Analysis of haematinic preparations available in Indian pharmaceutical market

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Abstract:

Iron deficiency anaemia is a major health problem worldwide. In India, prevalence of anaemia is very high (51% among non-pregnant women and 87% among pregnant women)\(^1\). Iron deficiency in India has multifactorial etiology like poverty, ignorance, helminthiasis, amoebiasis, diarrhoea, malabsorption, and multiple pregnancies. Haematinics are drugs used for the treatment and prevention of anemia. In clinical practice a patient of iron deficiency anaemia responds readily to treatment with iron supplementation. Large numbers of iron salts are available in market for iron therapy, the majority of which are proprietary multi-drug combinations\(^2\). The haematinics market in India is currently worth around Rs. 900 crores and is growing at 15% per annum.\(^3\)

The objective of this study was to analyze the haematinic formulations available in Indian market for their varieties of dosage forms, iron salts used, content of elemental iron, frequency of administration required, presence of additional nutrients, rationality, and cost.

Only 34% of haematinic formulations fit into the definition of rational formulation. Indian drug market is flooded with various combinations of drug formulations, the majority of which are proprietary multi-drug combinations and most of the patients are being made to ingest totally unnecessary drugs. So it is an urge to the drug regulation authorities to pay attention towards rationality of these drug formulations so as to reduce the cost of therapy and also to improve the quality of treatment.
INTRODUCTION:

Iron deficiency anaemia is a major health problem worldwide. In India, prevalence of anaemia is very high (51% among non-pregnant women and 87% among pregnant women)\(^1\). Iron deficiency in India has multifactorial etiology like poverty, ignorance, helminthiasis, amoebiasis, diarrhoea, malabsorption, and multiple pregnancies. Haematinics are drugs used for the treatment and prevention of anemia. In clinical practice a patient of iron deficiency anaemia responds readily to treatment with iron supplementation. Large numbers of iron salts are available in market for iron therapy, the majority of which are proprietary multi-drug combinations\(^2\). The haematinics market in India is currently worth around Rs. 900 crores and is growing at 15% per annum.\(^3\)

Haemopoiesis requires adequate supplies of minerals like iron, cobalt and copper; vitamins like folic acid, vitamin B12, vitamin C, pyridoxine, riboflavin; and various haematopoietic growth factors\(^4\). Each of these is effective individually in specific types of anaemia, but there is rampant and indiscriminate use of several of these agents simultaneously, without first determining their applicability to the case at hand. The rationality of such combinations is questionable. Combination of iron with other nutrients increases the cost as well as the frequency of side effects and hence leads to noncompliance\(^5\). The Drugs Technical Advisory Board (DTAB) of India has recommended that vitamin B complex and zinc should not be included in iron- and folic acid–containing haematinic preparations.\(^6\)

OBJECTIVE:

The objective of this study was to analyze the haematinic formulations available in Indian market for their varieties of dosage forms, iron salts used, content of elemental iron, frequency of administration required, presence of additional nutrients, rationality, and cost.

MATERIALS AND METHODS:

In this observational study, detailed information about the haematinic formulations was obtained from the Indian Drug Review (IDR) issue 1, 2012. The formulations were classified into the following categories: (A) Oral solid formulations, (B) Oral liquid formulations, and (C) Parenteral formulations. Each category was further subdivided into formulations containing:

- Iron salts alone
- Iron salts + folic acid + others (vitamins, minerals, essential amino acids and other chemicals)
- Iron salts + folic acid + vitamins C + others
- Iron salts + others
If information about the type of iron salt, quantity, and cost were not available, such formulations were not included for the cost analysis. Information about the additional nutrients, various types of dosage form and iron salts available in both solid and liquid oral formulations were also noted.

We found that the formulations containing iron salts alone were very few. Apart from deficiency of iron, deficiency of folic acid is also a common cause of anemia and also the National nutritional anemia prophylaxis program advises to provide iron along with folic acid. Besides, vitamin C is known to increase absorption of iron by facilitating its transport into intestinal cells. Hence allowing the inclusion of folic acid and vitamin C as a compromise, formulations having iron salts ± folic acid ± vitamin C were considered as "rational formulations".

A variety of substances designed to enhance the absorption of iron has been marketed, including surface-acting agents, carbohydrates, inorganic salts, liver extract, aminoacids and vitamins. However they are expensive and offer no obvious benefits. Several studies have found that addition of zinc or zinc plus other vitamins and minerals to iron salts have failed to have any additional benefit over and above iron plus folic acid in enhancing iron status or anemia. Thus iron preparations containing iron salts along with other vitamins, minerals, etc., were considered as “irrational formulations”.

It is important to note that the amount of elemental iron present in the iron preparation is important and not the amount of salt used.

With the knowledge of percentage of elemental iron in various iron salts used, the elemental iron content in the iron preparations will be calculated. The percentage of elemental iron in various preparations varies with the molecular weight of the iron compounds. Percentage of Elemental Iron in commonly used oral iron preparations is shown in Table: 1

<table>
<thead>
<tr>
<th>Iron Salts</th>
<th>Percentage of elemental iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulphate. Anhydrous</td>
<td>37</td>
</tr>
<tr>
<td>Ferrous sulphate</td>
<td>20</td>
</tr>
<tr>
<td>Ferrous Fumarate</td>
<td>33</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>12</td>
</tr>
<tr>
<td>Ferrous fructose</td>
<td>25</td>
</tr>
<tr>
<td>Ferrous succinate</td>
<td>23</td>
</tr>
<tr>
<td>Ferrous lactate</td>
<td>19</td>
</tr>
<tr>
<td>Ferrous carbonate</td>
<td>16</td>
</tr>
<tr>
<td>Ferrous glycine citrate</td>
<td>23</td>
</tr>
<tr>
<td>Iron choline</td>
<td>12</td>
</tr>
<tr>
<td>Ferric sulphate</td>
<td>27</td>
</tr>
<tr>
<td>Ferric ammonium citrate</td>
<td>18</td>
</tr>
<tr>
<td>Colloidal iron</td>
<td>50</td>
</tr>
<tr>
<td>Ferrous bisglycinate</td>
<td>20</td>
</tr>
<tr>
<td>Carbonyl iron</td>
<td>98</td>
</tr>
<tr>
<td>Sodium feredetate</td>
<td>14</td>
</tr>
</tbody>
</table>

Table: 1 Percentage of elemental iron in various iron salts
For comparison of cost, only the elemental iron content was taken into consideration since the elemental iron available from different iron salts differs significantly and the response (increase in hemoglobin) depends on the elemental iron available. The recommended therapeutic dose of iron is 100–200 mg elemental iron daily in three divided doses \(^6,15^\) and, hence, the cost of 100 mg of elemental iron available from each formulation was calculated. To find out whether the difference between the minimum and maximum cost value was due to differences in the iron salts present, we classified rational oral formulations according to the various iron salts present and calculated the average cost of the different iron salts. The average cost of rational iron formulations was calculated and compared with that of irrational ones.

To provide 100 mg of elemental iron per day in not more than three doses, the formulation should deliver approximately 33 mg elemental iron per dose. Hence, we also separated out those formulations which contained less than 33 mg elemental iron per dose. Analysis was done with the help of simple proportion method.

RESULTS:

Totally, 511 formulations were listed in the IDR as haematinics. Of these, 287 were oral solid formulations (Category A), 202 were oral liquid formulations (Category B), and 22 were parenteral formulations (Category C).

Information about the type of iron salt, its amount or its price was not mentioned in the IDR for certain formulations and these were therefore not considered for the cost analysis. Thus, from category A (solid oral), 26 formulations were dropped and from category B (liquid oral) and C (parenteral), 22 and 4 formulations were not included for cost analysis, respectively.

Several dosage forms were available for oral solid iron preparations, viz, capsules (138), tablets (112), film coated tablet (15), soft gelatin capsule (13), chewable tablet (7), sub-lingual tablet (1) and sustained release capsule (1). Among the oral liquids, the syrup form (158) was the most common, followed by drops (22), and suspensions (22). The dosage forms available for parenteral formulations were ampoules and vials.

As shown in Table 2, there were only 5 solid oral iron preparations containing iron salts alone. Among the liquid formulations there were 34 preparations. There were 2 solid oral preparations containing folic acid alone. As many as 71% of the solid oral preparations, 65% of the liquid oral preparations and 9% of parenteral iron formulations were classified as irrational. (Figure 1)
The range of cost (minimum and maximum cost value) of solid oral iron formulations for providing 100 mg elemental iron was Rs. 1.2 to Rs. 92.5, for liquid oral formulations it was Rs. 3.74 to Rs. 160, and for parenteral formulations it was Rs. 55 to Rs. 675.

Among the rational solid oral formulations containing iron salts alone, the cost ranged from Rs. 6.6 to Rs. 37.8, for those having iron with folic acid, the cost ranged from Rs. 6 to Rs. 43.8 and for those having iron with folic acid and vitamin C the range was Rs. 19 to Rs. 70. In the case of rational liquid oral formulations containing iron salts alone, the cost ranged from Rs. 5.8 to Rs. 54.3, for those having iron with folic acid the cost was Rs. 6.12 to Rs. 60.85 and for those having iron with folic acid and vitamin C the range was Rs. 8 to Rs. 43.3. Among rational parenteral formulations containing iron salts alone the cost was Rs. 150 to Rs. 675.

Table: 2 Iron Formulations
Table: 3 Average costs of Irrational and Rational formulations

<table>
<thead>
<tr>
<th>FORMULATIONS</th>
<th>IRRATIONAL (Rs)</th>
<th>RATIONAL (Rs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral- solid</td>
<td>13.25 (n=189)</td>
<td>25.5 (n=72)</td>
</tr>
<tr>
<td>Oral- liquid</td>
<td>16.8 (n=115)</td>
<td>27.3 (n=65)</td>
</tr>
<tr>
<td>Parenteral</td>
<td>56 (n=2)</td>
<td>295 (n=16)</td>
</tr>
</tbody>
</table>

As compared to the costs of irrational solid formulations (range: Rs.1.2 to Rs.92.5), the costs of rational solid formulations (range: Rs.6 to Rs.70) was in a significantly narrow range (p<0.0001); however, the average cost of rational products was significantly higher than that of the irrational ones (p<0.0001). Comparison of the average cost of irrational iron formulations with that of rational ones is shown in Table 3.

The most common iron salt found in solid oral preparations was carbonyl iron. Among the liquid oral preparations, it was ferric ammonium citrate and among the parenteral formulations iron sucrose was the common iron salt. (Figure 2 & 3) Comparison of the average cost of different iron salts of category-A formulations containing iron with folic acid shows that with salts like ferrous ascorbate, ferrous glycine sulphate, ferric hydroxide polymaltose complex, iron polysucrose, ferrous bisglycinate, sodium feredate, ferric ammonium citrate and ferrous gluconate the cost ranges from Rs. 11.5 to Rs. 43.1, whereas with iron salts like ferrous sulphate, ferrous succinate, carbonyl iron, and ferrous fumarate the cost was between Rs. 4.3 to Rs. 26.7.

We found that 53 out of 287 oral (solid) iron formulations would require administration more than 3 times a day to provide the 100 mg of elemental iron necessary for therapeutic purposes.
DISCUSSION:

Iron deficiency anaemia is the most common type of anaemia overall and it has many causes. India is among the countries with highest prevalence of anaemia in the world. The most economical and effective medication in the treatment of iron deficiency anaemia is the oral administration of iron supplements.

In our study, among the 511 iron formulations found in IDR 2012, 287 were oral solid formulations, 202 were oral liquid formulations and 22 were parenteral formulations. As many as 71% of the solid oral preparations, 65% of the liquid oral preparations and 9% of the parenteral preparations were classified as irrational (Figure 1).

Most of the formulations were classified under iron with folic acid and others subgroup. There were only 5 solid oral iron preparations and 34 liquid oral iron formulations containing iron salts alone. The list of other nutrients other than folic acid and vitamin C added in various haematinic formulations was quite long:

- Vitamins: Vitamin A, D, E, K, B-complex, pantothenic acid, biotin
- Minerals and other chemicals: zinc, copper, manganese, calcium, sodium, potassium, iodine, selenium, magnesium, phosphate, molybdate
- Essential amino acids like histidine, lysine, glycine
- Miscellaneous nutrients like protein, carbohydrate, dioctyl sodium sulfo succinate, haemoglobin, succinic acid, liver extract, yeast, alcohol, sorbitol, lycopene, menadione, tricholine citrate, docusate, lactate

Many iron preparations 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. There has been concern that the nutrients other than iron in the multiple micronutrients (MM) supplements could interfere with the absorption of iron and, therefore, these supplements are not as efficacious in treating anaemia. Studies have shown that iron absorption is poor in the presence of other minerals such as calcium, magnesium, and zinc. Three randomized controlled trials (RCT) from Tanzania, Mexico and Nepal have found that multiple micronutrients did not improve hematologic indicators when compared to patients who received iron-folic acid supplements.
Various forms of preparations were available including tablets, capsules, syrups, suspension, drops, film coated tablets, slow release tablets and chewable tablets, etc. Uncoated tablets and sugar coated tablets are least expensive and well absorbed. Iron in slow release form is supposed to reduce the side effects of iron therapy. Side effects of oral iron therapy are few and experienced by a very small minority. Absorption of iron is maximum from the duodenum and hence absorption of iron from prolonged release preparations is reduced as iron is released lower down in the gut. The cost of these sustained-action preparations is comparatively high. Slow release preparations, thus, are more expensive and less effective. Liquid preparations were in the form of syrups and drops. These are expensive and deteriorate on storage, but are useful for administration to infants and children who cannot swallow tablets. They usually lead to temporary staining of teeth and tongue which disappears on discontinuation of the drug.²

Carbonyl iron, which is commonly found among solid oral formulations, is a small particle preparation of highly purified metallic iron. Several studies suggest that overall bioavailability of carbonyl iron is high with less side effects than that of conventional iron preparations²⁴,²⁵. The most common salt found in liquid oral preparations, Ferric ammonium citrate is claimed to have good GI tolerability, but is less effective, as ferric salts are poorly absorbed than ferrous salts.⁶ Iron sucrose which is commonly found in parenteral preparations is a complex of poly nuclear ferric hydroxide in sucrose. It is effective, better tolerated and does not require test dose.⁴

Among the various iron salts, ferrous salts are preferred as they are better absorbed than ferric forms. There is no significant difference in absorption when a ferrous salt of iron is given in the form of sulphate, gluconate, lactate, fumarate or succinate, but iron is poorly absorbed in the form of carbonate, citrate and pyrophosphate, in ferric forms, colloidal iron preparations and as iron carbohydrate complexes.² Formulations containing iron salts like ferrous sulphate, carbonyl iron, and ferrous fumarate were cheaper than formulations containing other newer iron salts. Preparations of ferrous ascorbate, ferrous glycine sulphate, ferric hydroxide polymaltose complex, ferrous biglycinate were 4–5 times costlier than other iron salts.

The cost of solid oral formulations ranged widely from Rs. 1.2 to Rs. 92.5, the cost range of rational formulations narrowed significantly. Among the rational solid oral formulations containing iron with folic acid, the cost for 100 mg elemental iron ranged between Rs. 6 to Rs. 43.8. However the average cost of rational products was significantly higher than that of the irrational ones, except in the case of parenteral preparations.
Formulations containing less than 33 mg elemental iron require more than three administrations per day, and this can adversely affect patient compliance.

CONCLUSION:

Rational drug use is; “obtaining the appropriate drug in suitable duration and dosage, at the lowest price and with ease according to the clinical findings and personal characteristics”. Only 34% of haematinic formulations fit into the definition of rational formulation. Indian drug market is flooded with various combinations of drug formulations, the majority of which are proprietary multi-drug combinations and most of the patients are being made to ingest totally unnecessary drugs. So it is an urge to the drug regulation authorities to pay attention towards rationality of these drug formulations so as to reduce the cost of therapy and also to improve the quality of treatment.

References:


