4 became independent of parenteral iron after starting on the duodenal formulation of ferrous glycine sulfate.

*H. pylori* eradication has a beneficial effect on response to oral iron and could have been a compounding factor in the evaluation of response to therapy. However, as described in the Results, in the present study, this was not the case, as in all patients, response to oral iron was established prior to *H. pylori* eradication. Even in responsive patients, *H. pylori* eradication is still justified because of its beneficial long-term effects including prevention of relapse [19].

The present study has several limitations. First, although prospective, it was not a randomized clinical trial, and therefore, it may only be regarded as an observational study. Second, some of the medications employed in the control group were suboptimal in composition (ferric polymaltose) or formulation (slow-release preparations). Third, the argument that the favorable treatment outcome with ferrous glycine sulfate is explained by its specific duodenal formulation is based on indirect evidence and remains to be proven. It could be claimed that using a simple, highly bioavailable form of iron such as ferrous sulfate may have achieved the same favorable results. However, this is unlikely, because when analysis was confined to the 27 control patients receiving iron medications with satisfactory bioavailability, the differences between groups A and B remained unchanged. Despite the doubts related to mechanisms of efficacy, the favorable results of oral treatment employing ferrous glycine sulfate remain unchallenged. The practical implications of these findings are that a satisfactory response to oral treatment with ferrous glycine sulfate can be elicited in the vast majority of patients with IDA, obviating the need for expensive, inconvenient and occasionally risky intravenous iron administration.


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