e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2022; 12(3); 44-52

Original Research Article

A Molecular Pharmacokinetic Study on the Comparative Pharmacological Response and Patient Adherence to Ferrous Ascorbate, Ferrous Sulphate, Ferrous Fumarate and Ferric Ammonium Citrate: An Analytical Evidence-Based Clinical Research

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Received: 02-01-2022 / Revised: 29-01-2022 / Accepted: 22-02-2022
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Conflict of interest: Nil

Abstract

Background: Anaemia is a global health concern, during adolescence, pregnancy and lactation, controlled by oral haematinics, like ferrous ascorbate, ferrous fumarate, ferrous sulphate and ferric ammonium citrate.

Objectives: This analytical evidence-based clinical research was conducted for the molecular pharmacokinetic study on the comparative pharmacological response and patient adherence to ferrous ascorbate, ferrous sulphate, ferrous fumarate and ferric ammonium citrate, in tertiary patient healthcare hospitals.

Materials and Methods: 100 anaemic patients, who were treated for moderate iron-deficiency anaemia, were prescribed oral haematinics, such as, ferrous ascorbate, ferrous sulphate, ferrous fumarate and ferric ammonium citrate containing 60 mg of elemental iron, once to thrice daily, with or after meals. The comparative pharmacological response of the patients to the prescribed oral haematinics was evaluated by the efficacy assessment by measurement of haemoglobin concentration improvement and safety assessment, on 1st, 2nd, 3rd months and follow-up visits, and also the percentage rate of recovery. A comparative 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.

Results: The comparative pharmacological response of the patient to the prescribed oral haematinics, comprised of 100% patient recovery rate, high efficacy and safety of the patient. The comparative patient adherence to the treatment was very high.

Conclusions: This molecular pharmacokinetic study concluded that there was high patient recovery rate and patient adherence, thus emphasising on the effectiveness of the oral haematinics.

Keywords: Oral haematinics, Ferrous ascorbate, Ferrous fumarate, Ferrous sulphate, Ferric ammonium citrate, Patient recovery rate, Molecular pharmacokinetics, Patient response, Patient adherence, Evidence-Based Medicine.

Introduction

Anaemia is a global health concern, during adolescence, pregnancy and lactation, associated with cardiovascular complications, multi-system involvement, increased maternal and perinatal mortality, preterm delivery, low birth weight, extreme fatigue and impaired immune system; and controlled by oral haematinics, like ferrous ascorbate, ferrous fumarate, ferrous sulphate.

Objectives:

This analytical evidence-based clinical research was conducted for the molecular pharmacokinetic study on the comparative pharmacological response and patient adherence to ferrous ascorbate, ferrous sulphate, ferrous fumarate and ferric ammonium citrate, in tertiary patient healthcare hospitals.

Methods:

Ethical Approval:

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of 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 in compliance with the global regulatory requirements. Informed consent was obtained from each patient, before the study.

Inclusion Criteria:

The inclusion criteria were as follows:

(i) patients with moderate iron-deficiency anaemia, (ii) women patients aged 18-35 years of age, (iii) patients with haemoglobin concentration more than or equal to 9 gm/dl, (iv) patients not using any previous iron supplements, and (v) World Health Organisation definitions and criteria for anaemia.

Exclusion Criteria:

The exclusion criteria were as follows:

(i) less than 18 years and more than 35 years, (ii) patients presenting with mild or 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 ulcerative colitis (viii) haemosiderosis, (ix) bacterial infections, (x) haemochromatosis, (xi) haemolytic anaemia, and (xii) repeated blood transfusions.

Study Type:

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

Study Population:

The study population was 100 patients, who were treated for moderate iron deficiency anaemia.

Study Period:

The study period, for this research study project and the compilation of the study literature, was 9 months, from June, 2021 to April, 2022.

Place of Study:

The place of study was the departments of Pharmacology, Clinical Pharmacology, Rational Pharmacotherapeutics, Evidence-Based Medicine, Clinical Medicine, Internal Medicine, and Obstetrics and Gynaecology of Gouri Devi Institute of Medical Sciences and Hospital, Mamata Medical College and Hospitals, Rama Medical College Hospital and Research Centre, Rama University, Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, and Hazra

Polyclinic And Diagnostic Centre and Hi-Tech College of Nursing.

Methodology:

100 anaemic patients, who were treated for moderate iron-deficiency anaemia, were prescribed oral haematinics, such as, ferrous ascorbate, ferrous sulphate, ferrous fumarate and ferric ammonium citrate containing 60 mg of elemental iron, once to thrice daily, with or after meals, according to the progress of the disease, treatment regimen scheduling, occurrence or non-occurrence of adverse drug reactions and prognosis of the patient. The pharmacological response of the patients to the prescribed oral haematinics was evaluated by the efficacy assessment by measurement of haemoglobin concentration improvement and safety assessment, on 1st, 2nd, 3rd months and follow-up visits, and also the percentage rate of recovery. 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. Complete general physical examination and systemic examination, including obstetric and gynaecological examination, were performed. Then, thorough haematological evaluations were made. The patients' demographic characteristics, (duration of symptoms, pulse rate, respiratory rate and severity of anaemia, mild or moderate), efficacy assessment (by haemoglobin concentration improvement), safety assessment (by recording the occurrence of epigastric pain, heartburn, nausea, vomiting, staining of teeth, metallic taste, bloating, colic, diarrhoea and constipation on appropriate Adverse Event Case Report Form), the follow-up details, and their haemoglobin concentration improvement on 1st, 2nd, 3rd months and follow-up visits, were recorded and thoroughly analysed. The percentage rate of recovery of the patients were recorded on 1st, 2nd and 3rd months and follow-up visits.

Statistical Analysis:

The study data was statistically analysed with test of significance and various percentages, with subsequent graphical illustrative representations.

Qualitative Analytical Research Study:

A qualitative analysis of the retrieved literature derived from a thorough literature review from various available literature databases was also performed, to delineate the molecular pharmacokinetic characterisation of oral haematinics, like ferrous ascorbate, ferrous sulphate, ferrous fumarate and ferric ammonium citrate.

Results:

In this study, the overall percentage recovery rate of the patients was 100%, as depicted in Table 1 and Figure 1, and in all the 100 patients treated with oral haematinics, such as, ferrous ascorbate, ferrous sulphate, ferrous fumarate and ferric ammonium citrate, containing 60 mg of elemental iron, once to thrice daily, with or after meals, moderate iron deficiency anaemia was controlled, with a gradual significant rise in haemoglobin concentration, in the successive 3 months. Adverse effects were negligible and statistically non-significant among all the patients, as depicted in Tables 2a, 2b, 2c, 2d and Figure 2. Tolerability was good for the oral haematinics in all the patients. All the patients completed the study thoroughly. There were no drop-out patients due to adverse effects, none was lost to follow-up and none withdrew voluntarily. The patients' adherence to treatment was very high, as depicted in Figure 3.

Table 1: Percentage Recovery Rate of Anaemic Patients with Oral Haematinics

ORAL HAEMATINICS	PATIENT PERCENTAGE RECOVERY RATE
Ferrous ascorbate	100%
Ferrous sulphate	100%
Ferrous fumarate	100%
Ferric ammonium citrate	100%

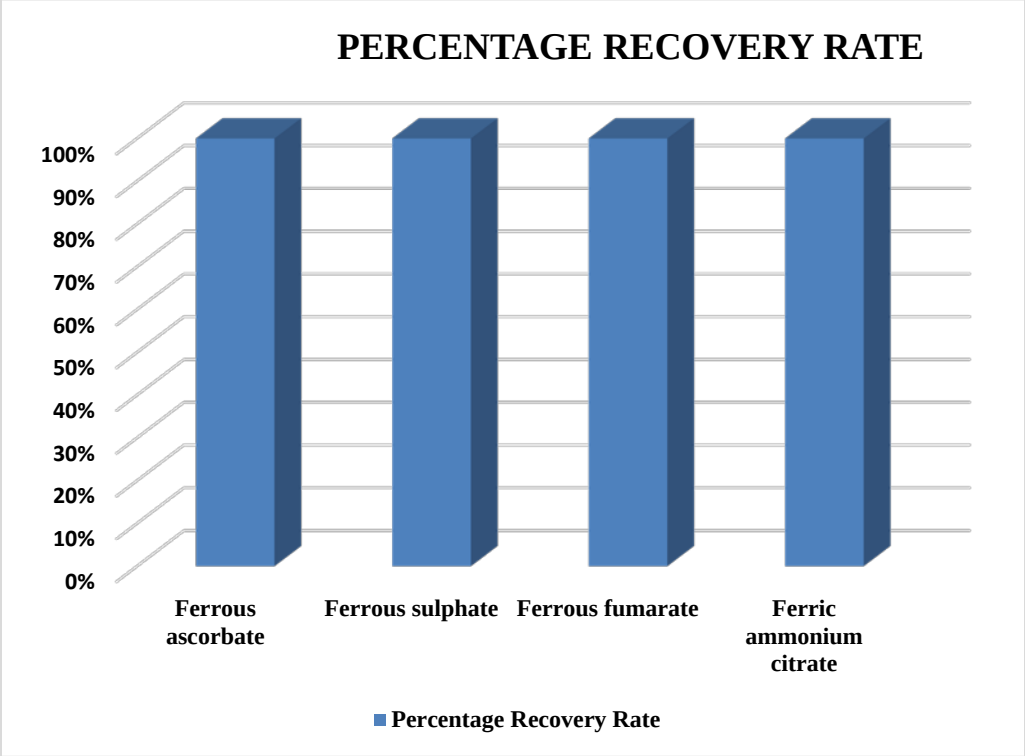

Figure 1: Percentage Recovery Rate of Anaemic Patients with Oral Haematinics

Table 2a: Occurrence of Adverse Drug Reactions with Ferrous Ascorbate

ADVERSE DRUG REACTIONS WITH FERROUS ASCORBATE	NUMBER OF PATIENTS HAVING THE ADVERSE DRUG REACTION	p-VALUE
Epigastric pain	0	Non-significant
Heartburn	0	Non-significant
Nausea	0	Non-significant
Vomiting	0	Non-significant
Staining of teeth	0	Non-significant
Metallic taste	0	Non-significant
Bloating	0	Non-significant
Colic	0	Non-significant
Diarrhoea	0	Non-significant
Constipation	0	Non-significant

Table 2b : Occurrence of Adverse Drug Reactions with Ferrous Fumarate

ADVERSE DRUG REACTIONS WITH FERROUS FUMARATE	NUMBER OF PATIENTS HAVING THE ADVERSE DRUG REACTION	p-VALUE
Epigastric pain	0	Non-significant
Heartburn	0	Non-significant
Nausea	0	Non-significant
Vomiting	0	Non-significant
Staining of teeth	0	Non-significant
Metallic taste	0	Non-significant
Bloating	0	Non-significant
Colic	0	Non-significant
Diarrhoea	0	Non-significant
Constipation	0	Non-significant

Table 2c : Occurrence of Adverse Drug Reactions with Ferrous Sulphate

ADVERSE DRUG REACTIONS WITH FERROUS SULPHATE	NUMBER OF PATIENTS HAVING THE ADVERSE DRUG REACTION	p-VALUE
Epigastric pain	0	Non-significant
Heartburn	0	Non-significant
Nausea	0	Non-significant
Vomiting	0	Non-significant
Staining of teeth	0	Non-significant
Metallic taste	0	Non-significant
Bloating	0	Non-significant
Colic	0	Non-significant
Diarrhoea	0	Non-significant
Constipation	0	Non-significant

Table 2d : Occurrence of Adverse Drug Reactions with Ferric Ammonium Citrate

ADVERSE DRUG REACTIONS WITH FERRIC AMMONIUM CITRATE	NUMBER OF PATIENTS HAVING THE ADVERSE DRUG REACTION	p-VALUE
Epigastric pain	0	Non-significant
Heartburn	0	Non-significant
Nausea	0	Non-significant
Vomiting	0	Non-significant
Staining of teeth	0	Non-significant
Metallic taste	0	Non-significant
Bloating	0	Non-significant
Colic	0	Non-significant
Diarrhoea	0	Non-significant
Constipation	0	Non-significant

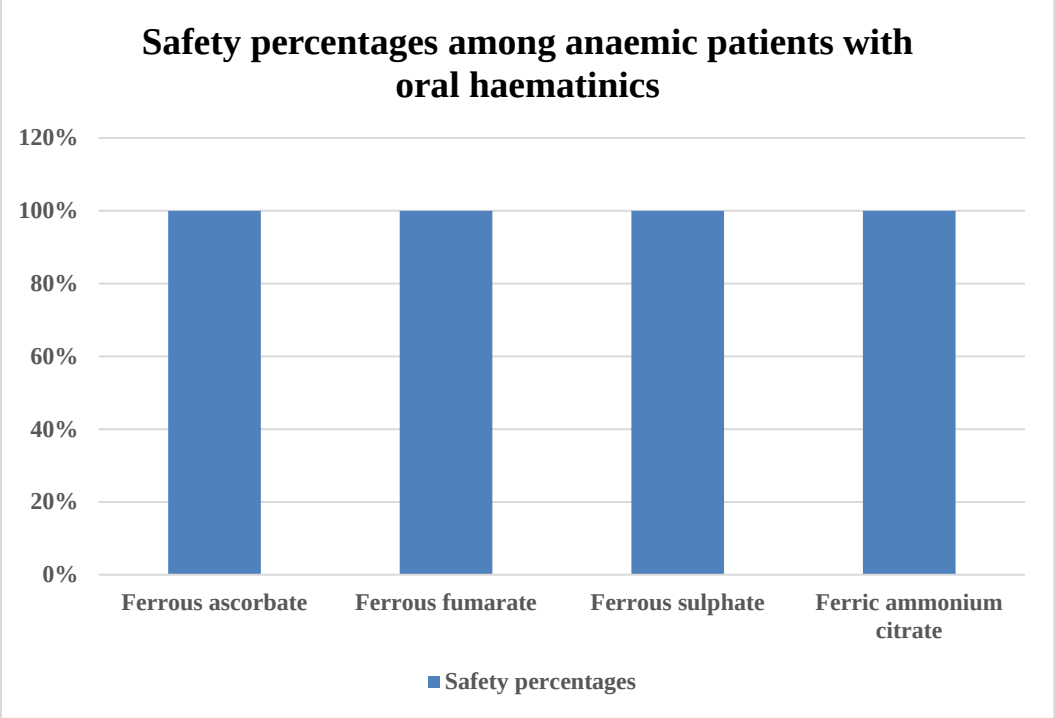

Figure 2: Safety Percentages Among Anaemic Patients with Oral Haematinics

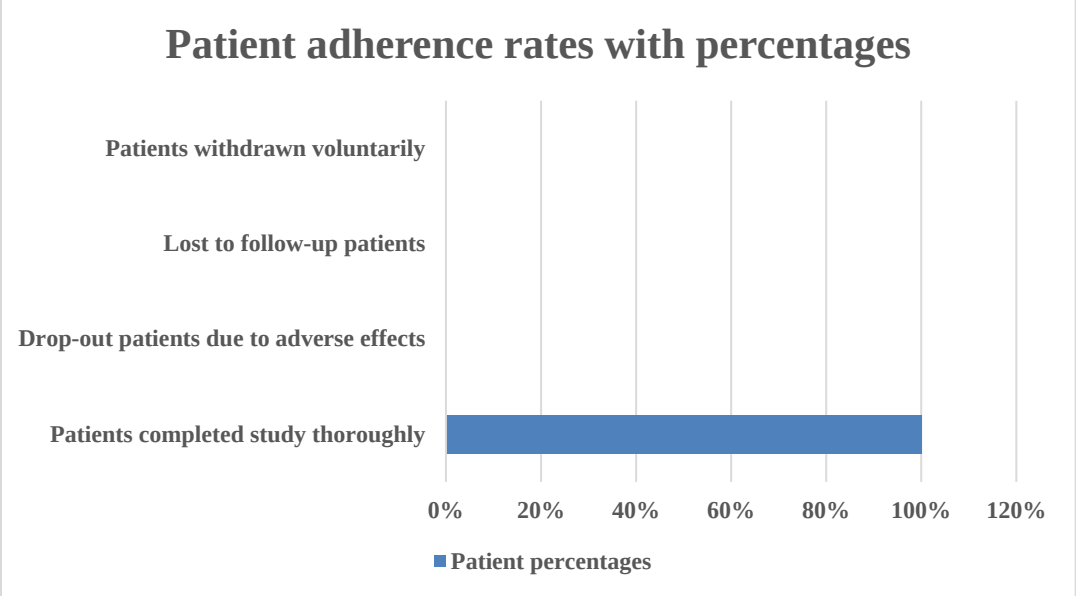

Figure 3: Patient Adherence Rate to The Treatment of Oral Haematinics

The qualitative analytical research study well-delineated certain elaborate and intricate molecular pharmacokinetic characterisations of oral haematinics, which furthered the molecular pharmacokinetic and pharmacodynamic interpretations about the oral haematinics.

Discussion:

In this study, on quantitative statistical analysis, the overall percentage recovery rate of the patients was 100%. In all the 100 patients treated with oral haematinics, such as, ferrous ascorbate, ferrous sulphate, ferrous fumarate and ferric ammonium citrate,

containing 60 mg of elemental iron, once to thrice daily, with or after meals, moderate iron deficiency anaemia was controlled, with a gradual significant rise in haemoglobin concentration, in the successive 3 months. Adverse effects were negligible and statistically non-significant among all the patients. Tolerability was good for the oral haematinics in all the patients. All the patients completed the study thoroughly. There were no drop-out patients due to adverse effects, none was lost to follow-up and none withdrew voluntarily. The patients' adherence to treatment was very high.

The qualitative analysis of the retrieved literature derived from a thorough literature review from various available literature databases was also performed to delineate the molecular pharmacokinetic characterisation of oral haematinics, which demonstrated certain below-mentioned distinctive pharmacokinetic elaborations.

Oral preparations are the treatment of choice, due to their higher effectiveness, higher safety, higher ease of administration, higher patient compliance, better accessibility, no occurrence of nosocomial infections and lower cost. When oral therapy is used, about 30% of the iron will be absorbed, requiring 180 mg of elemental iron daily for 1-3 months, according to the degree of anaemia.

Iron stores are less easily replenished by oral therapy than by injection, and oral therapy (at lower dose) should be continued for 3-6 months after the haemoglobin concentration has returned to normal or until the serum ferritin exceeds 50 mg/1(or as long as blood loss continues). Sustained or slow-release iron preparations have iron bound to resins, chelates (sodium feredetate) or plastic matrices. Iron is released in the lower small intestine, where it bypasses the duodenum, which is the site of maximal iron absorption, before becoming available. They are therefore relatively ineffective sources of iron and should not be used to treat iron deficiency. They cause fewer unwanted effects reflecting the small amount of iron absorbed.

Conventional oral iron preparations include ferrous sulphate, ferrous fumarate and ferric ammonium citrate, while newer preparations include ferrous ascorbate.

Ferrous ascorbate has the advantage of providing both ferrous iron and ascorbate in the same compound. It has excellent absorption as ascorbic acid enhances absorption of iron. When administered as ferrous ascorbate, ferrous salt delivers maximum amount of ferrous iron to the duodenal brush border and at the same time produces minimum gastrointestinal tract adverse effects.

Ferumoxytol is a semisynthetic carbohydrate-coated superparamagnetic iron oxide nanoparticle that is approved for treatment of iron deficiency in patients with chronic kidney disease. A variety of substances designed to enhance the absorption of iron include surface acting agents, carbohydrates, inorganic salts, amino acids, and vitamins. When present in an amount of ≥200 mg, ascorbic acid increases the absorption of medicinal iron by at least 30%[1-25].

The molecular pharmacokinetic characterisation of oral haematinics was visualised as very efficacious in the treatment of iron-deficiency anaemia in global epidemiology.

Conclusions:

The comparative pharmacological response of the patient to the prescribed oral haematinics, such as, ferrous ascorbate, ferrous sulphate, ferrous fumarate and ferric ammonium citrate, comprised of 100% patient recovery rate, high efficacy and safety of the patient. The comparative patient adherence to the treatment was very high. The qualitative analysis of the molecular pharmacokinetic and pharmacodynamic mechanisms focussed on effective haematinic functional pathways, which also maintained well-synchronised

pharmacological drug utilisation, among global anaemic patients.

Acknowledgements:

My gratitude to the Departments of Pharmacology, Clinical Pharmacology, Obstetrics and Gynaecology, Cardiology, Clinical Pathology, Molecular Diagnostics, Molecular Pharmacology, Clinical Medicine, Rational Pharmacotherapeutics, Evidence-Based Medicine, Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Mamata Medical College and Hospitals, Rama Medical College Hospital and Research Centre, Rama University, Gouri Devi Institute of Medical Sciences and Hospital, and Hi-Tech College of Nursing, for the successful completion of this research project.

Declarations:

Funding Sources: No funding sources for this research project

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