Safety and efficacy of iron (III)–hydroxide polymaltose complex: A review of over 25 years experience

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Safety and Efficacy of Iron(III)-hydroxide Polymaltose Complex

A review of over 25 years experience

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Abstract

The following review of iron(III)-hydroxide polymaltose complex (IPC, Maltofer®) shows that iron is significantly bioavailable after oral administration, especially in iron-deficient subjects. Numerous clinical trials in men, women, children and infants have shown that IPC is effective in treating iron deficiency anaemia (IDA). Due to its kinetic properties, IPC is best given with meals, and probably in an iron dose slightly higher than that of the classical iron salts. In terms of acceptance and patient compliance, IPC presents a clear advantage over ferrous salts. Many studies have shown a lower rate of treatment interruption with IPC than with ferrous salts. This is usually associated with a lower incidence of adverse events related to the upper gastro intestinal tract.

Zusammenfassung

Sicherheit und Wirksamkeit von Eisen(III)-hydroxid-Polymaltose-Komplex / Ein Rückblick auf über 25 Jahre Erfahrung

Die folgende Übersicht zum Eisen(III)-hydroxid-Polymaltose-Komplex (IPC, Maltofer®) zeigt, dass die Bioverfügbarkeit von Eisen nach oraler IPC-gabe signifikant ist, besonders bei Personen mit Eisenmangel. Zahlreiche klinische Studien mit Männern, Frauen, Kindern und Kleinkindern zeigten, dass IPC eine gute Wirksamkeit zur Behandlung von Eisenmangelanämie besitzt. Wegen seiner kinetischen Eigenschaften wird IPC am besten mit den Mahlzeiten und eventuell in einer etwas höheren Dosis als die klassischen Eisensalze eingenommen. Bezüglich Akzeptanz und Patienten-Compliance hat IPC einen klaren Vorteil gegenüber Eisen(II)-Salzen. Viele Studien mit IPC zeigten bei der Behandlung eine kleinere Unterbrechungsrate, was mit dem geringeren Auftreten von Nebenwirkungen im Magen-Darm-Trakt zu tun hat.

Key words

- **Antianemic drugs**
- **Iron deficiency anemia**
- **Iron therapy**
- **Iron(III)-hydroxide polymaltose complex, review**
- **Maltofer®**

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1. Introduction to iron deficiency

Iron has long been known to be essential for humans [1, 2]. Its therapeutic requirements in cases of insufficient supply, or excessive loss, have been well established, especially for children and women of child-bearing age. The average man and woman have 2100 and 1350 mg, respectively, of iron circulating in their blood. Apart from circulating red blood cells (RBCs) most iron occurs in the storage pool, i.e. in ferritin and haemosiderin, and just 200–400 mg of iron is found in myoglobin and in haem and non-haem enzymes.

The average daily diet generally contains 10–15 mg of iron, of which 10 % is absorbed [3]. Around 1 mg/day is lost through exfoliation of skin and mucosal cells. Menstrual blood loss in women plays a major role in iron metabolism, amounting to 0.7 mg iron/day on average. Usually, iron absorption and loss are balanced at 1 mg/day.

Iron deficiency anaemia (IDA) is estimated to affect more than 750 million people [4–6]. IDA may impair psychomotor development in infants and young children which may result in long-term defects in cognitive function. Agaoglu *et al.* showed that mean IQ score was significantly lower (by 12.9 points) in children aged 6–12 years with IDA [7]. Anaemia during pregnancy has been associated with an increased frequency of low birth weight, prematurity and perinatal mortality.

Three groups are at special risk of IDA: small children, especially in developing countries, where the prevalence of IDA may reach 63 %; young women at the beginning of the child-bearing age, for whom the prevalence of some degree of iron deficiency may be around 70 %, even in well-nourished populations; and pregnant women, for whom the iron requirement increases from 0.8 to 7.5 mg/day.

IDA responds promptly to oral iron therapy. A number of iron salt preparations are available. They are efficient, cheap and their side effect profile is well known, although often not accepted by patients. Iron salts can cause nausea, vomiting, abdominal cramps, constipation and diarrhoea [6, 8]. This often results in poor compliance with therapy. Although administration with food improves tolerability, it decreases iron bioavailability. Another important drawback is their potential toxicity in case of overdosage. In the USA, this results in a number of fatalities every year, usually in children [9].

The ideal oral iron therapy should have good therapeutic efficacy, no interaction with food or drugs, a wide safety margin with a minimal risk of accidental overdose; good gastrointestinal tolerance, and no other unwanted effects such as tooth staining or an unpleasant taste.

Ferrous salts, especially ferrous sulphate (FS), do not meet these criteria. FS is highly toxic, interacts with food and other medicines, and causes gastro intestinal side effects in up to 40 % of patients often resulting in poor compliance [8, 10, 11].

Most recently it also has been shown that FS leads to high levels of non-transferrin bound iron (NTBI), which has been associated with oxidative stress [13, 14].

Iron(III)-hydroxide polymaltose complex (IPC) was developed in order to provide an effective but well-tolerated oral iron treatment. The rationale for development was to produce a compound with good bioavailability across a wide range of conditions, with no troublesome interactions with food or other medications and with excellent tolerability and long-term safety.

2. Chemistry of IPC

The iron(III)-hydroxide polymaltose complex (IPC) Hw 6400 (Maltofer®) is a macromolecular complex in which polynuclear ferric oxyhydroxide is complexed with polysaccharide groups. Its molecular weight is 52300 Dalton [11]. It is highly water-soluble over a broad pH range (1–14) and, unlike simple ferric salts, does not precipitate in an alkaline environment [15]. Unlike other iron-polymaltose complexes, Hw 6400 is soluble in water at room temperature and gives no precipitation when hydrochloric acid is added [16]. It also does not react in vitro at pH 3–8 with chelating agents from food (e.g. phytic acid) or with drugs containing phenolic groups, e.g. tetracycline. IPC has a reduction potential of –332 mV; this ensures that it is not reduced in biological fluids and therefore will not provoke oxidative stress [14].

3. Toxicology

Compared with ferrous salts, IPC is non-toxic with LD50 values in mice and rats more than 10 times higher than those for ferrous sulphate. In long-term studies with dogs, IPC doses of up to 270 mg iron/kg/day for 52 weeks had no effect on any organ system.

4. Clinical information

4.1. Pharmacodynamics and pharmacokinetics

The pharmacokinetic profile of iron from IPC is quite different from that of ferrous salts. Both in rats and humans, only a very small increase in serum iron concentration, if any, is recorded in the first 6 h. In rats, serum iron concentrations then continuously increase, reaching a maximum after 24 h. Nevertheless after 2–3 weeks following application the incorporation of iron into the RBCs is not significantly different from that of iron salts [17].

Abbreviations

ID	iron deficiency
IDA	iron-deficiency anaemia
FH	Ferrum Hausmann tablets
GI	gastrointestinal
M	Maltofer
M-fol	Maltofer + folic acid
n/v	nausea and vomiting

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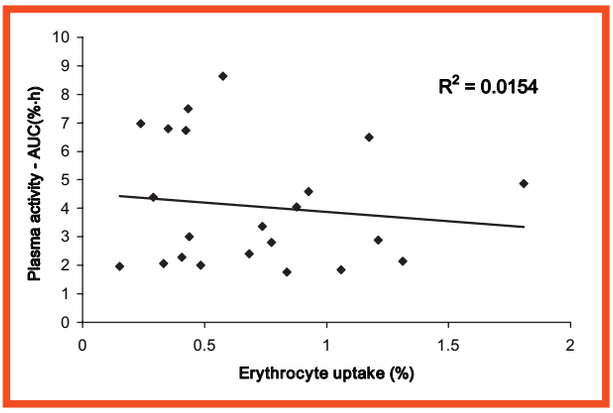

Fig. 1: Correlation between plasma ^{59}Fe activity and AUC values (plasma activity) following treatment with Maltofer and Amphojel (Potgieter *et al.* [18]).

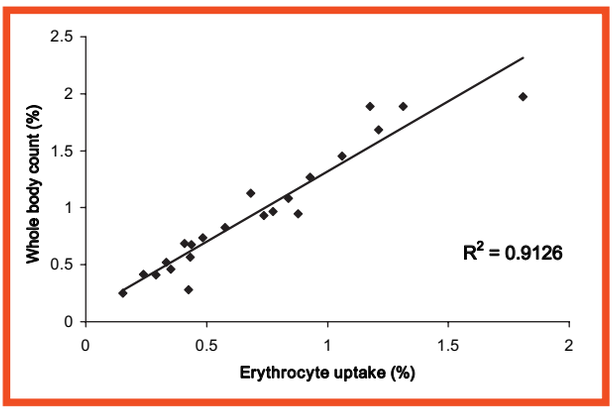

Fig. 2: Correlation of ^{59}Fe erythrocyte uptake and whole-body count following treatment with Maltofer and Amphojel (Potgieter *et al.* [18]).

In two studies in humans, Potgieter *et al.* have shown that there is no correlation between the serum iron AUC values (area under the curve values) and the utilisation ratio after application of radio-labelled original IPC (Fig. 1), but that there is a good correlation between RBC iron incorporation and whole-body counts (Fig. 2) [18, 19]. Therefore the suggestion that low AUC or C_{max} values predict low absorption ratios as proposed by Dietzfelbinger, Heinrich and Nielsen *et al.* does not apply to original IPC [20–22]. Furthermore, true bioavailability means the rate and extent to which an active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action [23]. In the case of iron this is the RBC and not the serum. Since the serum is not the site of action, the AUC and C_{max} simply represent a small ratio of the whole amount transferred to the site of action. Such ratios are not proportional to the AUC values but to the rate of transfer and/or the elimination rate to and from the serum (Geisser *et al.* [24]).

Jacobs *et al.* measured iron incorporation into haemoglobin from IPC and ferrous sulphate using a double isotope technique [25]. There was no difference in iron

Table 1: Iron incorporation into haemoglobin after 14 days treatment with either IPC or ferrous sulphate with or without food (adapted from Jacobs *et al.* 1979) [25].

Dose	IPC	%	$FeSO_4$	%	p-value
50 mg	14.5 ± 4.85	29.0	18.7 ± 3.85	37.4	>0.4
50 mg + food	9.0 ± 2.19	18.1	8.9 ± 2.33	17.7	>0.9

Values are mean ± SEM.

Table 2: Iron incorporation into haemoglobin after 14 days oral treatment with either IPC or an iron salt (adapted from Jacobs *et al.* 1984) [26].

Dose / form	Control (salt)	Iron incorporation into Hb (at 14 days)		
		% IPC	% salt	p-value
5 mg Fe liquid	$FeSO_4$	46.6 ± 17.1	47.8 ± 14.6	p > 0.20
50 mg Fe liquid	$FeSO_4$	27.1 ± 6.5	32.9 ± 13.4	p > 0.20
100 mg Fe solid	Fe fumarate	10.7 ± 4.7	10.3 ± 6.9	p > 0.20

Values are mean ± S.D.

incorporation between the preparations at a dose of 50 mg iron. Taking the dose with food significantly reduced iron bioavailability for $FeSO_4$, but not for IPC (Table 1).

In another study by Jacobs *et al.* the bioavailability of iron from IPC was compared with that from either ferrous sulphate or fumarate [26]. Participants were recruited from a venesection programme for idiopathic haemochromatosis or symptomatic erythrocytosis. IPC was labelled with ^{55}Fe, and the salts with ^{59}Fe. Incorporation of radioactive iron into haemoglobin was measured after 2 weeks by using a double isotope technique.

Participants received 5 mg iron in group 1, 50 mg in group 2 and 100 mg in group 3. In the first 2 groups, both compounds (with $FeSO_4$ as a reference) were administered as liquid formulations. Subjects in group 3 received either a chewable tablet of IPC or a reference solid preparation of iron fumarate.

As expected, increasing doses of iron were associated with decreased bioavailability, as measured by iron incorporation into haemoglobin (Table 2). However, within each dose group there was no statistically significant difference between IPC and the corresponding ferrous salt. Plasma ferritin levels were not reported, but the authors mention a negative correlation between iron bioavailability and plasma ferritin levels.

The higher iron bioavailability observed for IPC at low dose, compared to the previous study, may have been due to a higher degree of iron store depletion. If this is the case, it suggests that the difference in bioavailability between IPC and ferrous salts is probably less pronounced, and may in fact be absent in cases of iron deficiency.

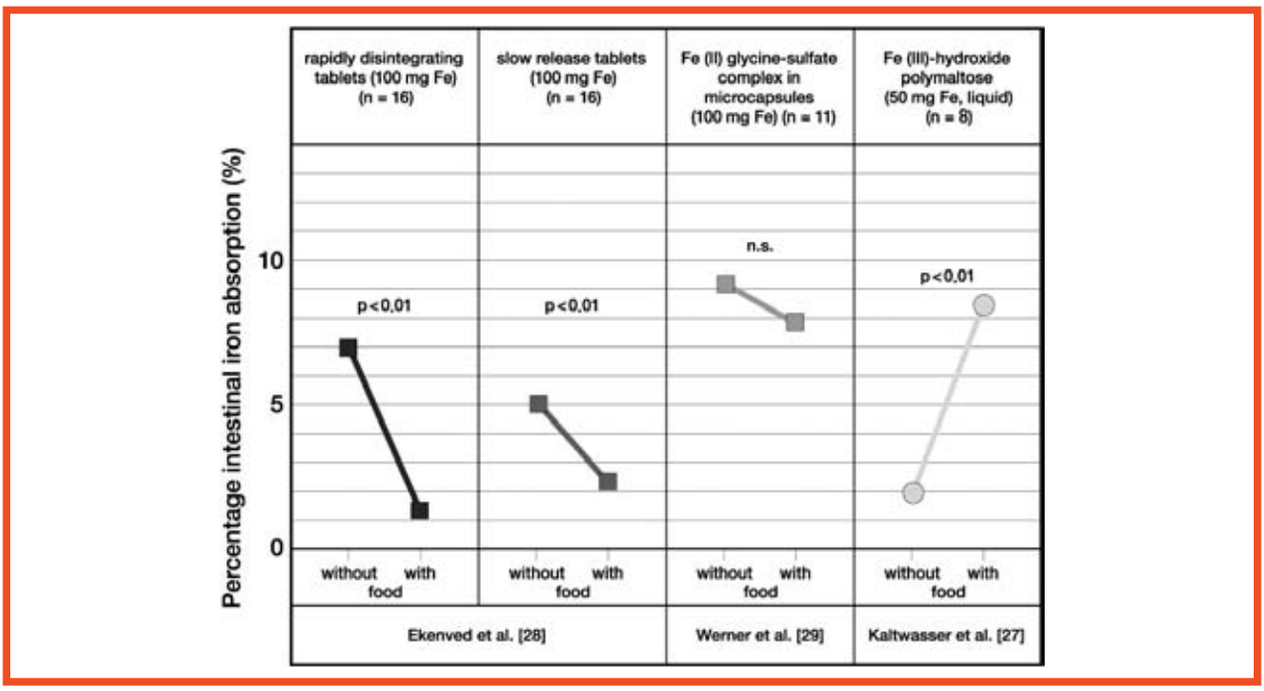

Fig. 3: Influence of a meal on absorption of different therapeutic iron preparations (Forth 1993 [30]).

Kaltwasser *et al.* investigated haemoglobin formation and iron utilization after administration of either IPC drops or a ferrous salt. Both treatments induced a haemoglobin increase that was significantly different from the control period. The iron utilization rates were 17 % for $FeSO_4$ and 12 % for IPC [27].

IPC appears to differ from other iron preparations in that iron absorption is increased rather than decreased by the presence of food, as shown in Fig. 3.

4.2. Drug-drug Interactions

Potgieter *et al.* compared the bioavailability of tetracycline with and without co-administration of IPC. They found no clinically significant reduction in the absorption of the tetracycline. Plasma levels were within the usual range accepted for bioequivalence (80–125 %) and the ratio for AUC0-∞ was almost within this window (79.1–102.0 %) [31].

Potgieter *et al.* examined the effects of co-administration of aluminium hydroxide on the uptake of iron from Maltofer film-coated tablets in anaemic patients. Although iron (^{59}Fe) uptake was lower when the drug was taken with aluminium hydroxide, the differences were neither statistically nor clinically significant. For example median erythrocyte uptake (%) was 0.607 without and 0.575 with aluminium hydroxide [18].

Lundqvist and Sjöberg used ^{59}Fe-labelled IPC to study the effects of food on iron uptake. They found that both subjects with and without iron deficiency benefited from the concomitant administration of an iron absorption enhancer (orange juice). They also showed that iron uptake was increased when IPC was given with food to anaemic subjects, whereas in normal subjects iron uptake was greater under fasting conditions [32].

Studies in rats have also shown that the uptake of ^{59}Fe-labelled IPC is not significantly affected by the presence of aluminium hydroxide, tetracycline, acetylsalicylate, sulfasalazine, calcium carbonate, calcium acetate, calcium/phosphate/vitamin D, D-penicillamine, paracetamol, or auranofin [33]. In vitro studies have also shown that the number and extent of interactions is much more limited with IPC than with ferrous salts [11].

We may conclude that IPC does not interact significantly with any food stuffs, food components or drugs, except for ascorbic acid, which shows a tendency to increase iron absorption without a measurable reduction of Fe(III) to Fe^{2+} at pH levels above 3. Moreover no reactions with iron chelating agents such as phenol-containing compounds have been reported.

4.3. Clinical trials

Tuomainen *et al.* conducted a 6-month placebo-controlled trial in 48 men with serum ferritin ≤ 30 µg/L. Patients were randomized to receive IPC (containing 200 mg of iron) plus placebo resembling $FeSO_4$, microencapsulated $FeSO_4$ (180 mg of iron) plus placebo IPC, or both placebo [34].

At 6 months, serum ferritin concentrations had increased 2.2-fold in the $FeSO_4$ group ($p < 0.001$) and 1.3-

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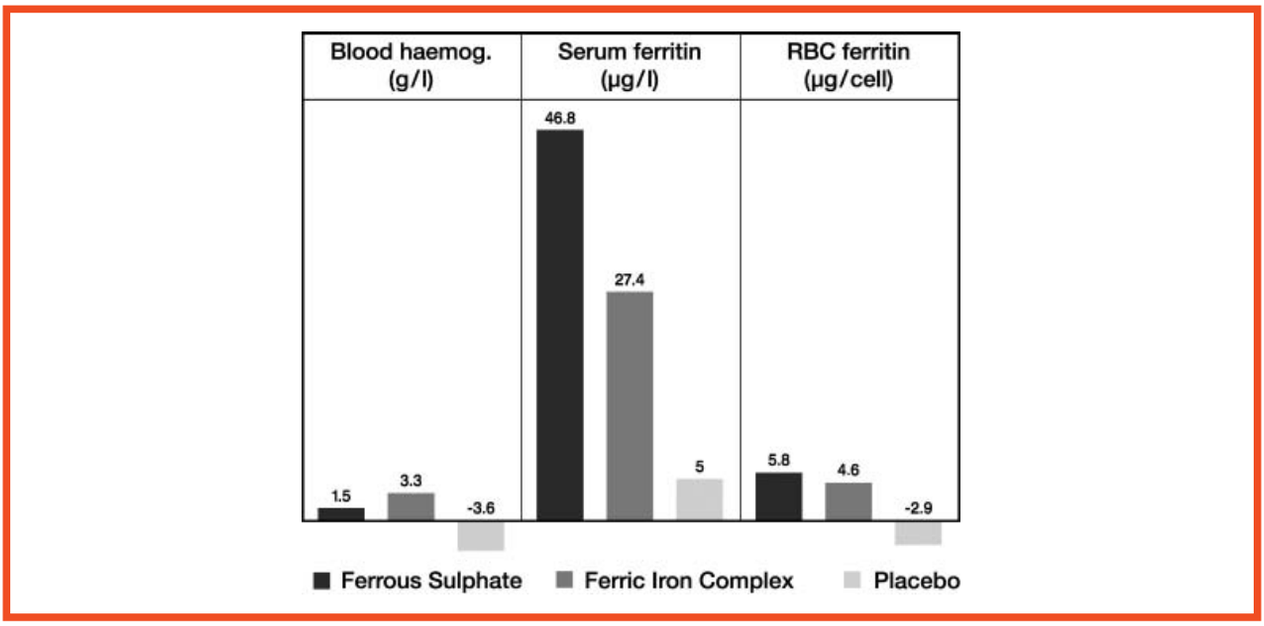

Fig. 4: Ferritin values. Changes in iron status in iron depleted male subjects after 6 months iron therapy with $FeSO_4$, IPC and placebo (Tuomainen 1999 [34]).

fold in the IPC group ($p < 0.001$ *versus* placebo). Erythrocytic ferritin, however, which is considered a better marker for iron stores, increased equally under both active treatments. Haemoglobin also increased in both groups (by 1.0 % with $FeSO_4$ and by 2.2 % with IPC, $p < 0.001$ *vs* placebo in both cases) (Fig. 4). Three subjects receiving 180 mg of iron as microencapsulated ferrous sulphate and 2 receiving 200 mg of iron as IPC reported gastric disturbances. This resulted in treatment discontinuation in one case in each group, while the dose was halved for the other three subjects.

Mackintosh and Jacobs studied 46 blood donors, 23 had low iron stores (ferritin <20 µg/L) but Hb ≥13.5 g/dL, and the other 23 (ferritin 50–150 µg/L) served as controls. Both groups were randomised to 100 mg IPC or placebo twice a day for 8 weeks [35].

In the iron-deficient group, iron therapy resulted in a significant rise in haemoglobin (14.3 to 15.0 g/dl, $p = 0.03$) and serum ferritin (16.2 to 43.2 µg/L, $p = 0.002$). In the placebo group, there was no significant change in the haemoglobin level, and a small but significant rise in ferritin. This increase was significantly lower than the increase seen in the IPC group. In the non-iron deficient control group, neither IPC nor placebo produced a significant change in haemoglobin or ferritin levels. This study shows that IPC effectively refilled depleted iron stores and simultaneously produced an increase in haemoglobin in iron deficient subjects without overt anaemia. Gastrointestinal disturbances were not reported despite specific enquiries about adverse effects such as anorexia and nausea [35].

Jacobs *et al.* investigated the effect of iron therapy on 159 blood donors with overt iron deficiency anaemia (Hb <133 g/L for men, <116 g/L for women). Subjects were randomised to either 60 mg of iron twice daily as $FeSO_4$ (group 1), 100 mg iron once daily as IPC (group 2), or 100 mg iron twice daily as IPC (group 3). Both IPC groups took tablets with meals. 80 % of the subjects in groups 1 and 3 reached normal Hb levels by 12 weeks, but in group 2 this figure was only 50 %. Similarly, the proportion of subjects improving their percentage transferrin saturation to within the normal range was significantly better in groups 1 and 3 than in group 2 ($p < 0.01$). The progression to normal was somewhat slower in group 3 than in group 1, but there was no difference by 12 weeks. Nausea and vomiting occurred in all 3 groups, but to a higher extent with ferrous sulphate administration. Treatment had to be stopped because of side effects in 11 cases (20 %) in the ferrous sulphate group but in no patients receiving IPC. The incidence of mild gastrointestinal adverse events was similar with both IPC dosages [36].

Langstaff *et al.* studied 104 patients with IDA in a general practice setting. A daily dose of 200 mg iron as IPC (chewable tablets) taken morning and evening with meals, was compared to 180 mg of iron as $FeSO_4$ (60 mg three times a day, 30 min before meals). Treatment duration was 9 weeks. The "intention-to-treat" analysis demonstrated highly significant increases in haemoglobin in both groups from entry to 3 weeks and from 6 to 9 weeks. Hb levels were significantly higher in the $FeSO_4$ group at 3 weeks and at 6 weeks, but there were no differences between groups at 9 weeks. Similar results were obtained for haematocrit, erythrocyte count, MCH, MCHC and MCV [37].

This study included a careful survey of adverse events (AEs). Five patients in the ferrous sulphate group and 3 in the IPC group stopped treatment because of adverse events, which were mostly gastrointestinal. The most

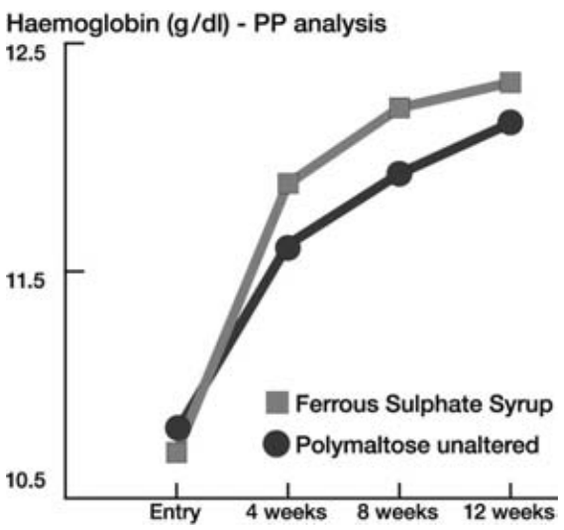

Fig. 5: Haemoglobin concentration in per-protocol patients with 12 weeks of treatment with IPC or ferrous sulphate (modified after Jacobs *et al.* 2000 [12]).

common AEs were indigestion, nausea and diarrhoea, and the first two were significantly more frequent, at any visit, in the ferrous sulphate group. After specific inquiry, adverse events reported by at least 10 % of patients in either group were change in stool colour (IPC 43 %, $FeSO_4$ 48 %), abdominal pain (10 % and 18 %), constipation (18 % and 11 %), lassitude (13 % and 13 %) and headache (7 % and 11 %).

Jacobs *et al.* compared IPC and $FeSO_4$ for the treatment of IDA in 143 regular blood donors in an open, randomised trial [11]. Both preparations were given on a 100 mg *b.i.d.* schedule. Hb levels increased to a similar extent in both groups (with no statistically significant difference at either 4 or 8 weeks) (Fig. 5) and similar increases in MCH, MCV and decreases in the percentage of hypochromic red cells were also observed. The withdrawal rate due to adverse events considered at least possibly drug-related was significantly higher (15/48) with $FeSO_4$ than with IPC (16/125; $p = 0.007$). Nausea was the main reason given for interrupting treatment in the $FeSO_4$ group. Tolerance was rated either good or adequate in about 80 % of the patients in IPC groups, and in about 60 % of patients receiving ferrous sulphate. The authors also noted that serum ferritin levels were higher with the ferrous salt and that this may indicate oxidative stress [12].

Sas *et al.* compared the effects of IPC, ferrous sulphate and ferrous fumarate + folic acid + vitamin B_{12} in 60 women with IDA. All three groups had similar increases in haemoglobin, RBC and Hct at 12 weeks. Treatments were generally well tolerated in all groups. Heartburn was reported once each in the sulphate and fumarate groups, vomiting once in the sulphate group, and diarrhoea once in the IPC group. No symptoms from the upper gastrointestinal tract were reported with IPC. Transaminases rose above the reference range in the sulphate, but not in the IPC group [38].

Schmidt *et al.* performed a randomised, double-blind trial in 30 children aged 24–81 months suffering from iron deficiency with or without anaemia. They received IPC (syrup) or ferrous sulphate, at a dose of 4 mg/kg between meals for 2 months. At the end of the study, Hb was significantly increased ($p < 0.01$) in both groups (+1.1 ± 1.14 g/dl with IPC, +1.8 ± 1.4 g/dl with $FeSO_4$). In the children with initial haemoglobin <11 g/dl the increases were +2.7 g/dl and +2.5 g/dl for IPC and $FeSO_4$, respectively. Serum ferritin levels were also significantly higher after treatment, from 12 ± 12 up to 32 ± 22 ng/ml for IPC, and from 12 ± 16 up to 65 ± 45 ng/ml for $FeSO_4$. Despite drug administration between meals, both treatments achieved a satisfactory increase in haemoglobin and serum ferritin [39].

Clinical tolerability was good in both groups. Staining of teeth was reported in 30 % of the patients in the sulphate group but in none of the IPC group. Loose stools were more frequent (33 %) in the IPC group than in the sulphate group (10 %). None of the products had a negative impact on weight increase. Occurrence of dark stools, a well-known and clinically irrelevant effect of iron therapy, was similar in both groups.

In a similar double-blind randomised trial by Murahovschi *et al.*, 49 iron deficient infants aged 6–40 months were randomised to either IPC or ferrous sulphate for 60 days, at a daily dose of 4 mg of elemental iron per kg. Both treatments resulted in improvements in haematological values, as shown in Table 3. In the ferrous sul-

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Table 3: Response of iron deficient infants randomised to IPC or ferrous sulphate (from Murahovschi *et al.* 1987) [40].

	IPC (N = 22)			Iron sulphate (N = 19)		
	Day 0	Day 30	Day 60	Day 0	Day 30	Day 60
RBC (10^6/mm^3)	4.81 ± 0.53	4.99 ± 0.85	5.08 ± 0.61	4.72 ± 0.63	4.82 ± 0.39	4.97 ± 0.26
Hb (g/dl)	10.3 ± 1.4	10.6 ± 1.5	11.0 ± 1.4	9.6 ± 1.3	10.3 ± 1.4	10.3 ± 1.4
Haematocrit (%)	33.7 ± 4.3	34.7 ± 4.5	36.2 ± 4.6	32.0 ± 4.3	33.4 ± 4.2	33.6 ± 4.3

Values are mean ± S.D.

Table 4: Effect of giving IPC with or between meals (from Andrade *et al.* 1992) [43].

	IPC (N = 93)			
	With meals (N = 50)		Between meals (N = 43)	
	Day 0	Day 90	Day 0	Day 90
RBC (10^3/mm^3)	3903	4233	3919	4344
Hb (g/dl)	9.84	11.19	9.85	11.10
Haematocrit (%)	31.5	35.0	30.5	34.3

All differences post- *vs* pre-treatment were statistically significant ($p < 0.05$, Student's t-test).

phate group, the increase tended to be faster during the first month, but was smaller during the second month (Table 3) [40].

After 2 months treatment, IPC proved to be equal in efficacy to ferrous sulphate in this group of iron-deficient children. Poor tolerability, resulting in early termination of the trial, was reported in 2 cases (8 %) in the IPC group and in 5 cases (21 %) in the $FeSO_4$ group. In all cases, the underlying cause was severe diarrhoea. Other symptoms (vomiting and constipation, one case each) were also reported in the $FeSO_4$ group.

Agaoglu *et al.* compared children (aged 6–12 years) with and without IDA and showed that mean IQ score was significantly lower (by 12.9 points) in the IDA group. Treatment with iron polymaltose (5 mg/kg/day with a multivitamin preparation for 4–6 months) was associated with a significant increase in mean IQ (of 4.8 points) and resulted in the difference in IQ between the two groups of children no longer being statistically significant [7].

Devaki *et al.* assessed the effects of iron supplementation on the immune system in 120 adolescents of varying iron status (some with IDA, some without). Those who received IPC (100 mg iron, 6 days a week for 8 months) showed increases in the bactericidal capacity of neutrophils (BCA), the nitro-blue tetrazolium reduction test (NBT), and phytohaemagglutinin (PHA) response which were not observed in the placebo group. No side-effects were attributed to IPC [41].

Vetter *et al.* compared 3 doses of IPC (200, 400, and 600 mg) in 63 anaemic adult patients. Mean haemoglobin values increased in all three groups in a dose-related manner, but interpretation of this finding is hampered by the fact that there were more patients with severe anaemia in the 600 mg group. Haemoglobin concentrations at the end of the study were similar for all groups. The mean time needed to raise the Hb level to the desired value also depended on dose, being 6.6, 8.3 and 11.3 weeks for the 200, 400 and 600 mg dose groups, respectively. This suggests that the daily dose may be increased to 400 or 600 mg a day if a rapid correction of iron deficiency is desired. All doses were well tolerated with 6, 7 and 9 drug-related AEs reported in the three groups [42].

Andrade *et al.* compared the effect of giving IPC with or between meals in infants and small children with IDA. There was no significant difference in the results from both groups confirming the fact that IPC can be taken with food without reducing its effectiveness (Table 4) [43].

Adverse events were reported in 3 patients (6 %) who took IPC with meals, and in 4 patients (8 %) who took it between meals. Two patients in each group stopped treatment because of gastrointestinal events (mainly diarrhoea).

Rosenberg *et al.* compared IPC syrup and ferrous fumarate (capsules) in 101 in-patients in a gynaecology unit presenting with iron deficiency symptoms and/or laboratory abnormalities. They observed similar weekly increases in haematological values with both treatments. Hb (g/dl) rose by +0.67 and +0.87 for IPC and fumarate, respectively; RBC (10^6/mm^3) rose by +0.23 and +0.40, respectively, and Hct (%) rose by +1.42 and +1.96, respectively [44].

Gürer *et al.* performed a comparative trial in 50 children (aged 8 months to 9 years) with IDA. Patients received 5 mg/kg/day of either Vifor's syrup formulation of IPC or $FeSO_4$. After one month of treatment, Hb, Hct, serum iron, total iron binding capacity (TIBC), transferrin saturation and ferritin had improved in both groups. The investigators concluded that there was "not a very important difference" in efficacy between the two treatments. However, adverse events were more common in the $FeSO_4$ group, the difference being mostly due to a higher incidence of tooth staining (40 *vs* 18 %, respectively) and diarrhoea (20 *vs* 0.4 %, respectively) [45].

Haliotis and Papanastasiou randomised 100 children (aged 12 to 113 (mean 40) months) with latent or overt

Table 5: Comparison of three iron plus folate preparations in pregnant, iron-deficient women (from *Geisser et al.* 1987) [47].

Product	Maltofer-Fol		Ferrum-H-Fol-B		Ferro-Folic-500	
Iron form Plus	Iron polymaltose folic acid		Iron fumarate folic acid, vit B_{12}		Iron sulphate folic acid, ascorbic acid	
Week	0	8	0	8	0	8
Haematocrit (%)	39.2 ± 3.3	38.4 ± 3.2	39.4 ± 3.2	38.6 ± 2.9	39.1 ± 3.4	38.1 ± 2.6
Haemoglobin (g/L)	125.0 ± 10.7	121.3 ± 10.1	123.0 ± 9.5	122.0 ± 8.2	124.0 ± 10.4	120.7 ± 7.2
RBC (1012/L)	4.38 ± 0.49	4.20 ± 0.39	4.50 ± 0.77	4.20 ± 0.40	4.38 ± 0.51	4.03 ± 0.38
MCV (fL)	89.9 ± 6.1	91.5 ± 6.8	90.0 ± 6.7	92.4 ± 6.2	89.6 ± 5.7	94.5 ± 5.5
Ferritin (µg/L)	34.3 ± 36.6	21.2 ± 15.6	30.3 ± 21.6	19.4 ± 16.0	26.3 ± 22.8	22.3 ± 14.7
Serum iron (µmol/L)	20.9 ± 7.1	21.6 ± 4.9	21.0 ± 6.6	20.1 ± 6.9	20.7 ± 6.3	20.7 ± 5.2

Table 6: Adverse events (AEs) reported in studies using iron(III)-hydroxide polymaltose complex (IPC).

First author	Date	Study population	N (IPC)	Treatment/ duration	AEs with IPC	Notes
Studies in adults						
Jacobs [12]	2000	Adults with IDA	120	IPC drops 12 wks	Nausea 11 %, constipation 20 %, tooth discoloration 0	$FeSO_4$ group: Nausea 45 %, constipation 13 %, tooth discoloration 11 %
Jacobs [36]	1993	Adults with IDA	108	IPC 12 wks	Mild side effects, no withdrawals	11 patients on $FeSO_4$ stopped for GI AEs
Langstaff [37]	1993	Adults with IDA	55	FH 9 wks	GI AEs in 17 %: nausea / indigestion (4), diarrhoea (0)	GI AEs in 24 % of $FeSO_4$ gp (N = 54): nausea / indigestion (12), diarrhoea (6)
Tuomainen [34]	1999	Adults with IDA	15	IPC 6 months	Stomach problems (2 = 13 %)	Stomach problems (3 = 20 %) in $FeSO_4$ group
Mackintosh [35]	1988	Blood donors +/- iron deficiency	22	IPC tablets 8 weeks	No AEs	IPC same as placebo
Vetter [42]	1994	Adults with IDA	63	M: 200, 400 or 600 mg 12 weeks	AEs in 52–67 % mainly GI; tolerability judged good or adequate by 71–93 %	
Rosenberg [44]	1979	Women with ID	49	FH syrup 5–24 days	Tolerance good or very good for 92 %: 4 AEs	Similar tolerance for Fe fumarate group
Studies in pregnant or breastfeeding women						
Al [52]	2005	Pregnant women	45	FH tablets + folic acid 4 weeks	14 cases of possibly drug-related GI AEs	
Kunz [53]	2003	Pregnant women	60	M-fol 90 days	Gastroenteritis (1); constipation (3); n/v (2), abdominal pain (1), tooth discoloration (1)	
Beruti [48]	1978	Pregnant women	30	IPC + folic acid + cyano-cobalamin 30 days	Excellent tolerability in 27 (90 %), nausea / epigastric pain in 3	
Sas [38]	1984	Women (5 pregnant) with IDA	20	FH syrup 12 weeks	Few AEs, diarrhoea (1)	Gastralgia (1), vomiting (1) in $FeSO_4$ group (N = 20)
Malikova [54]	2005	Breastfeeding women	50	M tablets 12 weeks	No AEs in mothers or infants	
Studies in infants, children and adolescents						
Soboleva [55]	2003	Infants and children (6 months to 4 years)	127	M drops 5–12 weeks	Treatment completed in all cases, 10 % constipation (6 % stopped treatment)	
Agaoglu [7]	2007	Children (6–12 years)	30	IPC	No side-effects	
Kavakli [56]	2004	Children (6 months to 15 years) with IDA	33	IPC 6 months	Stomach ache (2), constipation (2), diarrhoea (2), nausea (2)	$FeSO_4$ (N = 39): Stomach ache (1), constipation (1), diarrhoea (1), nausea (2), tooth discoloration (1)

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Table 6 cont.

First author	Date	Study population	N (IPC)	Treatment/ duration	AEs with IPC	Notes
Studies in infants, children and adolescents						
Gürer [45]	1998	Children with IDA	25	FH 4 weeks	Tooth staining (4), nausea (6), diarrhoea (1), constipation (1)	In Fe glycine sulphate gp (N = 25) Tooth staining (10), nausea (5), diarrhoea (5), constipation (0)
Haliotis [46]	1998	Children with latent ID	50	IPC 8 weeks	AEs reported by 6 patients (12 %): abdominal pain (2), diarrhoea (3), nausea (4), vomiting (2)	Iron protein succinylate (N = 50): abdominal pain (2), diarrhoea (1), nausea (3), vomiting (1)
Murahovschi [40]	1987	Children	25	IPC 8 weeks	Good tolerability in 88 %, severe diarrhoea in 2 (8 %)	$FeSO_4$ (N = 17):good tolerability in 66 %, severe diarrhoea in 5 (21 %), vomiting (1), constipation (1)
Schmidt [39]	1985	Children with ID or IDA	15	IPC 8 weeks	Good tolerability (no tooth staining)	Tooth staining in 3/10 with $FeSO_4$
Soboleva [57]	2001	Children	72	IPC +/- folic acid (variable)	2 cases of constipation, no other AEs	
Kazyokova [58]	2000	Children with IDA	69	M drops 4–9 weeks	No AEs	
Andrade [43]	1992	Children	97	IPC taken with or between meals 90 days	AEs in 7 patients causing 3 drug-related withdrawls: diarrhoea (2), n/v (1)	
Soboleva [59]	2004	Adolescents (15–18 years)	170	M drops or syrup or Ferrum-lek liquid (variable)	Constipation 6–8 %	IPC preparations superior to three Fe(II) preparations
Devaki [41]	2007	Adolescents	90	IPC 8 months	No side-effects	

iron deficiency anaemia, to receive iron protein succinylate or IPC. All received 4 mg/kg elemental iron, up to a maximum of 80 mg daily, for 2 months. Although the study was randomised, the group that received iron protein succinylate had significantly higher baseline Hb concentrations. Both groups showed similar increases in Hb after 2 months [46].

5. Combinations of iron and folic acid

IPC has been used in combination with folic acid in pregnant women. Geisser *et al.* compared three iron + folate preparations in a randomised trial in pregnant women with iron deficiency. The endpoints were haemoglobin and haematocrit, as well as erythrocytes, MCV, ferritin, and serum iron. None of the endpoint values showed any statistically significant difference between groups or over time (Table 5). The authors concluded that all three iron/folate products had similar effects [47].

This study shows a comparable effect of IPC as an iron supplier to that of ferrous sulphate and fumarate, which are the two iron salts most extensively used and investigated.

Beruti gave IPC and folic acid to 30 pregnant women with mixed iron-folate deficiency anaemia (Hb <100 g/L, Hct <35 %, plasma folic acid <5 ng/mL) in the 3rd trimester. He used a preparation of 100 mg of iron as IPC combined with 0.50 mg folic acid and 0.20 mg cyancobalamin, given twice a day for 10 days, then once a day for a further 20 days. He found significant increases in Hb, Hct, folic acid and RBC count [48].

6. Safety

Whenever IPC has been compared with a classical iron salt, the incidence, and often the severity of adverse events was either similar or lower than that observed with ferrous salts (Table 6). This lower incidence and milder grade were particularly evident for nausea, vomiting, and heartburn, whereas the difference was not as apparent for diarrhoea, although this was a relatively rare event for all treatments. The reduced incidence of upper gastrointestinal symptoms, which are a major cause of poor compliance with ferrous salts, may represent a welcome advantage for IPC.

In several clinical trials, early discontinuation of treatment due to adverse effects was lower with IPC than with ferrous iron preparations. It therefore appears that patient compliance may be better with IPC than with classical iron supply.

Overdose and accidental intoxication with iron preparations is common [9, 49]. In the USA about 10–12 children, usually of a very young age, die after accidental ingestion of iron tablets each year. Despite the wide use of Maltofer preparations, no case of accidental poisoning with a fatal outcome has been reported.

In recent years, increased attention has been devoted to the delicate cellular redox balance, and evidence has accumulated that iron may be a pro-oxidant factor [14]. Iron salt administration has even been suggested as a possible risk factor for a number of chronic diseases. Tuomainen *et al.* demonstrated that the susceptibility of very low and low-density lipoproteins to oxidation increased with ferrous sulphate by 8.8 % ($p < 0.05$) compared to placebo and by 12.8 % ($p < 0.05$) compared to IPC [34].

Jacobs *et al.* reported a higher increase in serum ferritin than in RBC ferritin with ferrous sulphate, but not with IPC [12]. Ferritin is known to act as a positive acute phase reactant and is therefore not a reliable measure for assessing iron stores in diseases characterised by an acute-phase reaction [50]. The authors suggest that part of the increase in serum ferritin observed under treatment with ferrous salts was due to a reaction induced by iron at the cellular level.

7. Different forms of iron polymaltose

The studies of IPC reported above have all used Maltofer. However, other iron-polymaltose or iron-carbohydrate compounds are available in some countries. These different forms have different physicochemical properties (Table 7) and this is likely to affect their bioavailability and tolerability. For example, compounds that are not soluble at gastric pH (1.2) will not have the same efficacy since they are likely to form aggregates or precipitates

Table 7: Physicochemical properties of different IPCs (from Geisser 2004) [16].

Preparation	Point of zero charge (pH)	Molecular mass (kD)	Degradation kinetics ($k \cdot 10^3 \cdot min^{-1}$) at $\theta = 0.1/0.5/0.9$
Maltofer drops	none	52.3	51/73/118
Eleron haematinic drops	6.1[a)]	140	19/27/48
Ferium drops	4.8	210 and 63.7	22/46/95
Ferium chewable tablets	–	85.5	77/76/91
Ferose drops	5.9[a)]	382 and 48.8	11/23/57
Mumfer-Z capsules	–	452 and 61.3	87/103/193
Orofer drops (Emcure)	4.2	49.7	32/50/87

[a)] Turbidity at the original pH of the solution. The zero point of charge could not be determined.

Table 8: Global analysis of efficacy: variations in Hb, MCV, serum ferritin, and RBC-ferritin following treatment with IPC.

Efficacy variable	Form	N of patients treated with IPC	Dose	Duration of therapy	Results		Comparison with control		Ref
					Pre-treatment value	(mean change)	Pre-treatment value	(mean change)	
Hb	Drops	24 23 24	100 mg *bid*	12 weeks	107.8 g/L 108.9 g/L 107.8 g/L	+ 13.5 g/L + 13.7 g/L + 9.6 g/L	$FeSO_4$ 107.1 g/L	$FeSO_4$ + 16.1 g/L	[12]
		93	2.5 mg/kg	90 days	A: 98.4 g/L B: 98.5 g/L	A: + 13.5 g/L B: + 12.5 g/L	No control		[43]
		50	4 mg/kg daily max 80 mg/day	2 months	107 g/L	+ 14 g/L	IPSucc 111 g/L	IPSucc + 14 g/L	[46]
	Syrup	12	2 mg/kg *bid*	60 days	115 g/L	+ 10.8 g/L	$FeSO^4$ 106 g/L	+ 18.5 g/L	[39]
		22	2 mg/kg *bid*	60 days	103.2 g/L	+ 7.0 g/L	96.4 g/L	$FeSO_4$ + 6.7 g/L	[40]
		20	100 mg/d	12 weeks	104.3 g/L	+ 13.4 g/L	$FeSO_4$ 108.3 g/L Fumar 104.2 g/L	$FeSO_4$ + 13.0 g/L Fumar + 12.5 g/L	[38]
		49	100 mg/d	5-24 days	109 g/L	+ 6.7 g/	108 g/L	Fumar + 8.7 g//L	[44]
	Tablets	15	100 mg *bid*	6 months	145 g/L	+ 3 g/L	$FeSO_4$ 145 g/L Placebo 144 g/L	$FeSO_4$ + 1.5 g/L Placebo – 3.6 g/L	[34]
		22	100 mg *bid*	8 weeks	A: 143.1 g/L B: 146.1 g/L	+ 7.1 g/L + 4.1 g/L	A: Placebo + 142.5 g/L B: Placebo + 146.0g/L	A: Placebo + 6.2 g/L B: Placebo + 6.0 g/L	[35]
		53 55	100 mg/d 100 mg *bid*	12 weeks	A: 116.3 g/L B: 114.3 g/L	+ 9.6 g/L + 16.6 g/L	$FeSO_4$ 114.0 g/L	$FeSO_4$ + 18.1 g/L	[36]
		22	100 mg *bid*	3 weeks 6 weeks 9 weeks	107.4 g/L 107.4 g/L 107.4 g/L	+ 6.0 g/L + 9.3 g/L + 12.9 g/L	3 weeks 109.3 g/L 6 weeks 109.3 g/L 9 weeks 109.3 g/L	3 weeks + 8.3 g/L 6 weeks + 12.8 g/L 9 weeks + 14.6 g/L	[37]

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Table 8: cont.

Efficacy variable	Form	N of patients treated with IPC	Dose	Duration of therapy	Results		Comparison with control		Ref
					Pre-treatment value	(mean change)	Pre-treatment value	(mean change)	
Hb	Tablets	15 13 17	100 mg *bid* 200 mg *bid* 200 mg *tid*	12 weeks	110 g/L 107 g/L 100 g/L	+ 10.8 g/L + 10.0 g/L + 22.7 g/L	no control		[42]
	Un-known	15	3 mg/kg *tid*	60 days	85 g/L	+ 34 g/L	86 g/L	+ 35 g/L	[60]
		14	3-6 mg/d	6 months	100 g/L	+ 16 g/L	96 g/L	+ 29 g/L	[61]
MCV	Drops	24 23 24	100 mg *bid*	12 weeks	A: 73.9 µm^3 B: 71.6 µm^3 C: 72.8 µm^3	A: + 5.7 µm^3 B: + 6.3 µm^3 C: + 5.5 µm^3	$FeSO_4$ 73.7 µm^3	+ 6.9 µm^3	[12]
		93	2.5 mg/kg	90 days	A: 76.7 µm^3 B: 76.5 µm^3	A: + 2.68 µm^3 B: + 1.90 µm^3	no control		[43]
		50	4 mg/kg daily max 80 mg/day	2 months	70.5 µm^3	+ 4.2 µm^3	72.9 µm^3	+ 4.9 µm^3	[46]
	Syrup	22	2 mg/kg *bid*	60 days	70.2 µm^3	+ 1.2 µm^3	65.3 µm^3	+ 2.4 µm^3	[40]
	Tablets	15	100 mg *bid*	6 months	88 µm^3	+ 3 µm^3	$FeSO_4$ 88 µm^3 Placebo 89 µm^3	$FeSO_4$ + 3 µm^3 Placebo + 1 µm^3	[34]
		22	100 mg *bid*	3 weeks 6 weeks 9 weeks	83.6 µm^3 83.6 µm^3 83.6 µm^3	+ 2.1 µm^3 + 2.6 µm^3 + 3.0 µm^3	3 weeks 82.2 µm^3 6 weeks 82.2 µm^3 9 weeks 82.2 µm^3	3 weeks + 3.2 µm^3 6 weeks + 5.0 µm^3 9 weeks + 4.4 µm^3	[37]
		15 13 17	100 mg *bid* 200 mg *bid* 200 mg *tid*	12 weeks	81.8 µm^3 80.5 µm^3 76.6 µm^3	+ 2.8 µm^3 + 3.7 µm^3 + 7.0 µm^3			[42]
Ferritin	Drops	24 23 24	100 mg *bid*	12 weeks	A: 2.94 µg/L B: 3.20 µg/L C: 3.81 µg/L	A: + 2.58 µg/L B: + 2.72 µg/L C: + 5.50 µg/L	$FeSO_4$ 3.50µg/L	+ 8.55 µg/L	[12]
		50	4 mg/kg daily max 80 mg/day	2 months	11.1 µg/L	+ 20.2 µg/L	IPSucc 12.7 µg/L	+ 25.1 µg/L	[46]
	Syrup	12	2 mg/kg *bid*	60 days	12.3 µg/L	+ 20.3 µg/L	$FeSO_4$ 12.3 µg/L	+ 53.7 µg/L	[39]
		22	2 mg/kg *bid*	60 days	30.5 µg/L	(–19.2 µg/L)	$FeSO_4$ 16.5 µg/L	(–3.2 µg/L)	[40]
	Tablets	15	100 mg *bid*	6 months	20.5 µg/L	+ 27.4 µg/L	$FeSO_4$ 22 µg/L Placebo 20 µg/L	$FeSO_4$ + 47 µg/L Placebo + 5 µg/L	[34]
		22	100 mg *bid*	8 weeks	A: 16.2 µg/L B: 71.1 µg/L	A: + 27.0 µg/L B: + 10.7 µg/L	A: Placebo 16.7 µg/L B: Placebo 68.6 µg/L	A: Placebo + 10.6 µg/L B: Placebo – 10.8 µg/L	[35]
		53 55	100 mg/d 100 mg *bid*	12 weeks	A: 13.5 µg/L B: 14.8 µg/L	A: + 3.0 µg/L B: + 7.2 µg/L	$FeSO_4$ 18.5 µg/L	$FeSO_4$ +17.8µg/L	[36]
		15 13 17	100 mg *bid* 200 mg *bid* 200 mg *tid*	12 weeks	6.6 µg/L 5.0 µg/L 5.3 µg/L	+ 7.8 µg/L + 3.2 µg/L + 5.8 µg/L			[42]
	Un-known	15	3 mg/kg *tid*	60 days	19.6 µg/L	+ 15.7 µg/L	15.9 µg/L	+ 25.7 µg/L	[60][a]
		14	3-6 mg/d	6 months	22.6 µg/L	– 10.8 µg/L	20.2 µg/L	+ 36.4 µg/L	[61][b]
RBC Ferritin	Tablets	15	100 mg *bid*	6 months	16.9	+ 4.6	$FeSO_4$: 15.9 Placebo: 17.7	$FeSO_4$: +5.8 Placebo: –2.9	[34]
		24 23 24	100 mg *bid*	12 weeks	A: 1.3 fg/1000 B: 1.1 fg/1000 C: 0.83 fg/1000	A: +0.86 fg/1000 B: +0.31 fg/1000 C: +0.43 fg/1000	$FeSO_4$ 1.40 fg/1000	+ 0.80 fg/1000	[12]

[a] Ferritin units stated as ng/dL in paper but this gives baseline values of < 0.2 µg/L which seems unlikely given the normal range of 15–300 µg/L. So, units assumed to be µg/L.
[b] Ferritin units stated as mg/dL in paper but this gives baseline values of about 200,000 µg/L which is unfeasible given the normal range of 15–300 µg/L. So, units assumed to be µg/L.

which have a smaller surface area for the release of iron compared with a solution of the same compound. Complexes with a higher molecular weight normally have a slower rate of iron release, leading to poorer absorption and reduced efficacy [11, 16].

A direct comparison of Maltofer with Hematin in anaemic children aged 6–24 months showed a higher proportion of responders (who achieved a haemoglobin level of at least 11 g/dL) in the Maltofer group and Maltofer was also better tolearated with fewer adverse effects than Hematin [51].

8. Conclusions

Several studies have demonstrated that IPC has a significant effect on the endpoint of iron therapy, i.e. Hb formation and/or restoration of iron stores, in infants, children and adults (Table 8). IPC appears to have a somewhat slower onset of action than classical ferrous salts. However, the newest study (conducted according to GCP) by Jacobs *et al.* has not shown any difference at any time point [12]. Furthermore, after about 3 months of therapy the effects are similar. Dose-ranging studies suggest that a daily dose of 2×100 mg is more effective than 100 mg, with no increase in adverse events. One study also supports a daily dose of up to 600 mg iron.

An important difference between IPC and ferrous salts is that the bioavailability is actually increased when IPC is taken with meals, so this is the recommended method of treatment.

IPC is indicated as oral iron therapy for the treatment of any kind of iron deficiency such as the treatment of actual iron deficiency anaemia, treatment of latent iron deficiency (depletion of iron stores) and for the prevention of iron deficiency during pregnancy and lactation.

Furthermore, IPC has been successfully used for the repletion of iron stores in regular blood donors, and for the correction of iron deficiency with or without anaemia in infants and small children.

IPC is generally well tolerated and appears to cause significantly less gastrointestinal disturbance than ferrous salts. Both the incidence and severity of adverse events in most clinical trials has been lower with IPC than with ferrous sulphate. IPC is also safer in cases of accidental overdose, and no fatalities have been reported.

Recent studies suggest that ferrous sulphate may be associated with oxidative stress reactions, but there are indications that this concern does not apply to IPC.

Taking into consideration the definition of therapeutic equivalency, which states that two preparations are equivalent if they demonstrate the same efficacy *and* safety, it can be concluded that IPC is superior to iron salts, due to the fact of that it displays equal efficacy, but has a superior safety profile.

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References

[1] Woods S, De Marco T, Friedland M. Iron metabolism. *Am J Gastroenterol.* 1990;85:1–8.

[2] Harju E. Clinical pharmacokinetics of iron preparations. *Clin Pharmacokinet.* 1989;17:69–89.

[3] Linker CA. Blood. In: Tierney LM, Mcphee SJ, Papadakis MA, eds. *Current Medical Diagnosis and Treatment.* 36th ed. London: Practice-Hall; 1997. p. 463–465.

[4] DeMaeyer EM, Dallman P, Gurney JM, *et al.* Preventing and controlling iron deficiency anaemia through primary health care. Geneva: World Health Organisation; 1989.

[5] Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. *New Engl J Med.* 1991;325:687–694.

[6] Cook JD, Skikne BS, Baynes RD. Iron deficiency: the global perspective. In: Hershko CH, Konjin AM, Aisen PH, eds. *Progress in Iron Research.* New York: Plenum Press; 1994. *Adv Exp Med Biol.* 1994;356:219–228.

[7] Agaoglu L, Torun O, Unuvar E, Sefil Y, Demir D. Effects of iron deficiency anemia on cognitive function in children. *Arzneimittel-Forschung (Drug Research).* 2007;57(6a):426–430.

[8] Brock C, Curry H, Hanna C, *et al.* Adverse effects of iron supplementation: a comparative trial of a wax-matrix iron preparation and conventional ferrous sulfate tablets. *Clin Ther.* 1985;7:568–573.

[9] Anderson AC. Iron poisoning in children. *Curr Opin Ped.* 1994;6:289–294.

[10] Litovitz TL, Klein-Schwartz W, Rodgers GC Jr, Cobaugh DJ, Youniss J, Omslaer JC, May ME, Woolf AD, Benson BE. 2001 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med.* 2002;20:391–452.

[11] Geisser P, Baer M, Schaub E. Structure/histotoxicity relationship of parenteral iron preparations. *Arzneimittel-Forschung (Drug Research).* 1992;42:1439–1452.

[12] Jacobs P, Wood L, Bird AR. Better tolerance of iron polymaltose complex compared with ferrous sulphate in treatment of anaemia. *Hematology.* 2000;5:77–83.

[13] Hutchinson C, Al-Ashgar W, Liu DY, Hider RC, Powell JJ, Geissler CA. Oral ferrous sulphate leads to a marked increase in pro-oxidant nontransferrin-bound iron. *Eur J Clin Invest.* 2004;34:782–784.

[14] Geisser P. Iron therapy with special emphasis on oxidative stress. Rorschach (Switzerland): Löpfe-Benz AG; 1998.

[15] Geisser P, Müller A. Iron pharmacokinetics after administration of ferric-hydroxide-polymaltose complex in rats. *Arzneimittel-Forschung (Drug Research).* 1984;34(11):1560–569.

[16] Geisser, P. Iron Therapy, Oxidative Stress and Immunology. In: Chandra RK, ed. Nutrition and Immunology in the 21st Century. New Dehli (India)/Ontario (Canada): TSAR Health; 2004. p. 53–65.

[17] Geisser P, Müller A. Pharmacokinetics of Iron Salts and Ferric Hydroxide-Carbohydrate Complexes. *Arzneimittel-Forschung (Drug Research).* 1987;37:100–104.

Arzneimittel-Forschung (Drug Research) 2007;57(6a):439–452

[18] Potgieter MA, Potgieter JH, Venter C, Venter JL, Geisser P. Effect of oral aluminium hydroxide on iron absorption from iron(III)-hydroxide polymaltose complex in patients with iron deficiency anemia. A single-centre randomised controlled isotope study. *Arzneimittel-Forschung (Drug Research)*. 2007;57(6a):392–400.

[19] Potgieter MA, Potgieter JH, Venter C, Venter JL, Geisser P. Effect of oral tetracycline on iron absorption from iron(III)-hydroxide polymaltose complex in patients with iron deficiency anemia. A single-centre randomized controlled isotope study. *Arzneimittel-Forschung (Drug Research)*. 2007; 57(6a):376–384.

[20] Dietzfelbinger H. Bioavailability of bi- and trivalent oral iron preparations. *Arzneimittel-Forschung (Drug Research)*. 1987;37:107-112.

[21] Heinrich HC. Bioverfügbarkeit und therapeutische Wirksamkeit oraler Eisen(II)- und -(III)präparate. *Schweizerische Apotheker-Zeitung*. 1986;124:1231–1256.

[22] Nielsen P, Gabbe EE, Fischer R, Heinrich HC. Bioavailability of iron from oral ferric polymaltose in humans. *Arzneimittel-Forschung (Drug Research)*. 1994;44:743–748.

[23] EMEA. Note for Guidance on the Investigation of Bioavailability and Bioequivalence. London, 26 July 2001. CPMP/EWP/QWP/1401/98.

[24] Geisser P, Philipp E. True iron bioavailability and iron pharmacokinetics. *J Pharmacokinet Pharmacodyn*. Submitted.

[25] Jacobs P, Wormald LA, Gregory MC. Absorption of iron polymaltose and ferrous sulphate in rats and humans. *S Afr Med J*. 1979;55:1065–1072.

[26] Jacobs P, Johnson G, Wood L. Oral iron therapy in human subjects, comparative absorption between ferrous salts and iron polymaltose. *J Med*. 1984;15:367–377.

[27] Kaltwasser JP, Werner E, Nichzial M. Bioavailability and therapeutic efficacy of bivalent and trivalent iron preparations. *Arzneimittel-Forschung (Drug Research)*. 1987;37: 122–129.

[28] Eckenved G. Influence of food on the absorption from different types of iron tablets. *Scand J Haematol*. 1976;28:79–88.

[29] Werner E, Kaltwasser JP. Orale Eisentherapie. Intestinale Absorption und ihre Beeinflussung durch eine Mahlzeit. *Dtsch. med. Wschr*. 1977;102:1061–1064.

[30] Forth W. Iron, bioavailability, absorption, utilization. In: *Pharmakologie und Toxikologie*. Band 2. Mannheim: Wissenschaftsverlag; 1993.

[31] Potgieter MA, Pretorius SG, Jacobs YL, Venter C, Venter JL, Geisser P. Effect of an oral iron(III)-hydroxide polymaltose complex on tetracycline pharmacokinetics in patients with iron deficiency anaemia. *Arzneimittel-Forschung (Drug Research)*. 2007;57(6a):385–391.

[32] Lundqvist H, Sjöberg F. Food interaction of oral uptake of iron. A clinical trial using ^{59}Fe. *Arzneimittel-Forschung (Drug Research)*. 2007;57(6a):401–416.

[33] Funk F, Canclini, C, Geisser P. Interactions between iron(III)-hydroxide polymaltose complex and commonly used medications. Laboratory studies in rats. *Arzneimittel-Forschung (Drug Research)*. 2007;57(6a):370–375.

[34] Tuomainen TP, Nyyssönen K, Porkkala-Sarataho E, *et al.* Oral supplementation with ferrous sulphate but not with non-ionic iron polymaltose complex increases the susceptibility of plasma lipoproteins to oxidation. *Nutr Res*. 1999;19:1121–1132.

[35] Mackintosh W, Jacobs P. Response in serum ferritin and haemoglobin to iron therapy in blood donors. *Amer J Hematol*. 1988;27:17–19.

[36] Jacobs P, Fransman D, Coglan P. Comparative bioavailability of ferric polymaltose and ferrous sulphate in iron-deficient blood donors. *J Clin Apheresis*. 1993;8:89–95.

[37] Langstaff RJ, Geisser P, Heil WG, *et al.* Treatment of iron-deficiency anaemia: a lower incidence of adverse effects with Ferrum Hausmann than ferrous sulphate. *Brit J Clin Res*. 1993;4:191–198.

[38] Sas G, Nemesanszky E, Bräuer H, *et al.* On the therapeutic effects of trivalent and divalent iron in iron deficiency anaemia. *Arzneimittel-Forschung (Drug Research)*. 1984; 34:1575–1579.

[39] Schmidt BJ, Morais MB, Fisberg M, *et al.* Comparação terapêutica entre o sulfato ferroso e o ferro trivalente em forma de complexo dehidróxido férrico polimaltosado na deficiência orgânica de ferro. *Folha Med*. 1985;90:25–29.

[40] Murahovschi J, Stein ML, Caraffa RC, *et al.* Tratamento da ferropenia e da anemia ferropenica com o complexo de hidroxido de ferro polimaltosado por via oral, de crianças em fase de recuperaçao de infecçoes respiratorias. Ensaio duplo-cego, comparativo com sulfato ferroso. *Rev Paul Ped*. 1987;5:97–104.

[41] Devaki PB, Chandra RK, Geisser P. Effect of oral supplementation with iron(III)-hydroxide polymaltose complex on the immunological profile of adolescents with varying iron status. *Arzneimittel-Forschung (Drug Research)*. 2007; 57(6a):417–425.

[42] Vetter W, Steurer J. Single-centre, open, randomised, parallel-group study comparing the efficacy and tolerability of oral ferric polymaltose complex in doses of 200 mg, 400 mg and 600 mg per day. Clinical Report [internal report]. St. Gallen (Switzerland): Vifor (International) Inc.; 2000.

[43] Andrade JVD, Rodrigues PPB, Fontoura IB, D'Agnoluzzo R, Horta VF, Alves JGB. Tratamento da anemia ferropriva com hidróxido de ferro polimaltosado – Estudo multicêntrico comparativo entre tratamento ministrado com e sem alimentação concomitante. *Arq bras Med* (Suppl). 1992;66: 253–258.

[44] Rosenberg F, Frigge H, Mickan J, *et al.* Zur Resorption dreiwertigen Eisens. *Therapiewoche*. 1979;29:3325–3326.

[45] Gürer D, Olgun T, Kayaalp N, Nohoglu A. Comparison of the effectiveness of ferrous and ferric irons in the treatment of iron deficiency anaemia. Şişli Etfal Community Hospital, Department of Pediatrics (Turkey); 1998.

[46] Haliotis FA, Papanastasiou DA. Comparative study of tolerability and efficacy of iron protein succinylate versus iron hydroxide polymaltose complex in the treatment of iron deficiency in children. *Int J Clin Pharmacol Ther*. 1998; 36:320–325.

[47] Geisser P, Hohl H, Müller A. Klinische Wirksamkeit dreier verschiedener Eisenpräparate an Schwangeren. *Schweizerische Apotheker-Zeitung*. 1987;14:393–398.

[48] Beruti EJ. Oral treatment of multi-deficiency anaemias of pregnant women with a combination of ferric polymaltosate, folic acid and vitamin B_{12} [internal report]. St. Gallen (Switzerland): Vifor (International) Inc.; 1978.

[49] Mills KC, Curry SC. Acute iron poisoning. *Emerg Med Clin North Am*. 1994;12:397–413.

[50] Ten Kate J, Wolthuis A, Westerhuis B, *et al.* The iron content of serum ferritin: physiological importance and diagnostic value. *Eur J Clin Chem Clin Biochem*. 1997;35:53–56.

[51] Almache ON, Del Águila CM. Estudio controlado de dos compuestos de polimoltosado férrico en el tratamiento de anemia ferropénica en niños de 6 meses a 2 años. *Revista del AWGLA.* 2005;1:31–38.

[52] Al RA, Unlubilgin E, Kandemir O, Yalvac S, Cakir L, Haberal A. Intravenous *versus* oral iron for treatment of anemia in pregnancy: A randomized trial. *Obstet Gynecol.* 2005;106: 1335–1340.

[53] Kunz J, Billeter U, Rothe E. Multicentre open non-controlled Phase III study to document the tolerability and efficacy of Maltofer Fol as an oral solution in the treatment of iron deficiency in pregnant women and the prophylaxis of iron and folic acid deficiency in pregnant women [internal report]. St. Gallen (Switzerland): Vifor (International) Inc.; 2003.

[54] Malikova GB, Rassadina MV. The effect of the anti-anaemic drug maltofer on iron metabolism indices in breast-feeding mothers and their breast-fed infants. *Pediatriya.* 2005; 4:83–86.

[55] Soboleva MK. Iron deficiency anaemia in infants: diagnosis and present-day therapy. *Voprosy gematologii immunopatologii v pediatrii.* 2003;2:32–37.

[56] Kavakli K, Yilmaz D, Cetinkaya B, Balkan C, Sozmen EY, Sagin FG. Safety profiles of Fe(2+) and Fe(3+) oral preparations in the treatment of iron deficiency anemia in children. *Pediatr Hematol Oncol.* 2004;5:403–410.

[57] Soboleva MK. Iron-deficiency anaemia children and breastfeeding mothers and its treatment and prophylaxis with Maltofer and Maltofer-Fol. *Pediatria.* 2001;6:27–32.

[58] Kazyukova TV, Fallukh A, Levina AA, Tsaregorodtseva LV, Vykhristyuk OF, Bimbasova TA, et al. Treatment of iron deficiency anaemia in young children. *Pediatriya.* 2000;2:56–61.

[59] Soboleva MK. Efficacy of iron preparations and their side effects in the treatment of iron-deficiency anaemia in young children. *Drugs in Paediatrics.* 2004;2:1–5.

[60] Borbolla JR, Cicero RE, Dibildox MM, Sotres RD, Gutiérrez GR. Complejo polimaltosado férrico vs sulfato ferroso en el tratamiento de la anemia por deficiencia de hierro en lactantes. *Revista Mexicana de pediatria.* 2000;67:63–67.

[61] Sözmen EY, Kavakli K, Cetinkaya B, Akçay YD, Yilmaz D, Aydinok Y. Effects of iron(II) salts and iron(III) complexes on trace element status in children with iron-deficiency anemia. *Biological Trace Element Research.* 2003;94:79–85.

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