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Research Article

A CLINICAL PHARMACOLOGICAL STUDY OF QUANTITATIVE SPECIFIC SYMPTOMATOLOGYIN GLOBAL ANAEMIC PATIENTS, AND PHARMACOVIGILANCE EVALUATION OF FERROUS ASCORBATE SUPPLEMENTS

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ABSTRACT

Introduction: Anaemia, especially during adolescence, pregnancy and lactation, is associated with extreme weakness, impaired immune system, preterm delivery, low birth weight, and maternal and perinatal morbidity and mortality. It can be controlled by oral haematinicsupplements like ferrous ascorbate, ferrous fumarate, ferrous sulphate or ferric ammonium citrate which tends to rise the haemoglobin concentration.
Objectives: The objective of this clinical pharmacological study was to assess the quantitative specific symptomatology in global anaemic patients, and a pharmacovigilance safety evaluation of ferrous ascorbate supplements.
Methods: A multi-centre, prospective, open-labelled study on25mild to early moderate grades, global anaemic patients, was performed. The occurrence of specific symptoms among global anaemic patients, that is, weakness and skin pallor, and the detailed specific anaemic symptoms assessment, were recorded and analysed according to their types of occurrences. A pharmacogenomic safety analysis was also conducted, after the treatment of these patients with oral ferrous ascorbate supplements, containing 60 mg of elemental iron, once daily, with meals, for 3 months, in accordance with the followed haematinic treatment regimens, and the respective grades of anaemia, from which the patientswere suffering. The monitoring of adverse drug reactions occurrence, like epigastric pain, heartburn, nausea, vomiting, staining of teeth, metallic taste, bloating, colic, diarrhoea and constipation, was done among the patients, with Adverse Event Case Report Forms, on days 0, 30, 60, 90, and on further follow-ups.
Results: In this study, most of the anaemic patients manifested the specific symptoms of weakness and skin pallor together. The safety assessment showed that the occurrence of adverse effects was statistically non-significant.
Conclusions: Co-existing specific symptomatology of weakness and skin pallor was predominant. Ferrous ascorbate was safe and tolerable among all the anaemic patients.

INTRODUCTION

Anaemia, especially during adolescence, pregnancy and lactation, is associated with extreme weakness, impaired immune system, preterm delivery, low birth weight, and maternal and perinatal morbidity and mortality. Iron deficiency is the most common nutritional cause of microcytic, hypochromic anaemia. Iron is an essential component of myoglobin; haeme enzymes such as the cytochromes, catalase, and peroxidase; and the metallo-flavoprotein enzymes, including xanthine oxidase and the mitochondrial enzyme α-glycerophosphate oxidase. Iron deficiency has been associated with behavioural and learning problems in children, abnormalities in the metabolism in muscle, catecholamine metabolism and impaired heat production. The ubiquitous role of iron has led to widespread studies on early and accurate detection of iron deficiency and its prevention. It can be controlled by oral haematinic supplements like ferrous ascorbate, ferrous fumarate, ferrous sulphate or ferric ammonium citrate which tends to rise the haemoglobin concentration.[1, 2, 3]

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The average daily iron requirement for an infant is 67 mg/kg, for a child is 22 mg/kg, for a male adolescent is 21 mg/kg, for a female adolescent is 20 mg/kg, for a male adult is 13 mg/kg, for a female adult is 21 mg/kg and for a mid-to-late pregnancy is 80 mg/kg.[2, 4]

The average iron requirements for pregnancy includes 170 mg for external iron loss, 450 mg for expansion of red cell mass, 270 mg of foetal iron, 90 mg of iron in placenta and cord, and 150 mg for blood loss at delivery.[2, 4]

OBJECTIVE

The objective of this clinical pharmacological study was to assess the quantitative specific symptomatology in global anaemic patients, and a pharmacovigilance safety evaluation of ferrous ascorbate supplements.

METHODS

Ethical Approval

At first, the clearance and the approval from the Institutional Ethics Committee were obtained. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practices, contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, ICH-E6 and ICH-E17, and incompliance with the global regulatory requirements. The patients who were included in the study were assured confidentiality, and an informed consent was obtained from each individual.

Selection Criteria of the patients

Thepatients were selected based on the inclusion and theexclusion criteria given below, and the patients fulfillingthese criteria, were included in the study.

Inclusion Criteria

(i) patients with mild or moderate iron-deficiency anaemia,(ii) women patients aged 13-32 years of age, (iii) patients with haemoglobin concentration more than or equal to 7gm/dl, (iv) patients not using any previous iron supplements, and (v) WHO definitions and criteria for anaemia.

Exclusion Criteria

(i) less than 13 years and more than 32 years, (ii) patients presenting with severe anaemia, (iii) patients with a history of hypersensitivity to the iron supplements, (iv) high risk pregnancies, (v) cardiac, renal or any other associated complications, (vi) any chronic disease intervening with the study data, (vii) patients suffering from gastrointestinal diseases, like peptic ulcer, regional enteritis and ulcerativecolitis (viii) haemosiderosis, (ix) bacterial infections, (x)haemochromatosis, (xi) haemolytic anaemia, and (xii)repeated blood transfusions.

Study Population

The study was conducted on 25 mild to early moderate grades, global anaemic adult male patients, and female patients who were not pregnant or lactating.

Study Design

It was a multi-centre, prospective, open-labelled, and analytical study.

Study Period

This research study and the compilation of the study literature was conducted within a span of 1 year, that is, November, 2012 to April, 2013, and from July, 2021 to February, 2022.

Place of Study

The place of this research study and the compilation of the study literature were the Departments of Pharmacology, Clinical Pharmacology, Rational Pharmacotherapeutics, Pharmaco-Haemo-Vigilance, Internal Medicine, Cardiology, Obstetrics, Gynaecology and Reproductive Endocrinology, and Pathology, in Dr.MoumitaHazra's Polyclinic AndDiagnostic Centre, Hazra Nursing Home, Mamata Medical College, Rama Medical College and Research Centre, J. J. M. Medical College, and Mahuya Diagnostic Centre.

Study Procedure

In this study, 25 anaemic patients were prescribed oral ferrous ascorbate supplements, containing 60 mg of elemental iron, once daily, with meals, for 3 months, in accordance with the followed haematinic treatment regimens, and the respective grades of anaemia, from which the patients were suffering. Assessment of patients' participation and adherence to treatment (including patients who completed the study thoroughly, number of drop-out patients due to adverse effects, patients who were lost to follow-up and patients who withdrew voluntarily) was done. A detailed history was obtained with the proforma. The patients' present and past history, obstetric and gynaecological history for female patients, family history, personal history, socio-economic and reproductive history, and medication history, were recorded. The occurrence of specific symptoms among global anaemic patients, that is, weakness and skin pallor, and the detailed specific anaemic symptoms assessment, were recorded and analysed according to their types of occurrences. Complete generalphysical examination and systemic examination, in cludingobstetric and gynaecological examination, were performed. Then, thorough haematological evaluations were made. The patients' demographic characteristics, (duration ofsymptoms, pulse rate, respiratory rate and severity ofanaemia, mild or early moderate grade), and safety assessment (by recording the occurrence of epigastric pain, heartburn, nausea, vomiting, staining of teeth, metallictaste, bloating, colic, diarrhoea and constipation onappropriate Adverse Event Case Report Forms), the follow-updetails, and their haemoglobin concentration improvement on 1st,2nd, 3rd months and follow-up visits, were recorded and thoroughly analysed.

A pharmacovigilance safety analysis was also conducted, after the treatment of these patients with oral ferrous ascorbate supplements, by the monitoring of adverse drug reactions occurrence, like epigastric pain, heartburn, nausea, vomiting, staining of teeth, metallic taste, bloating, colic, diarrhoea and constipation, with Adverse Event Case Report Forms, on days 0, 30, 60, 90, and on further follow-ups.

Biostatistical Analysis

The research findings were statistically analysed by the test of significance and p-value, and subsequent tabular representations.

RESULTS

In this study, among 25 anaemic patients, 21 or 84% patients manifested the specific symptoms of both weakness and skin

pallor together; 4 or 16% patients had only weakness; 0 or 0% patients had only pallor; and 0 or 0% patients had no weakness as well as no pallor, as depicted in Table 1, thus, marking the pre-dominance of occurrence of both weakness and skin pallor together, as the type of occurrence of specific symptomatology, within these mild to early moderate grade anaemic patients.

Table 1 Specific Symptomatology Occurrence of Mild to Early Moderate Anaemia

Serial no.	Specific symptoms of anaemia	Number of patient occurrence	Percentages of patient occurrence
1.	Weakness only	4	16%
2.	Skin Pallor only	0	0%
3.	Both Weakness and Skin Pallor	21	84%
4.	No Weakness or Skin Pallor	0	0%

The safety assessment showed that only 1 patient had mild metallic taste, as an adverse effect, after ferrous ascorbate treatment, as depicted in Table 2, but this adverse effect completely disappeared within 24 hours of completing the ferrous ascorbate treatment. Therefore, the occurrence of adverse effects was statistically non-significant.

Table 2 Occurrence of Adverse Effects of Ferrous Ascorbate and Their Frequency

Serial No.	Adverse Drug Reactions of Ferrous Ascorbate Treatment	Number of patient occurrence	p-Value
1.	Epigastric pain	0	Non-significant
2.	Heartburn	0	Non-significant
3.	Nausea	0	Non-significant
4.	Vomiting	0	Non-significant
5.	Staining of teeth	0	Non-significant
6.	Metallic taste	1	Non-significant
7.	Bloating	0	Non-significant
8.	Colic	0	Non-significant
9.	Diarrhoea	0	Non-significant
10.	Constipation	0	Non-significant

DISCUSSION

In this study, most of the anaemic patients manifested the specific symptoms of weakness and skin pallor together. The safety assessment showed that the occurrence of adverse effects was statistically non-significant.

In the developed countries, the normal adult diet contains ~6 mg of iron per 1000 calories, providing an average daily intake for adult men of between 12 and 20 mg and for adult women of between 8 and 15 mg. The average dose for the treatment of iron-deficiency anaemia is ~200 mg of iron per day (2-3 mg/kg), given in three equal doses of 60-65 mg; half the average adult dose for children weighing 15-30 kg; small children and infants can tolerate relatively large doses of iron, like 5 mg/kg. These doses are a compromise between the desired therapeutic action and the toxic effects. Prophylaxis and nutritional iron deficiency may be managed with modest doses. For prevention of iron deficiency in pregnant women, doses of 15 to 30 mg of iron per day are adequate to meet the 3 to 6 mg daily requirement of the last two trimesters. To treat iron-deficiency anaemia, where the circumstances do not demand haste, a total dose of ~100 mg (35 mg three times daily) may be used. For patients who require maximal therapy to encourage a rapid response or to counteract continued bleeding, as much as 120 mg of iron may be administered 4 times a day. Sustained high rates of red-cell production require an uninterrupted supply of iron, and oral doses should be spaced equally to maintain a continuous high concentration of iron in plasma. The duration of treatment depends upon the rate of recovery of haemoglobin (Hb) (which depends on the severity of anaemia) and the desire to create iron stores.

An anaemic patient treated with 25 mg of iron per day would respond with a rise of 1% of Hb (0.15 g Hb/100 ml) per day; and the reticulocyte response would occur between 4 and 12 days. An increase in the Hb of at least 2 g/dl after 3 weeks of therapy is a reasonable criterion of an adequate response. Thus, an individual with Hb of 50 g/l may achieve a normal complement of 150g/l in ~50 days, whereas an individual with Hb of 100 g/l may take only half that time. The creation of stores of iron requires many months of oral iron administration. The rate of absorption decreases rapidly after recovery from anaemia, and after 3-4 months of treatment, stores may increase at a rate of not much more than 100 mg/month. Much of the strategy of continued therapy depends on the estimated future iron balance. Patients with an inadequate diet may require continued therapy with low doses of iron. If the bleeding has stopped, no further therapy is required after the Hb has returned to normal. With continued bleeding, long-term, high dose therapy is indicated.[2, 4, 5, 6, 7, 8, 9, 10, 11, 12]

Intolerance to oral preparations of iron primarily is a function of the amount of soluble iron in the upper gastrointestinal tract. Adverse effects of oral haematinics include heartburn, nausea, upper gastric discomfort, and diarrhoea or constipation. The best way of treatment is to initiate therapy at a small dosage, to demonstrate freedom from symptoms at that level, and then gradually to increase the dosage to that desired. Nausea and upper abdominal pain are very common at high dosage. Constipation and diarrhoea, perhaps related to iron-induced changes in the intestinal bacterial flora are not more prevalent at higher dosage, nor is heartburn. For liquid iron therapy, the iron solution must be placed on the back of the tongue with a dropper to prevent transient staining of teeth. The normal individual is able to control absorption of iron despite high intake, and it is only individuals with underlying disorders that augment the absorption of iron who run the hazard of developing iron overload in haemochromatosis.[2, 4, 6, 7, 8, 9, 10, 11, 12]

Parenteral iron therapy should be used only when clearly indicated because acute hypersensitivity, including anaphylactoid reactions, can occur in 0.2-3% of patients. Other reactions to intravenous iron include headache, malaise, fever, generalized lymphadenopathy, arthralgias, urticaria, and in some patients with rheumatoid arthritis, exacerbation of the disease.[2, 4]

Therefore, this clinical pharmacological study would certainly remain a significant milestone in the innovative medical progress towards the development of more appropriate, more efficacious, safer, more obtainable and more economic oral haematinics, in the days to come.

CONCLUSION

Thus, this research study concluded that the co-existing specific symptomatology of weakness and skin pallor was predominant; and ferrous ascorbate was safe and tolerable among all the anaemic patients.

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