Bioavailability of Oral Iron Drugs as Judged by a ^{59}Fe-Whole-body Counting Technique in Patients with Iron Deficiency Anaemia

Therapeutic efficacy of iron(II)-glycine sulfate

Peter Nielsen, Rosemarie Kongi, Peter Buggisch, and Roland Fischer

Institut für Biochemie und Molekularbiologie II: Molekulare Zellbiologie, Zentrum für Experimentelle Medizin[a] und Medizinische Klinik und Poliklinik I, Zentrum für Innere Medizin[b], Universitätsklinikum Hamburg-Eppendorf (Germany)

Summary

The bioavailability of the oral iron compound iron(II)-glycine sulfate (ferro sanol duodenal®, FSD, 1 × 100 mg Fe/d) was studied in 56 patients with iron deficiency anaemia using a ^{59}Fe-labelling technique and ^{59}Fe-whole-body counting. This technique measures the individual iron loss and allows in patients with substantial blood loss under iron medication a reliable information on the bioavailability of the drug. In all patients, the increased loss of iron (mean 5.8 ± 4.4 mg/d) was clearly compensated by the iron utilisation (mean: 11.1 ± 5.6 mg/d) from a daily dosage of 100 mg iron from FSD. A significant increase in the haemoglobin concentration was observed within the monitored treatment period of 6–10 weeks (mean Hb increase from 10.7 ± 1.7 to 12.1 ± 1.8 g/dl). FSD has therefore documented a bioavailability of at least 11 % from a single daily dose of 100 mg Fe and was effective in the treatment of the anaemia in almost all patients under study.

Key words

- **^{59}Fe-whole-body counting**
- **Iron bioavailability**
- **Iron(II)-glycine sulfate complex**
- **Oral iron therapy, haemoglobin regeneration, iron utilisation**

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Zusammenfassung

Untersuchung zur Bioverfügbarkeit von oralen Eisenpräparaten mit einem ^{59}Fe-Ganzkörperdetektor an Patienten mit Eisenmangelanämie / Therapeutische Wirksamkeit von Eisen(II)-glycin-sulfat

Die Bioverfügbarkeit von Eisen(II)-glycin-sulfat-Komplex (ferro sanol duodenal®, FSD, 1 × 100 mg Fe/Tag) wurde an 56 Patienten untersucht. Die Patienten mit unklarer Eisenmangelanämie wurden routinemäßig mit einer ^{59}Fe-Markierungstechnik untersucht, um jeweils die Ursache der unklaren Eisenmangelanämie aufzuklären. Bei dieser Untersuchungsmethode zur genauen Blutverlustquantifizierung wird dem Patienten eine kleine Menge (^{59}Fe)Eisenaskorbat (0,56 mg Fe) oral verabfolgt. Die intervallmäßige Messung der ^{59}Fe-Ganzkörperre-

tention mit dem Hamburger Ganzkörperzähler erlaubt dann eine quantitative Aussage über evtl. bestehende Blut- und damit Eisenverluste. Unter der angesetzten oralen Therapie mit Eisen(II)-glycin-sulfat-Komplex (FSD) konnte so die Menge des individuell aus der Therapie utilisierten Eisens genau bestimmt werden. Bei allen Patienten konnte der jeweils erhöhte Eisenverlust (im Mittel 5,8 ± 4,4 mg/d) durch die Eisenutilisation von 11,1 ± 5,6 mg aus der täglichen 100 mg Eisen(II)-Dosis kompensiert werden, und es kam im Beobachtungszeitraum von 6–10 Wochen zu einem signifikanten Hämoglobinanstieg von 10,7 ± 1,7 g/dl auf 12,1 ± 1,8 g/dl. FSD in der Dosierung 1 × 100 mg Fe/d dokumentiert damit eine Bioverfügbarkeit von im Mittel 11 % und zeigt damit auch seine therapeutische Wirksamkeit zur Behandlung der Anämie bei allen untersuchten Patienten.

1. Introduction

In Western countries with a typical high-energy nutrition containing sufficient amounts of iron (6 mg Fe/1000 kcal), iron deficiency anaemia (ID) should be regarded as a serious clinical symptom which needs diagnostic evaluation of the underlying disease. Because the daily iron loss in adults is in the range of 1–2 mg/d, a moderate to severe ID anaemia resulting in a deficit of 1000 to 2500 mg iron is in most cases the consequence of abnormal blood loss (hypermenorrhoea or gastrointestinal bleeding) [1]. Therefore, in all these patients, a complete gastrointestinal evaluation including coloscopy and gastroduodenoscopy is obligatory. In many cases, however, the underlying origin of the iron deficiency remains unclear due to an unrecognized hypermenorrhoea, a gastrointestinal trickle bleeding, or malabsorption syndromes. Especially in these complicated cases, we are using a sensitive ^{59}Fe-labelling technique to conclusively exclude or identify quantitative evidence of an ongoing blood loss (> 2–3 ml/d) [2]. Other non-invasive methods (blood pool scintigraphy, angiography) are much less sensitive and are clearly positive only at bleeding rates of about 100 ml/d.

Parallel to the diagnostic clarification, an adequate treatment of the severe iron deficiency should be emphasised. The efficacy of pharmaceutical iron preparations has been studied in the past in some detail and this, indeed, is a relevant problem, because small galenic changes can lead to significant differences in intestinal absorption [3–8]. Only soluble iron can be absorbed and the limited solubility under the pH-situation in the intestinal tract (> 6.4) is a problem mainly for ferric iron, which easily forms the poorly soluble ferric hydroxid. In addition, only ferrous iron is absorbed directly in substantial amounts in duodenal enterocytes by the DMT1-transporter in the brush border membrane [9]. Small amounts of ferric iron from food (or from ferric iron drugs?) can be reduced by a ferrireductase (dcytB) prior to absorption via DMT1. The term "bioavailability" is frequently used in this context to describe the rate and extent to which a drug reaches its "site of action". In practice with a given drug, post-absorptive plasma time curves are measured and the bioavailability is derived from the maximal increase or the area under the curve (AUC). However, for iron as a trace element the pharmacological definition of bioavailability is less adequate than in the case of xenobiotics [10], because the absorption, distribution and utilisation of iron is regulated in a complex mechanism which is still not fully understood today, is strongly dependent from the state of iron repletion, or is influenced by different diseases in patients. Therefore, all classical methods for measuring iron bioavailability have limitations and shortcomings. In the present study, we were able to use a special ^{59}Fe-whole-body counting technique which gives the information on how much iron from a drug is used for the haemoglobin production in the anaemic patients. This approach follows the more nutritional definition of iron "bioavailability", namely the rate and extent of the metabolic utilisation of iron in humans. In a similar approach in the field of magnesium therapy, Lücker (1991) has used the term "therapeutical availability" in order to distinguish this model from the classical concepts of bioavailability [11].

In agreement with the described limitations for ferric iron absorption, all ferric iron preparations tested so far in humans showed only a very limited bioavailability of 0.8–1.6 % from a 100 mg test dose [3–5, 7]. Among different iron preparations tested in the past using ^{59}Fe-labelled compounds, the rate of iron release from the galenic formulation and the solubility at the neutral pH in the duodenum seem to be the factors that determine the bioavailability of a given preparation [4, 5, 8]. It should be noted that according to the actual administrative regulation in Germany (BfArM), all iron preparations have to document their sufficient biological availability in appropriate studies on the classical bioavailability or on bioequivalence in comparison to a reference compound [11]. Concerning the many influences from the patient side and also methodological difficulties, iron belongs to a group of problematic substances, and not all iron preparations on the pharmaceutical market have so far presented a conclusive data base on their respective bioavailability or bioequivalence. In the present study, we describe an unequivocal method, in which the bioavailability and the therapeutic efficacy of the oral drug under study is investigated in a very reliable manner under realistic conditions (4–6 week treatment period in patients with iron deficiency anaemia).

2. Patients and methods

2.1. Patients

Patients with unclear chronic haemorrhagic or post-haemorrhagic iron deficiency are routinely admitted to our day hospital unit to be analysed for blood loss quantification using a ^{59}Fe-labelling technique [2]. Any kind of iron medication was restricted within the last two weeks before the investigation. All patients gave their free and informed consent in written form to be diagnostically investigated with this routine radionuclear technique. The additional radiation burden for the patients from this technique (10 µmol = 0.56 mg Fe, 70–150 kBq ^{59}Fe administered, 50-y equivalent dose = 225–825 µSv) is relatively low, and is well below the natural radiation burden of 2400 µSv/year in Germany. This would theoretically allow investigations also in risk groups according to the accepted rules in radioprotection. Thus, in single cases with a clear diagnostic indication (suspected iron malabsorption, suspected blood loss), this technique has been used also in small children. In pregnant women, however, the acute indication was in clinical practice so far not obvious.

2.2. Measuring of ^{59}Fe-whole-body retention

The ^{59}Fe-whole-body retention was measured 14 days after oral administration of 10 µmol ^{59}Fe (70–150 kBq) in a 4 π geometry whole-body counter for humans with liquid organic scintillator in the energy range of 980–3000 keV [12]. Fourteen days after oral administration, the activity, measured immediately after administration of ^{59}Fe, was taken as the 100 % reference value. The ^{59}Fe erythrocyte incorporation was calculated from the measured ^{59}Fe-whole-body radioactivity and the blood volume. With a detection limit of 2–3 ml blood loss per day, the total blood loss was derived from the measured ^{59}Fe-whole-body elimination rate, the measured ^{59}Fe blood activity, and the calculated blood volume. Blood volumes (BV) were calculated from the body surface area with body weight (W) and height (H) using for males

$$BV = 0.0236 \cdot H^{0.725} \cdot W^{0.425} - 1.229,$$

for females

$$BV = 0.0248 \cdot H^{0.725} \cdot W^{0.425} - 1.954$$ [13].

The daily iron loss (IL) was calculated from the daily blood loss (BL)

$$IL = BL \cdot Hb \cdot Fe_{Hb}$$

with Hb = actual haemoglobin concentration in g/dl and Fe_{Hb} = 3.47 mg Fe/g Hb = mean iron content of Hb. The daily iron utilisation (ΔIU) was calculated from IL corrected for the haemoglobin change ΔHb in a treatment interval Δt of 6–10 weeks by

$$\Delta IU = IL + \Delta Hb/\Delta t \cdot Fe_{Hb} \cdot f \cdot BV$$

(f = correction factor venous blood/total blood = 0.913).

2.3. Iron medication

One to two weeks after the ^{59}Fe absorption test, all patients received a single dose of 1 × 100 mg Fe/d in form of iron(II)-glycine sulfate complex (1 × 1/d ferro sanol duodenal®, Schwarz Pharma, Monheim, Germany) (FSD). Patients were advised to take the drug in the morning, 30 min before breakfast together with a glass of water. Iron typical side-effects (constipation, diarrhoea, nausea or epigastric pain) in mild form were reported from 5 of the 56 patients. In no case, the iron medication had to be stopped because of side-effects. The compliance was tested by interviewing the patients on each of the investigation dates.

3. Results

In the time period between 1998 and 2004 about 200 patients were referred to our unit for evaluating the origin of their unclear iron deficiency anaemia. A scheme of our routine diagnostic procedure is outlined in Fig. 1. Most of these patients had a complete diagnostic workup in the past including coloscopy and gastroduodenoscopy. In all these patients, the iron metabolism was studied in detail using the 10 µmol ^{59}Fe-ascorbate whole-body elimination test [2]. This technique can measure the individual blood loss in ml/day for each patient during the investigation period of 6–10 weeks. Under treatment with a given oral iron supplement, the iron utilisation rate (mg/d) from the respective drug was calculated from actual haemoglobin concentration and from the daily iron loss.

56 patients with iron deficiency were treated with the iron preparation iron(II)-glycine sulfate (Table 1) and the iron utilisation was followed for the next 6–10 weeks. The diagnostic procedure revealed a hypermenorrhoea with ^{59}Fe elimination rates that typically increased stepwise only during menstruation periods (Fig. 2, top) in 18 patients or a continuously increased iron loss due to gastrointestinal bleeding in 38 patients (Table 1, Fig. 2, bottom). The increased daily iron loss of 4.8 ± 2.7 mg/d in patients with hypermenorrhoea was compensated by the iron utilisation of 9.6 ± 4.2 mg/d from the drug and resulted in a significant haemoglobin increase from 11.3 g/dl to 12.6 mg/dl after 6–10 weeks of treatment. In patients with ongoing gastrointestinal bleeding, the loss of iron was even higher but was also

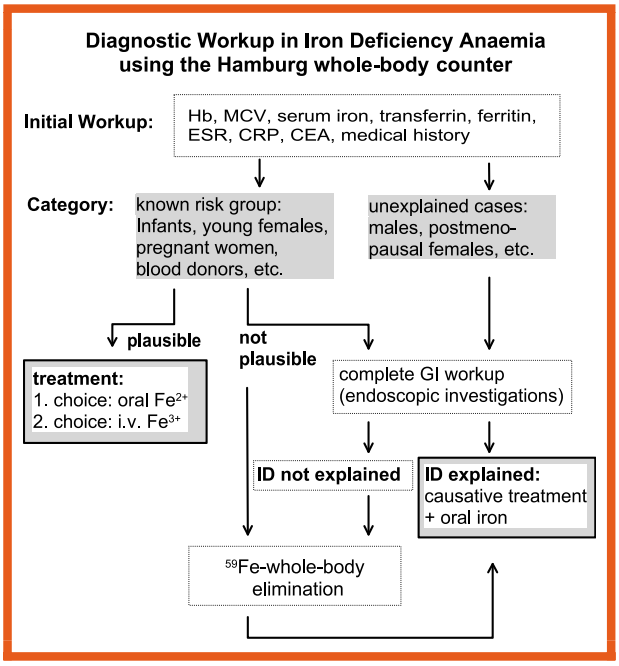

Fig. 1: Diagnostic strategies in patients with unclear iron deficiency anaemia measuring also the ^{59}Fe whole-body retention. MCV, mean corpuscular volume; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CEA, carcino-embryonic antigen.

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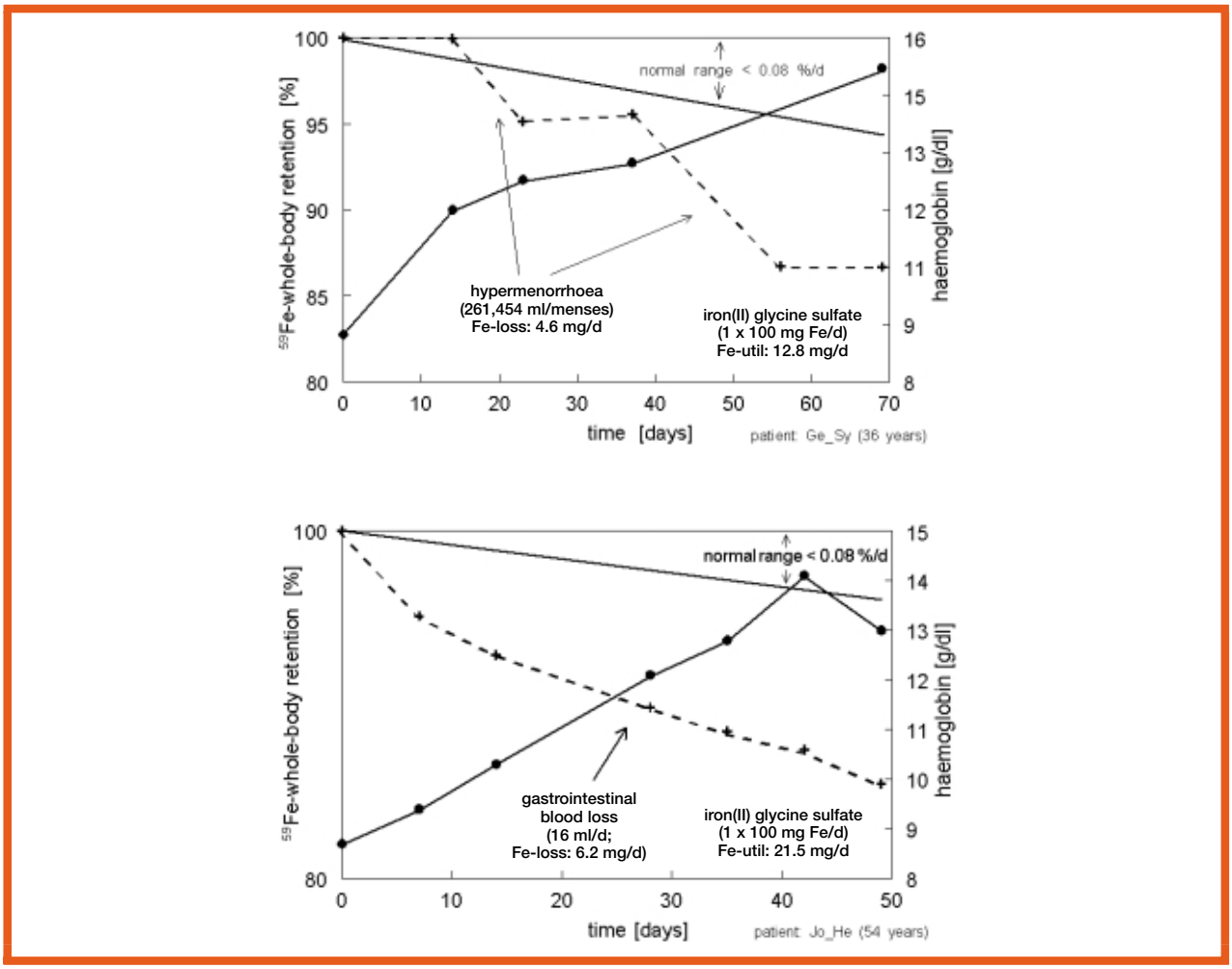

Fig. 2: ^{59}Fe whole-body elimination rate (crosses) and haemoglobin concentration (bold circles) in two typical patients with severe iron deficiency anaemia due to hypermenorrhoea (top) or gastrointestinal blood loss (bottom). The iron utilisation from the iron supplement was calculated from the respective Hb-increase corrected for the individual blood loss (for details see text).

compensated by a higher iron utilisation rate. This regulation of iron utilisation is also seen by comparing individual iron utilisation rates in groups with different starting haemoglobin concentration (Table 2). Patients with very severe anaemia utilised more iron from the drug than patients with slightly decreased or normal haemoglobin.

In some patients, only a limited haemoglobin increase (from 7.3 g/dl to 7.8 g/dl after 5 weeks on 1 × 100 mg/d Fe) (Fig. 2, bottom) was observed. However, in this case the iron drug was therapeutically effective and could compensate for the substantial blood loss (gastrointestinal blood loss, 46 ml/d, 12.7 mg Fe/d).

Table 1: Iron utilsation and haemoglobin increase from 100 mg/d iron(II)-glycine sulfate in patients with iron deficiency anaemia caused by hypermenorrhoea or gastrointestinal blood loss.

Diagnosis	n	Age	Blood loss	Fe loss (mg/d)	Hb1 Hb2 (g/dl)	Fe util (mg/d)
Hypermenorrhoea	18	41.4 ± 11.3	331 ± 229[a)]	4.8 ± 2.7	11.3 ± 1.1 12.6 ± 1.4 ($p < 0.0001$)	9.6 ± 4.2
GI blood loss (male + female)	38	46.8 ± 19.8	17.6 ± 15.2[b)]	6.3 ± 4.9	10.3 ± 1.9 11.8 ± 2.0 ($p < 0.0001$)	12.0 ± 6.0
All	56	45.1 ± 17.5	118 ± 199[b)]	5.8 ± 4.3	10.7 ± 1.7 12.1 ± 1.8 $p < 0.0001$)	11.1 ± 5.6

Hb1, haemoglobin concentration before treatment. Hb2, haemoglobin concentration after 6-10 weeks of treatment. Fe util, iron utilisation. Endpoint of a linear Hb-increase, see Fig. 2.
[a)] ml/menses. [b)] ml/d.

Table 2: Iron utilisation from 100 mg/day iron(II)-glycine sulfate in relation to the severity of iron deficiency anaemia.

Start haemoglobin	Iron loss (mg/d)	Iron utilisation (mg/d)
Hb 8–10 g/dl (n = 20)	6.8 ± 4.8	13 ± 6.4
Hb 10–12 g/dl (n = 21)	6.1 ± 5.0	11.2 ± 6.0
Hb > 12 g/dl (n = 15)	6.4 ± 2.3	8.8 ± 4.2

4. Discussion

The bioavailability of oral iron drugs has been studied in the past in some detail, especially preparations on the German pharmaceutical market [3–8]. Due to the limited solubility and absorbability of iron in the duodenum and upper jejunum, the complex chemistry of iron at neutral pH and the strong influence of the galenic composition of the respective drug, the discussion concerning an optimal iron drug was often quite controversial.

Different methods have been used to study the bioavailability of iron drugs, but most methods suffer from serious limitations. No enforced national or international standards have been made available so far which will ensure bioavailability of iron drugs. The reference method was the administration of ^{59}Fe-labelled compounds and the use of a whole-body counter [3, 4]. However, the radioactive burden, although being very low for such a non-diagnostic purpose, became more and more an ethical problem. Moreover, the preparation of a radiolabelled product with galenic composition identical with the commercial product is complicated and expensive. The simpler method of measuring the post-absorptive serum iron increase in patients after administration of a 100–200 mg test dose is not very sensitive and has a limited dynamic range [14]. This method can differentiate between preparations with very low (ferric iron preparations, 0.8–1.6 % from a 100 mg Fe/single dose) and normal or high bioavailability (some ferrous iron preparations, 5–18 %), whereas smaller differences, e.g. between different ferrous iron preparations, can hardly be investigated using this method [3]. A third method is to follow the haemoglobin regeneration rate in patients with iron deficiency anaemia under treatment with a given iron drug. From the blood volume and the actual haemoglobin concentration, the iron utilisation can be calculated. This technique is the best proof for an iron preparation because a treatment interval and not only a single dose is tested in a realistic therapeutic group of patients. However, patients with severe iron deficiency anaemia are strongly suspected to suffer from a significant blood loss, which, if not corrected for, can strongly influence the iron utilisation rate from an iron preparation. This is clearly demonstrated in this series of anaemic patients, in which only 8 of the 56 showed no significant blood loss during the investigation period. In this study we could overcome this problem by correcting for the individual iron loss in patients with iron deficiency anaemia using the ^{59}Fe-whole-body counting technique. Using this specific diagnostic technique we are able to monitor the therapeutic availability, i.e. bioavailability of any given pharmaceutical iron preparation, with high precision. Without this technique available, the therapeutic availability of iron from the drug would have been substantially underestimated in 48/56 patients. In other words, a given iron drug can have a high bioavailability and is able to compensate for a substantial blood loss, but is apparently not therapeutically effective as far as only the haemoglobin increase is taken as endpoint.

The pharmaceutical market in Germany actually contains more than 30 single iron preparations, not mentioning combinations with other trace elements or vitamins. Most of these compounds are quite new with very limited data on their reported bioavailability. From our experience, we suspect that some registered iron preparations have a very limited iron bioavailability. At the moment, there is a great uncertainty among physicians and patients in Germany regarding which kind of iron medication (oral/parenteral) is effective, safe, and still prescribable. The market for parenteral iron medication is increasing at the moment, although many arguments make quite sure that these preparations should be regarded as a second-line treatment and used only in special patients (e.g. patients with renal anaemia under erythropoetin treatment).

In this retrospective study, we report results from the iron compound, iron(II)-glycine sulfate, in a larger group of patients with iron deficiency anaemia. FSD has shown a bioavailability of 11 % from a 100 mg Fe daily dose. This therapeutical availability of iron is high enough to compensate the blood loss and improve the anaemia in most cases. In non-bleeding patients, an haemoglobin increase of about 1 g/dl/week can be monitored using a dose of 100 mg/d. In strongly bleeding patients the daily dose could be increased to 2 × 100 or even 3 × 100 mg/d, however, this would also induce more adverse effect which could negatively influences the compliance in the patients. We advice to physicians treating patients with iron deficiency anaemia only to use oral iron compound which have clearly demonstrated a similar good bioavailability (in mean > 10 %) as with iron(II)-glycine sulfate shown in the present study in patients under realistic treatment conditions. Otherwise, it is not clear, if a therapeutic drop-out is caused by the drug itself. This advise is also favoured under the actual financial pressure for all health systems, in which ineffective oral drugs would produce unnecessary costs not only for the medication but also for additional diagnostic investigations or therapeutic alternatives, such as parenteral iron or blood transfusions.

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5. Literature

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Correspondence:
PD Dr.med.Dr.rer.nat Peter Nielsen,
Institut für Biochemie und Molekularbiologie II:
Molekulare Zellbiologie,
Zentrum für Experimentelle Medizin,
Universitätsklinikum Hamburg-Eppendorf,
Martinistr. 52, Haus N41,
20246 Hamburg (Germany)
E-mail: nielsen@uke.uni-hamburg.de