CHAPTER 6

PHARMACOLOGY OF FERROUS FUMARATE

The oral treatment of iron deficiency anaemia with inorganic salts of iron occasionally results in gastrointestinal distress, and massive doses produce necrosis of the gastric mucosa and liver. Attempts were, therefore, made to find out less toxic forms of iron for oral therapy and it has led to the introduction of the ferrous gluconate and ferrous succinate, and more recently the ferrous fumarate. Thus, ferrous fumarate, an organic iron compound, is a new contestant in the field of oral ferro-therapy.

PROPERTIES

Ferrous Fumarate is an anhydrous salt of a combination of ferrous iron and fumaric acid (ethylene-1:2-
dicarboxylic acid). It is highly stable, reddish brown, odourless, almost tasteless, micro-crystalline powder containing 32.5 to 33 per cent of Elemental Iron (ferrous form) as compared with 31 to 33 per cent in exsiccat ferrous sulphate. It is not readily oxidised in air, and can be put up in uncoated tablets. Ferrous fumarate's colour and resistance to oxidation indicate that it is not a simple ionic combination of ferrous and fumarate ions. The empirical formula of ferrous fumarate is $\text{FeC}_4\text{H}_2\text{O}_4$.

**ABSORPTION AND UTILIZATION**

Ferrous fumarate is quickly absorbed in the alimentary tract and is utilised effectively. The haemoglobin rise is well within the expected range of response. Available data, though limited, indicates that the drug is probably as effective for this purpose as other orally administered ferrous compounds. Thus, it may be expected to produce an adequate rise in haemoglobin levels and a satisfactory increase in haematocrit value in patients with iron deficiency anaemia.

**SIDE EFFECTS**

Ferrous Fumarate is usually well tolerated orally, and does not produce gastric or intestinal disturbances.
quite so frequently as many other oral iron preparations. Nevertheless, at least 4 per cent of the patients are reported to have a mild or severe gastro-intestinal symp­toms, sometimes with severe sickness, though very few have had to discontinue its use on this account. Few patients have complained of slight epigastric discomfort and mild constipation.

Some of the patients occasionally experience the gastro-intestinal disturbances like anorexia, nausea, vomiting, cramping, diarrhea and constipation which are so typical of orally administered iron salts. These compl­ints are generally mild and tend to subside as the therapy is continued. However, in some instances ferrous fumarate may be used satisfactorily in patients unable to tolerate other iron preparations given orally.92

Some of the workers thought that Ferrous Fumarate in therapeutic doses cause alimentary bleeding and hence stressed the importance, in certain cases, of a search for occult blood loss from the gastro-intestinal tract. The problem of the effect of oral iron on tests for occult blood loss in the stools is a vexed one, and a review of the medical literature of last 50 years on this subject reveals an extraordinary and inexplicable divergence of opinion. However, in the last decade, it has been generally accepted that oral iron does not give false positive
results with such tests, and therefore, the investigation and treatment of iron deficiency patients may proceed together. Illingworth (1959), using the Benzidine test and the Orthotoluidine test in vitro as well as in vivo, confirmed that this is a correct procedure with all oral iron preparations except ferrous fumarate because the test for occult blood gives a positive result with the faeces of a normal patient on a meat-free diet who is receiving ferrous fumarate orally. These findings were supported by Swan and Jowett (1959) and also by Holliday and Cuthill (1960).

However, the carefully controlled work of Cumming and Nutt (1962) and of Blumgart and Bowen (1963) has provided conclusive evidence that Ferrous Fumarate in therapeutic doses does not cause alimentary bleeding.

TOXICITY

The toxic effects of Ferrous Fumarate on laboratory animals as well as on human subjects have been studied by Berenbaum, Child, Davis, Sharpe, Tomich and Chalmers (1959).

A. Animal Studies:

1. Acute oral Toxicity in Mice.

The LD₅₀ values (i.e. the dose that will kill half the number of animals) were as follows:
TABLE NO. 3

RELATIVE TOXICITIES OF DIFFERENT ORAL IRON COMPOUNDS

<table>
<thead>
<tr>
<th>Iron compound</th>
<th>LD$_{50}$(mg. Fe/kg.)</th>
<th>Relative toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Ferrous Fumarate</td>
<td>630</td>
<td>1.0</td>
</tr>
<tr>
<td>b. Ferrous Succinate</td>
<td>560</td>
<td>1.1</td>
</tr>
<tr>
<td>c. Ferrous Gluconate</td>
<td>320</td>
<td>2.0</td>
</tr>
<tr>
<td>d. Ferrous Sulphate</td>
<td>230</td>
<td>2.7</td>
</tr>
</tbody>
</table>

2. Emetic Activity in Cats:

The dose of ferrous fumarate required to produce vomiting was three times greater than the equivalent doses of the other three iron preparations.\(^{14}\)

3. Irritant Effects on Gastric Mucosa in Rabbits:

Rabbits given large doses of ferrous sulphate tablets developed severe gastric necrosis and chemical hepatitis. Ferrous gluconate produced similar but less intense effects, whereas ferrous succinate and ferrous fumarate usually cause little or no inflammatory reaction.\(^{14}\)

Thus, it is obvious that the acute toxicity of ferrous fumarate in experimental animals is low.

B. Human Studies:

No such toxic effects were observed in human subjects who were treated with the therapeutic doses
cf ferrous fumarate. The tablets were acceptable to all the patients. Thus, ferrous fumarate is supposed to be well tolerated clinically.

INDICATIONS

Ferrous Fumarate is employed clinically for the treatment of iron deficiency anaemia in which it is supposed to give equally effective haematological responses as other oral iron compounds. Such anaemias are commonly seen in infancy or pregnancy in which the demand for iron is increased or in situations in which there is a deficient intake of iron or an excessive loss of iron as in haemorrhage or heavy menstrual flow. Thus, it is clear that the preparation is indicated for the prophylaxis and treatment of iron deficiency anaemias in infants as well as in adults.

CONTRAINDICATIONS

As with all drugs of this class, ferrous fumarate is contraindicated in cases of peptic ulcer, regional enteritis, and ulcerative colitis. It is also contraindicated in patients with unusual sensitivity to orally given iron salts and in such cases preparations which are suitable for parenteral use should be employed.
Thus, as such there are no special contra indications for ferrous fumarate but an occasional patient may have to discontinue its use on account of very severe gastro-intestinal irritation and nausea.

**PREPARATIONS**

Ferrous fumarate is manufactured under various trade names like Fersamal, Fumaron, Firon, Hemoton and Toleron.

It is available in tablet form as well as in liquid form:

(a) Uncoated tablets of 200 mg. and 324 mg. Each 200 mg. of the drug is equivalent to about 65 mg. of elemental iron.

(b) Sweetened aqueous suspension containing 100 mg. per teaspoonful (3.5 ml.).

**DOSAGE**

Ferrous Fumarate is administered orally. The recommended effective dosage for adults is 1 tablet (200 mg.) or 7 ml. of the syrup three times daily, but double these doses can be given and are well tolerated. For infants it is 1/2 to 1 teaspoonful (1.75 to 3.5 ml. containing 50 to 100 mg.) three times daily.
1. Ferrous Fumarate contains a high percentage of Elemental Iron and is substantially free from ferric iron.

2. The iron contained in Ferrous Fumarate is very stable and is therefore not readily oxidised in the atmospheric air.

3. Ferrous Fumarate tablets do not require sugar coating because they are resistant to oxidation.

4. Uncoated tablets permit rapid disintegration of the tablets when ingested.

5. Ferrous Fumarate tablets, which disintegrate so rapidly in the mouth, may thereby make a material contribution to the treatment of those patients who cannot swallow tablets and who have formerly had to take liquid iron preparations (which may rapidly oxidise, generally stain the teeth and are distasteful) or parenteral iron preparations (which are less economic, painful and hazardous).

6. If a tablet of Ferrous Fumarate is sucked, it leaves a very slightly unpleasant taste which classes it apart from sweets, but there is no metallic astringent
sansation or 'iron taste' which characterises the uncoated tablets of most of the iron compounds.

7. Ferrous Fumarate is probably as effective as other oral iron preparations and produces an adequate rise in haemoglobin levels.

8. Ferrous Fumarate makes available an iron preparation which has a very low incidence of gastro-intestinal side effects, which, when present, are mild.

9. Ferrous Fumarate is said to be particularly suitable and safe for administration in infants because of the low incidence of side effects.

10. Ferrous Fumarate Tablets which are light brown in colour do not resemble sweets thus preventing accidental intake of these tablets by children because they are not likely to be attracted by the appearance and flavour of the tablet-coating.