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CONVENTIONAL AND NEWER ORAL IRON PREPARATIONS

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ABSTRACT

Iron deficiency anaemia is a major health problem world wide. In India, prevalence of anaemia is very high. Oral iron therapy is the commonest treatment of this disease .Large number of iron salts is available in market for oral iron therapy. In clinical practice oral iron supplementation commonly used are Fe sulfate, Fe fumarate. These conventional iron preparations have more gastrointestinal intolerance but are cheap. There are many new iron salts marketed (Fe bisglycinate, Carbonyl iron, Iron polymaltose complex etc) which claim to have low gastrointestinal intolerance, increase Hb level faster and improve iron stores better than conventionally used iron salts. This review is aimed towards collection of information about conventional and newer oral iron preparations. Literature search is done by using internet, text books of Pharmacology and Medicine and Journals available in medical college library.

The newer preparations do have less side effects, but are very costly and there are many studies which shows controversy with these newer preparations, which should be further evaluated. Thus conventional iron preparations still can be considered as best cost effective choice with tolerable side effects for prophylaxis and treatment of iron deficiency anaemia.

Key words: ferrous fumarate, ferrous bisglycinate, carbonyl iron, iron polymaltose complex.

INTRODUCTION

The use of iron therapy refers back to the time when ancient physicians prescribed it in a hope to develop the strength of steel by drinking water or wine in which sword was been rusted. The use of iron is mentioned in Greek mythology, in the story of Iphiclus, who was cured of impotence by drinking iron rust dissolved in wine[1].

As we know iron deficiency anaemia is a major problem worldwide. Iron deficiency in India has multifactorial etiology like poverty, ignorance, helminthiasis, amoebiasis, diarrhea, malabsorption, multiple pregnancies. In clinical practice a patient of iron deficiency anaemia (mild to moderate) responds readily to treatment with oral iron supplementation. Commonly Fe sulfate, Fe fumarate, Fe gluconate are used, but common adverse drug reactions found with these preparations are mainly gastrointestinal intolerance like nausea, vomiting, constipation, diarrhea, abdominal pain[2].

Now different new iron salts are marketed which claim to have low gastrointestinal intolerance, therefore better patient compliance. Few of these newer preparations also claim to increase haemoglobin level faster and as well as improve the iron storage better than conventionally used ferrous sulfate and ferrous fumerate.

1)Conventional oral iron preparations

In 1832 Blaud introduced iron therapy in the form of what came to be called "Blaud's" pills, containing ferric carbonate as its main constituent[3]. After that it was observed that, ferrous iron was better absorbed than ferric iron. To this day practically all medicinal iron preparations contain ferrous compounds. Ferrous sulfate, fumarate and gluconate are commonly used. Other iron compounds previously or still in use include ferrous succinate, lactate, glycine sulfate, glutamate, citrate, tartarate, colloidal ferric hydroxide.

The most common iron salt used for oral administration is ferrous sulfate, It is known to produce intestinal side effects (nausea, vomiting, constipation, bloting) in many users. Ferrous fumarate and gluconate have less gastrointestinal side effects and are readily absorbed than ferrous sulfate[4].Ferrous succinate is claimed to be more completely absorbed, but is more expensive and has no advantage over ferrous fumarate and ferrous sulfate[5]. Ferrous calcium citrate has very low iron content and does not supply adequate elemental iron unless several tablets are taken which is inconvenient for the patient. Colloidal ferric hydroxide has high elemental iron(52.26%).As iron is in colloidal form undergoes ready conversion to soluble form by the action of gastric acid and is easily reduced to ferrous form by mucoproteins available in the secretions of the stomach and small intestine, This might be assuring its greatest and better absorption with minimal gastric irritation.

2) Newer oral iron preparations

Iron polymaltose complex(IPC)- Among ferric iron preparations, iron polymaltose complex has very poor bioavailability, but recent studies suggest that IPC has less adverse reactions than ferrous sulfate and can be considered as a useful alternative formulation for the treatment of iron deficiency anaemia in pregnant women who cannot tolerate other iron preparations(ferrous form)[6,7].Contradictory to above reports B.C Mehta in his study had quoted several reports showing ineffectiveness or poor effectiveness of IPC[8].Thus therapeutic efficacy of IPC is questionable and is 4 to 5 times costlier than other iron salts.

Ferrous bisglycinate- Fe bisglycinate is a amino acid chelate.When ferrous iron reacted with glycin (smallest of all amino acid) forms a bisglycinate chelate, which is more stable. This higher stability of amino acid chelate prevents the molecule from being destroyed in the gut, produces less G I irritation and also due to its atomic structure and chemistry it protects the ferrous iron from undesirable chemical reactions in the stomach and intestine that limit iron absorption. Thus absorption of bisglycinate is not reduced in presence of phytates. In different studies ferrous bisglycinate has shown a greater efficacy than conventional iron, in reducing iron deficiency and iron deficiency anaemia in very short-term treatment with significant low doses and has high bioavailability and regulation[2,9],but are very costly.

Carbonyl iron- Carbonyl iron is a small particle preparation of highly purified metallic iron, "Carbonyl" refers to the manufacturing process in which the controlled heating of vaporized iron pentacarbonyl leads to the deposition of unchanged elemental iron as microscopic spheres of diameter less than 5µ .The stomach acid solubilizes this iron. In the process of this solubilization, H+ ions are consumed, there by increasing the pH and as a result the absorption of iron is slow but complete (permitting continued release for 1to3 days) with less side effects. The slow absorption decreases chance of toxicity if tablets are consumed accidentally by child[10]. Iron poisoning is the second commonest cause of accidental poisoning among small children. Other studies also suggest that overall bioavailability of carbonyl iron is high with less side effects than conventional iron preparations[11,12].

Na-Feredetate- Pankaj sarkate et al in their study concluded that this new formulation effectively increases Hb profile and is tolerated well[13].

The percentage of elemental iron in various preparations varies with the molecular weight of the iron compounds.

Table-1 Percentage and amount of iron in some commonly used oral iron preparations[5,14].

Preparation	Iron compound (mg/tab)	Elemental iron mg/tab (%)
Fe-sulfate(hydrous)	300	60 (20%)
Fe-sulfate(dried)	200	65 (32.5%)
Fe-fumarate	200	66 (33%)
Fe-gluconate	300	36 (12%)
Fe-succinate	100	35 (35%)
Fe-bisglycinate	300	60 (20%)
Carbonyl iron	100	98 (98%)
Na-feredetate	231	33 (14%)

Current status of oral iron therapy

Indications

I)Prophylactic:- Supplementation with medicinal iron has the advantage of producing rapid improvements in iron status. It can be targeted at the population groups in greatest need of iron or at greatest risk of becoming iron deficient.

1)**Pregnant women**;- Pregnant women is a priority group for iron supplementation, as anaemia in pregnancy may lead to increase in morbidity and mortality in both mother and fetus and cause premature labor. The supplementation should occur primarily during the second half of pregnancy, when iron requirement is greatest.

2)**Infants**;- Iron supplementation should be started in full term infants by 4 months in a dose of 1mg/kg/day and in preterm infants by 2 months of age in a dose of 2mg/kg/day.

3)**Children**;- In rapidly growing children (pre school and school children) a 2-3 week course based on a lower dose between 30-60mg elemental iron daily(in tablet or liquid form) several times a year, is needed

Other risk groups where iron supplementation is needed are menstruating women, professional blood donors and patients operated for partial gastrectomy.

II) Therapeutic;- Oral iron is also used for treatment of iron deficiency anaemia due to nutritional deficiency, anaemia of infancy and pregnancy, anaemia due to acute or chronic blood loss as in menorrhagia, peptic ulcer and hook worm infestation, chronic piles etc.

Dosage forms.

Uncoated (compressed) tablets are sugar coated tablets. These are the least expensive formulations and disintegrate well in the stomach. However, they become oxidized over time and hence less effective especially in humid climate.

Some dosage forms of ferrous sulfate are enteric coated to delay tablet dissolving and prevent some intestinal side effects, but some studies showed that, enteric-coated iron preparations show poor clinical efficacy probably due to poor absorption[15].

There are many gastric-delivery systems (GDS), available for iron supplementation. This is a bioadhesive polymer such as cross-linked polyacrylic acid, when incorporated in a tablet allows it to adhere to the gastric mucosa or epithelium. GDS release iron slowly but continuously in stomach and hence eliminate gastrointestinal side effects and reducing the administration frequency of an iron supplement to once daily. This dosage form is very costly.

There are many iron-containing syrups and liquid preparations (drops) available. They are useful for administration to infants and children, who are unable to swallow solid preparations. Usually they are expensive, deteriorate in storage, and contain minerals and vitamins that are unnecessary for most patients. Liquid formulations may stain teeth and makes faeces black due to formation of iron sulfide and gives metallic taste.

Combinations with other nutrients.

During pregnancy, women tend to become deficient in both iron and folate. It is therefore desirable to combine both haematinics in one tablet. The addition of folic acid (400µg) to ferrous sulfate(60mg of elemental iron) may be justified in certain cases like pregnancy. As ascorbic acid is a known enhancer of iron absorption from intestine, it has been incorporated in many iron preparations. Addition of at least 200mg ascorbic acid increases medicinal iron absorption by about 30%[16].

There are many other preparations of iron which contain different vitamins and trace elements. These types of preparations are called short gun therapy of anaemia. They are irrational preparations as there is no added advantage and cost is very high. A technical advisory board (India) has recommended that B-complex vitamins and zinc should not be included in iron, folic acid containing haematinic preparations. When iron and zinc supplements are given together in a water solution and without food, greater doses of iron may decrease zinc absorption[17].

Dosage

Erythropoietic activity following iron administration is directly related to the severity of anaemia. The best absorption of therapeutic iron occurs during the first few weeks of treatment. The first month of therapy would thus appear to be the most important time for ensuring the success of treatment. A positive response to treatment can be defined as a daily increase in haemoglobin concentration of 0.1g/dl from the forth day onwards. Although the response in terms of haemoglobin concentration is virtually complete after two months, iron therapy should continue for another two or three months to build up iron stores[5].

For adolescents and adults the recommended dose is 200mg elemental iron (infant and children 3-5mg/kg) given daily in 2 or 3 divided doses. Prophylactic dose is 30-60mg iron daily. For pregnant women WHO recommends that all pregnant women be supplemented with 60mg iron daily in pill that also contain 400µg folic acid given after eight weeks of pregnancy[18].[The higher dose(100mg) in Indian women is required as they start pregnancy with low or absent stores due to poor nutrition and frequent infections like hook worm and malaria[19].

Recently there are many studies, showing comparison of daily versus weekly iron supplementation (in pregnant and lactating women) They concluded that weekly supplementation is simple, economical, with less side effects and recommended to adopt the strategy for controlling anaemia[20]. This should be further evaluated in a larger trial.

Untoward effects of oral iron preparations[21].

The oral administration of iron can cause gastrointestinal side-effects in some individuals such as epigastric discomfort, nausea, vomiting, constipation, and diarrhoea. The frequency of these side-effects is directly related to the dose of iron or % of elemental iron in tablet. In addition, iron consumed with a meal is better tolerated than when it is taken on an empty stomach, although the amount of

iron absorbed is reduced. Liquid preparations may cause blackening of teeth and makes faeces black due to formation of iron sulfide and metallic taste.

The major reason for the failure of iron therapy is non-compliance due to the side-effects caused by an excessively high initial dose of iron. In cases of gastrointestinal intolerance, it is vital not to discontinue therapy. Rather, the dose of iron should be reduced and then gradually increased again until the full dose is reached and is well tolerated. If slow-release preparations are available and affordable, they should be used. With plain tablets, the frequency of side-effects can be reduced if the patient takes them with meals. Take a reduced dose with an absorption promoter e.g. ascorbic acid and can try an alternative iron salts which has less gastric intolerance.

Iron poisoning.

After aspirin, the second commonest cause of accidental poisoning among small children is iron.[22] Most deaths occur in children, particularly 12 to 14 months. As little as 1 to 2 gm of iron may cause death. The colored sugar coating of many commercially available tablets may attract the child and he may consume them. So should be kept away from their reach.

Pharmacoeconomic evaluation.

There are very few studies who have done cost effective analysis and found that, there is vast difference in cost of conventional and newer iron preparations. Conventional iron preparations are cheaper and newer iron preparations are 4to5 times costlier than conventional iron preparations[6].

Fortification of staple food with iron.

One of the strategies to overcome the problem of high prevalence of iron deficiency in developing countries is to fortify food products with iron. A project for salt Fortification was done by Food and Nutrition Board of government of India in collaboration with the National institution. However this was done only in field trials in few places and has to be implemented further. However fortification of food is accompanied with unsolved problems such as unacceptable taste, colour, stability and bioavailability of iron. The most difficult challenge is to find the ideal combination of iron fortification compound and food vehicle[23].

Recently there are many studies where newer iron preparations are used for iron fortification. The study by Hertrampf F and Olivares M concluded that Fe bisglycinate is better absorbed from milk, wheat, whole maize flour and precooked conflour than ferrous sulfate[24].Fortification of bisglycinate was also tried with water. Study by Hallerg L, where carbonyl iron was used to fortify wheat flour, showed that bioavailability of carbonyl iron was low[25]. Other compound which is also used for fortification is Na feredetate.

The main limitations to the widespread use of newer iron preparations in national fortification programs are the cost and the potential for promoting organoleptic changes in some food matrices[26]. Additional research is required to establish the bioavailability of different iron preparations in different food matrices.

CONCLUSION

There are many new oral iron preparations available in market today, claimed to have less adverse effects and having more efficacy. After literature search through journals, it was found that there are lot of controversial reports about efficacy of these new iron preparations. Conventional preparations like Fe sulfate, Fe fumarate though having gastritis as side effect can be minimized by taking it with food. After going through cost analysis of conventional and newer oral iron preparations it was found that newer oral iron preparations are 4-5 times costlier than conventional oral iron preparations. Thus conventional preparations still can be considered as best cost effective choice with tolerable side effects for prophylaxis and treatment of iron deficiency anaemia. Also most difficult challenge is to find the ideal combination of iron fortification

compounds and food vehicle and should be further implemented.

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