Drug Therapy

Iron Formulations in Pediatric Practice

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Iron deficiency anemia is the most widely prevalent nutritional deficiency of the world. The condition is considerably more prevalent in the developing world. Children are particularly vulnerable as iron deficiency is associated with a high risk of long-term impairment in mental and motor development. They also suffer from lower scores in IQ test, lack of concentration, short attention span and easy distractibility(1). Particularly worrying is that the developmental deficits associated with iron deficiency anemia have been shown to be irreversible(2). Children between 6 and 24 months are a particularly high-risk group for development of iron deficiency due to the low content of bioavailable iron in the weaning foods of developing countries. For this reason the National Consultation on Control of Nutritional Anemia has recommended targeting children in the age group of 6 to 24 months(3). Considering that 74 percent of children aged 6-35 months are anemic (4), implementation of these recommendations is of enormous significance. Obviously for supplementing such young children medicinal iron can be used only in liquid form as drops and syrup formulations. A recent consultation has also recommended liquid preparations (concentrated drops) as the current pediatric tablets available in the national program are difficult to administer(5). However, there is considerable confusion in deciding on a suitable liquid iron preparation in terms of (*i*) bioavailability; (*ii*) side effects; (*iii*) cost effectiveness. This communication is an attempt to resolve the issue and compares various iron salts mainly ferrous salts, ferric salts, iron amino acid chelates, iron polymaltose complex and carbonyl iron.

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Ferrous salts

All dietary iron has to be reduced to ferrous form to enter the mucosal cells. Hence bivalent iron salts like ferrous sulfate, fumarate, gluconate, succinate, glutamate and lactate have been preferred over ferric salt preparations. In addition these salts are amongst the cheapest preparations of iron available for medicinal use. Ferrous sulfate (FS) (20 % elemental iron) is commonly used for tablet preparations. However, liquid formulations of the salt are only available as elixirs in sorbitol base as syrup preparations are poorly stable (the salt is easily oxidizable in moist environment) which negates the cost advantage. Ferrous Fumarate (FF) (33% elemental iron) has a similar efficacy and GI tolerance to ferrous sulphate, is moderately soluble in water, environmentally more stable and is almost tasteless. Ferrous fumarate is less soluble than ferrous sulfate in water but is soluble in dilute acid such as gastric juice. It does not precipitate proteins and does not interfere with the proteolytic or diastatic

activities of the digestive system.

Bioavailability

These salts have uniformly good bioavailability. However, the bioavailability decreases markedly in the presence of dietary inhibitors like phytates, tannic acid *etc*. They cannot be added to other foods/milk/fortified formulas for the same reason.

Clinical efficacy

Despite being efficacious and cheap with good bioavailability, ferrous salts have several disadvantages particularly the high incidence of gastrointestinal side effects (~23 %)(6). Teeth are known to be stained with liquid preparations if the drops are not placed carefully at the back of the tongue. Ferrous sulphate has a salty astringent taste which is not palatable for most children.

Safety issues

Any over dosage of the salt can easily override the 'mucosal barrier' to cause acute toxicity [In the United States of America, The Poisons Control Center reported in 1997 that during the decade 1986-1996 there were 100,000 reports of acute iron intoxication in children under 6, underlining the possible hazards of widespread usage(7)].

Ferric salts

Ferric salts have traditionally not been preferred over ferrous salts as the ferric ion first requires reduction to ferrous form in the intestinal lumen and usually this reducing capacity is not enough to reduce doses of iron therapeutically administered. The bio-availability of iron from ferric salts is 3 to 4 times less than that of ferrous sulphate. Whereas 100 mg of ferrous sulfate iron/ day is sufficient for an optimal oral compensation iron therapy in adults and to produce initial hemoglobin regeneration rates of about 0.26 g/100 mL/day, 400 to 1000 mg of ferric iron/day are necessary for the same therapeutic effect because of the poor bioavailability of ferric iron. Ferric salts do however carry the inherent advantage of a poor poisoning potential given the limited reducing ability of the gastric contents. Other properties are essentially similar to ferrous salts. Ferric ammonium citrate (18% elemental iron) is the most commonly used of these salts.

Iron Amino-acid chelates

Iron amino-acid chelates are conjugates of the ferrous or ferric ion with amino-acids. Although numerous conjugates have been formulated the most studied of these are ferrous bis-glycinate (20% elemental iron content), ferric trisglycinate and ferrous glycine sulphate. They have no effect on the color or taste of food products.

Bioavailability

Their main advantage lies in their relatively high bioavailability in the presence of dietary inhibitors. It is theorized that the chelates prevent iron from binding to inhibitors in food or precipitating as insoluble ferric hydroxide in the pH of the small intestine(8). In a study by Fox, *et al.*(9) in infants the absorption of iron from ferrous bis-glycinate was found to be equivalent to that of ferrous sulphate-ascorbic acid combination. A recent study in adults has also demonstrated good absorption of ferrous bisglycinate (5-6 times higher) in the presence of phytates from maize(10).

Clinical efficacy

Comparison of ferrous sulphate with ferrous bisglycinate in infants of 6 to 36 months of age showed equivalent rise in hemoglobin in the two groups(11)(*Table I*). However, the group receiving ferrous

TABLE I: *Randomized Control Studies Comparing the Clinical Efficacy of Various Iron Salts.*

Author/ Year/ Country	Salt	Age	Sample size	Study design	Outcome parameters	Results
Ashmead, *et al*. 2001 Latin America(11)	Ferrous bisglycinate	6 to 36 mo.	40	RCT: Two groups: FeSO4 vs. FBG @ 5 mg/kg for 28 days	Hemoglobin and Ferritin	Both groups had significant hemoglobin - ($p < 0.001$); group treated with FBG had significant - ($p < 0.005$) in plasma ferritin. Iron bioavailabilities were 26.7% for $FeSO_4$ and 90.9% for FBG.
Szarfarc, *et al*. 2001 Brazil(33)	Ferrous bisglycinate (FBG)	Pregnant Women	145 (n=71 vs. n=74)	RCT: Two groups: FeSO4 40 mg/d vs. FBG 15 mg/day for a min. of 13 weeks	Hemoglobin, transferrin saturation and serum ferritin	Iron depletion was found in 30.8% of the women treated with ferrous bisglycinate and in 54.5% of the women that consumed ferrous sulfate. Higher non-compliance rates were seen with ferrous sulphate.
Aronstam et al 1982 UK(12)	Ferrous Glycine sulphate	adults	40	RCT-crossover: Ferrous fumarate or FGS for 4 weeks after which they were switched to the other drug	Hemoglobin, PCV and MCV	Significant - in Hb, PCV and MCV were similar. In 3 patients, side effects were severe with ferrous fumarate with interruption of treatment in 2 and withdrawal from the study in the other. FGS group had no withdrawal of treatment.
Sozmen, *et al*. 2003 Turkey(18)	Iron Polymaltose complex (IPC)	8-168 mo.	25 (n=14 vs n=11)	RCT: Two groups: FeSO4 vs. IPC @ 6 mg/kg for 3 mo. f/b 3 mg/kg for 3 mo.	Hemoglobin, Serum Iron, Plasma Cu, ceruloplasmin & Zinc	Hematological parameters showed equivalent rise in the two groups. Copper and ceruloplasmin metabolisms were affected by ferrous iron supplementation.
Jacobs, *et al.* 1993 South Africa(34)	Iron Polymaltose complex (IPC)	Healthy blood donors	159 (Gp1:51; Gp2: 53; Gp3: 55)	RCT: Three groups: FeSO4 @ 60 mg OD vs. IPC @100 mg OD vs. IPC @ 100mg BD	Hemoglobin, %age transferrin saturation, serum ferritin	80% of patients in Groups 1 & 3 reached normal Hb levels by 12 weeks, compared to 50% in Gp. 2. Similarly, the proportion of patients improving their transferrin saturation to normal was significantly better in Groups 1 & 3 than in Gp. 2 ($P < 0.01$). However serum ferritin level, was better in Group 1 ($p < 0.01$); there was no difference in this respect between Groups 2 & 3
Devasthali,. *et al.* 1991 India(26)	Carbonyl iron	Healthy blood donors	49	RCT: Two groups FeSO4 vs Carbonyl iron	Hb,MCV, Retic. count, platelet count, se iron, TIBC, transferrin saturation or FEP	Mean values for hemoglobin concentration, mean corpuscular volume, corrected reticulocyte count, platelet count, serum iron, total iron-binding capacity, transferrin saturation or erythrocyte protoporphyrin did not differ significantly between the two groups throughout the study. After 16 weeks of therapy, the mean increase in hemoglobin iron was similar in both groups ($p = 0.2$). Estimates of net

TABLE I Contd'... *Randomized Control Studies Comparing the Clinical Efficacy of Various Iron Salts.*

Author/ Year/ Country	Salt	Age	Sample size	Study design	Outcome parameters	Results
						changes in total body iron suggested that the overall bioavailability of carbonyl iron was high, about 70% that of ferrous sulfate.
Gordeuk VR, *et al.* 1990 Ohio, USA(25)	Carbonyl iron	18-40 years-Women	99	RCT: Two groups: 100 mg carbonyl iron vs. placebo for 56 days	Hb, net iron absorption, rates of deferral from repeat donation	At Day 56, estimated net iron absorption from therapy or diet, or both, was sufficient to replace iron in 85 percent of those receiving carbonyl iron but in only 29 percent of those taking placebo (p less than 0.001). The rates of deferral from repeat donation were 8 percent in the carbonyl iron group and 36 percent in the placebo group ($p < 0.01$).
Gordeuk VR, *et al.* 1987 Ohio, USA(29)	Carbonyl iron	Menstrua-ting women	75	RCT: 3 groups: 1) carbonyl iron 600 mg; 2) FeSO4, 300 mg (60 mg Fe++); or 3) placebo, each given TDS *1wk	Hb, MCV, FEP, Se ferritin, Se iron, TIBC, and %age sat. of TIBC	The prevalence of gastrointestinal side effects was similar in both groups taking iron. At the end of the study there was no laboratory evidence of change in iron status in women who received carbonyl iron (n = 15). In those treated with ferrous sulfate (n = 17) the mean TIBC increased ($p < 0.001$), and in the placebo group (n = 19) there were decreases in mean MCV (p less than 0.01), serum ferritin ($p <0.001$), and per cent saturation ($p = 0.027$) with an increase in mean TIBC ($p = 0.004$).

Note: Only RCTs involving comparison with placebo group or other iron salts are included in this Table.

bisglycinate had a higher rise in serum ferritin. Also, a lesser incidence of side effects was observed in this group. Ferrous glycine sulphate (FGS) is the only salt of this group available in India. An adult study using this salt(12) showed equivalent rise in hemoglobin, packed cell volume and mean corpuscular volume with FGS and FF. No studies in children were found on Medline search. Cost considerations offer a frequently voiced objection to the general use of these salts.

Safety issues

These conjugates have low pro-oxidant properties thereby limiting free radical damage and are environmentally stable(13). Also mixtures with other micronutrients and vitamins lose less vitamin B_2 and B_6, retinol, ascorbic acid and vitamin K compared to FS(14). Formal tests carried out in accordance with the US-FDA guidelines have documented a No Observable Adverse Effect Level (NOAEL) of at least 500 mg per kg rat body weight, the highest dose tested. This and other results of the detailed toxicity test, as well as other tests of safety and efficacy, have resulted in the US-FDA acknowledging that this product is Generally Recognized as Safe (GRAS)(15).

Iron (III) Polymaltose Complex (IPC)

IPC is a novel iron preparation, which contains non-ionic iron and polymaltose in a stable complex.

Bioavailability

IPC and FS have been demonstrated to have equivalent bioavailability in infants(16). Absorption of IPC is not affected by food or milk, enabling administration without consideration of the timing of feed. Also, to date there are no reports of any interactions with foods or medicines(17).

Clinical efficacy

The usefulness of IPC in the treatment of IDA has recently been a topic of much debate. In a recent trial in 2003 comparing IPC with FS in 25 children aged 8-168 months the two preparations were found to cause equivalent increases in hemoglobin and iron levels(18). Also IPC was found to have no deleterious effect on copper and zinc levels while children supplemented with FS were found to have lower plasma copper levels after one month of supplementation(18). In addition, there are no reports that it stains the teeth as has been observed with FS. Further the incidence of side effects is reported to be lower with IPC. A non- blinded randomized trial of 543 patients found a lower rate of stomach related side effects in the IPC group (12.2 % vs. 27.2 %; $p < 0.001$)(19).

However, there are several reports of inadequate or slower rise in hemoglobin. In 1993 in study by Langstaff, *et al*.(20) Hb rise was significantly higher with ferrous sulphate as compared to IPC after 3 and 6 weeks of treatment but similar after 9 weeks. In a recent report by Mehta, *et al*.(21) where over a period of sixteen months, 27 patients diagnosed to have IDA failed to respond to IPC given for 4-52 weeks and later responded to ferrous fumarate in 4-13 weeks. Similar data was obtained by Nielsen, *et al*.(22) and Hierich, *et al*.(23).

Safety issues

Iron of IPC is absorbed in the intestine through a self-limiting competitive interchange of ligands, so that the intestinal transport system is saturated in case of over dosage. Accidental intoxication with IPC is therefore rarely seen. Muller, *et al*. observed that the LD_{50} of FS is 350 mg/kg, while the LD_{50} of IPC could not be recorded even at doses of over 2000 mg/kg(24).

Carbonyl Iron

Carbonyl iron is a small particle preparation of highly purified metallic iron. 'Carbonyl' describes the process of manufacture of the iron particles (from iron pentacarbonyl gas). Given the small particle size (<5 mcm) the stomach acid solubilizes this iron. In the process of this solubilization H+ ions are consumed thereby increasing the pH. Also, as a result the absorption of iron is slow (permitting continued release for 1 to 2 days) and self limited by the rate of acid secretion by the stomach mucosa.

Bioavailability

As a food fortification, carbonyl iron has been shown to be well absorbed and utilized in hemoglobin synthesis, both in experimental animals and in humans(25). Its advantages include lack of change in color or taste of the foodstuff and environmental stability.

Clinical efficacy

In a trial by Devasthali et al(26) in female adults after 16 weeks of therapy, the mean increase in hemoglobin was similar with carbonyl iron and FS ($p = 0.2$). Estimates of net changes in total body iron suggested that the overall bioavailability of carbonyl iron was high, about 70% that of ferrous sulfate. In similar trials using high-dose and low-dose carbonyl iron the preparation was found to be effective and safe in prevention and treatment of iron deficiency with lesser side effects compared to FS(27). Similar trials have been conducted in menstruating women(28).No studies in children were found on Medline search.

Safety issues

Carbonyl iron is much less toxic than ionized forms of iron. In humans the lethal dose of FS is ~ 200 mg/kg. Toxicity studies of carbonyl iron in animals demonstrated a lethal dose of 50,000 to 60,000 mg/kg (compared to 200 mg/kg of FS). In a recent case series no serious toxicity was reported in all 33 patients with mean carbonyl iron ingestions of 11.2 mg/kg(29).

Other iron formulations

As regarding colloidal iron, despite extensive literature search, no data is available. Several other iron preparations are in various stages of development or being gradually phased out. Prominent in the latter group are heme based preparations. Hemoglobin as a source of iron was promoted on the basis of the high bioavailability of heme iron. However the iron content of hemoglobin is 0.34 %. As a result 300 mg of hemoglobin is required to deliver 1 mg of elemental iron which leads to large volumes and inhibitory costs.

Newer preparations under study include ferrous oxalate, microencapsulated ferrous sulphate and microencapsulated ferrous fumarate. Ferrous oxalate has been recently found to have good efficacy and low toxicity in studies conducted on piglets(30). Recently, a supplement containing microencapsulated ferrous fumarate (plus ascorbic acid) has been developed which can be sprinkled on any complementary food at the table given by the caregiver. Iron being encapsulated does not change the color and taste of the food and has been found to be equally bioavailable to FS(31). Similarly, a ferrous sulphate preparation microencapsulated with phospholipids was found to have equivalent bioavailability to $FeSO_4$(32).

Are any oral iron formulations better than ferrous sulfate?

In addition to the relative advantages and side effects already considered in the above sections, other factors which may be considered a part of the discussion include the

relative biological value, cost considerations and commercial availability. These are compared in *Table II.*

Conclusion

In terms of efficacy all available iron preparations are effective though timing of response may vary. Iron amino acid chelates offer the most advantages theoretically. However the only congener available (FGS) has not been extensively studied and is twice as costly as FS. IPC has been proven to have lesser side effects but the efficacy and response rates have been questioned. Carbonyl iron has not been evaluated extensively in children but if extrapolated

TABLE II–*The Relative Biological Value, Cost With a Few Illustrative Brands of Various Iron Salts.*

Type of iron	Relative biological value#	%age absorption@	Elemental Iron (mg)	Pack (ml)	Shelf life (years)	Cost for 100 mg elemental iron (Rs.)	Brand
Drops							
IPC	–	46.6%	50/ml	10	2	4	Fevorit
Colloidal Iron	–	–	25/ml	15	1	7.2	Tonoferron
Ferrous Glycine Sulphate	–	–	7.8/ml	30	2	5.4	Fezocar
Syrup							
Fer. Ammonium citrate	86	15.5%	20/ml	15	2	6	Dexorange, Richfer Plus
IPC*	–	46.54%	50/5 ml	150	2	2	Fevorit, Vitcofol.com, Trifer, Orofer,
Ferrous fumarate	93	–	33/5 ml	200	1.5	2.5	Vitcofol, Hemsi
Colloidal Iron	–	–	80/5 ml	200	1	2	Tonoferron Ped Syrup
Ferrous Sulph	100	47.74%	33.4/5 ml	100	1.5	2	Fesovit
Ferrous glycine sulphate	–	–	50 /5ml	200	2	3	Hemfer-A
Carbonyl iron	70	–	50 /5 ml	200	2	1.8	Ferox, Fexid, Feresis

* Commercially available other IPC preparations (*e.g.*, ferium, orofer, ferose have similar pricing and composition).

\# RBV=Iron utilization from test sample * 100/ iron utilization from FeSO4

@ % age Iron absorption=[(mg Fe intake-mg Fe in feces)*100]/mg Fe intake

NB:Additives variable in preparations; IPC has long shelf life (2-5 yrs); Addition of B12 in formulations reduces shelf life to <2 yrs.

form adult data it is safe and effective. Unfortunately none of the recently available iron salts has been adequately studied in the Indian setting either individually or in comparison.

In terms of cost-effectiveness amongst the available drop preparations there is no advantage of one over the others. However for syrup preparations ferrous salt based products are marginally cheaper. Large-scale production of ferrous sulfate based liquid preparations may bring down the cost substantially especially if a cheaper base can be identified.

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