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Original Research Article

A clinical pharmacological evidence-based analytical research study on the clinical pharmacokinetic dose-dependent correlation of oral haematinics with the obstetric and gynaecological global anaemic patients' recovery rate

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ABSTRACT

Background: The goal of iron therapy is to repair the haemoglobin deficit and replenish storage iron. Oral haematinics 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. This analytical evidence-based clinical research was conducted for the molecular pharmacokinetic study of the pharmacological response and adherence of the patients to oral haematinics, in global tertiary medical care centres.
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, according to the progress of the disease, treatment regimen scheduling, occurrence or non-occurrence of adverse drug reactions and prognosis of the patient. The pharmacokinetic dose-dependent percentage recovery rate of the patients on 1st (30th day), 2nd (60th day) and 3rd (90th day) months and follow-up (105th day) visits, was finally deduced from the patients' recovery features of symptoms and signs, and the confirmatory laboratory investigations recordings, with the efficacy and safety evaluation findings.
Results: During the oral haematinics treatment, the pharmacokinetic dose-dependent percentage recovery rate of the patients was 29% on 30th day, 62% on 60th day, 93% on 90th day and 100% on 105th day of treatment.
Conclusions: All the oral haematinics treated global anaemic patients had shown 100% recovery rate in tertiary medical care centres.

Keywords: Oral haematinics, Drug dose, Patient recovery rate, Clinical pharmacokinetics, Clinical pharmacology, 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. Anaemia is defined as "fall of haemoglobin concentration below a statistically defined threshold laying at two standard deviations below the median of a healthy population of the same age, sex, and stages of pregnancy", and controlled by oral haematinics, like ferrous ascorbate, ferrous fumarate, ferrous sulphate, with a gradual significant rise in haemoglobin concentration. According to World Health Organization (WHO), more than 30% of the world's population is anaemic, majority suffering from iron deficiency anaemia; mostly found in under-developed and developing countries.[1-3]

The main causes of iron deficiency are inadequate iron absorption, increased iron requirements, inadequate iron intake, increased iron losses, poor bioavailability in a population whose diet is predominantly cereal-based. Iron is essential not only to oxygen transport by red cells but as a catalyst for oxidative metabolism in all cells. The goal of iron therapy is to repair the haemoglobin deficit and replenish storage iron. Oral haematinics 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.[1-7]

Objective

This analytical evidence-based clinical research was conducted for the molecular pharmacokinetic study of the pharmacological response and adherence of the patients to oral haematinics, in global tertiary medical care centres.

METHODS

The experimental design was a multi-centre, prospective, observational and analytical study. The study population was 100 global patients, who were treated for moderate iron deficiency anaemia.

Study period

The study period, including the entire research study as well as the compilation of the study literature, was 1 year 7 months, from May 2013 to June 2013; May 2021 to June 2021; and from September 2021 to November 2022.

Place of study

The place of study were the departments of pharmacology, clinical pharmacology, rational pharmacotherapeutics, evidence-based medicine, cardiology, clinical medicine, internal medicine, and obstetrics and gynaecology of Hazra Nursing Home, Hazra Polyclinic and Diagnostic Centre, Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Mamata Medical College, Mamata Hospitals, Narayana Medical College, Narayana Hospitals, J. J. M. Medical College and Hospitals, Bapuji Hospital, Chigateri General Hospital, Rama Medical College Hospital and Research Centre, Rama University, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, and K. D. Medical College Hospital and Research Center.

Selection criteria of the patients

Inclusion criteria

The inclusion criteria were as follows: patients with moderate iron-deficiency anaemia, women patients aged 18-35 years of age, patients with haemoglobin concentration more than or equal to 9 gm/dl, patients not using any previous iron supplements, and WHO definitions and criteria for anaemia.

Exclusion criteria

The exclusion criteria were as follows: less than 18 years and more than 35 years; patients presenting with mild or severe anaemia; patients with a history of hypersensitivity to the iron supplements; high risk pregnancies; cardiac; renal or any other associated complications; any chronic disease intervening with the study data; patients suffering from gastrointestinal diseases, like peptic ulcer, regional enteritis and ulcerative colitis; haemosiderosis; bacterial infections; haemochromatosis; haemolytic anaemia; and repeated blood transfusions.

Study procedure and 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. 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 patients' 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 pharmacological response and the recovery rate of the patients to the prescribed oral haematinics were thoroughly evaluated by the efficacy assessment by measurement of haemoglobin concentration improvement and safety assessment, on 1st, 2nd, 3rd months and follow-up visits. The pharmacokinetic dose-dependent percentage recovery rate of the patients on 1st (30th day), 2nd (60th day) and 3rd (90th day) months and follow-up (105th day) visits, was finally deduced from the patients' recovery features of symptoms and signs, and the confirmatory laboratory investigations recordings, with the efficacy and safety evaluation findings.

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. Written informed consent was obtained from each patient, before the study.

Statistical methods and analysis

The study data was statistically analysed with averages, test of significance and various percentages, alongside illustrated representations.

RESULTS

The clinical demographics of the patients were comparable.

During the oral haematinics treatment, the pharmacokinetic dose-dependent percentage recovery rate of the patients, as depicted in figure 1, was 29% on 30th day, 62% on 60th day, 93% on 90th day and 100% on 105th day of treatment, with the gradual significant rise in haemoglobin concentration, in the successive 3 months. Adverse effects were negligible and statistically non-significant, and tolerability was good for the oral haematinics among all the patients. The patients' adherence to treatment was very high. 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.

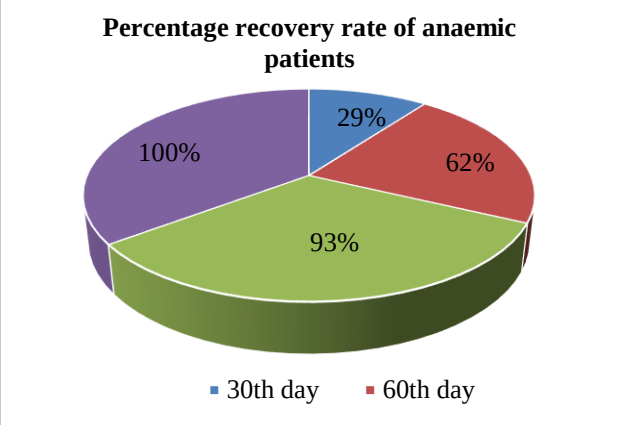

Figure 1: Pharmacokinetic dose-dependent percentage recovery rate of the anaemic patients.

DISCUSSION

The clinical demographics of the patients were comparable. In this analytical research study, it was obtained that, during the oral haematinics treatment, the pharmacokinetic dose-dependent percentage recovery rate of the patients was 29% on 30th day, 62% on 60th day, 93% on 90th day and 100% on 105th day of treatment, with the gradual significant rise in haemoglobin concentration, in the successive 3 months. Adverse effects were negligible and statistically non-significant, and tolerability was good for the oral haematinics among all patients. The patients' adherence to treatment was very high. 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.

A qualitative analysis of the retrieved literature derived from a thorough literature review from various available literature databases was 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%.

The importance of iron deficiency in heart failure with preserved ejection fraction is unknown. In heart failure, with reduced ejection fraction, some studies have shown that iron deficiency is an independent predictor of mortality. In a study, it was demonstrated that iron deficiency is equally prevalent in heart failure with preserved ejection function and heart failure with reduced ejection function, but is negatively prognostic only in heart failure with reduced ejection fraction. Persistent iron deficiency is strongly associated with mortality. The relationship between iron deficiency and mortality in heart failure with preserved ejection fraction and determine the prognostic importance of change in iron deficiency status over time.

The molecular pharmacokinetic characterisation of oral haematinics was visualised as very efficacious in the treatment of iron-deficiency anaemia in global epidemiology.[1-7]

In continuation of the anti-anaemic haematinic treatment of oral haematinics, whenever required, intravenous iron, in the form of ferric carboxymaltose can be given over 15 min. Intravenous ferric carboxymaltose is convenient for patients, allows greater throughput within the hospital system and is more cost effective compared with oral and other IV iron preparations that require a slower infusion rate. However, the administration of IV iron has recently been associated with the development of transient hypophosphataemia in some patients. The precise mechanism for this effect remains unclear, but it is likely related to a variable effect of IV iron formulations on the intracellular metabolism of fibroblast growth factor 23 (FGF23), increasing the fractional excretion of phosphate and reducing production of active vitamin D. The phosphate-lowering effect of iron and FGF23 has been demonstrated in women with significant uterine bleeding, although, not demonstrated in other studies where regular IV iron is required, e.g., inflammatory bowel disease and chronic kidney disease. In yet another study, changes in bone and haematinic biomarkers differ between patient groups following IV ferric carboxymaltose. For patients with lower serum phosphate concentrations, limiting the dose and measuring levels 7 days after administration might mitigate clinically significant hypophosphataemia.

Iron deficiency correlates with disease severity and mortality in pulmonary arterial hypertension. While oral iron supplementation was shown to be insufficient in such patients, the potential impact of parenteral iron on clinical measures required investigations. Along with targeted therapy, correction of iron deficiency by parenteral iron supplementation with ferric carboxymaltose appears feasible and safe, has sustained effects on iron status, and

In another study, iron deficiency anaemia was associated with gestational diabetes, and non-anaemic iron deficiency with stillbirth, although the risk estimates were imprecise. Iron deficiency was present in almost 15.4%, and often persisted despite 4 weeks intensified iron supplementation.[7]

There were no limitations in this study.

CONCLUSION

Therefore, from this study, it was concluded that during the oral haematinics treatment of the global anaemic patients in tertiary medical care centres, the pharmacokinetic dose-dependent percentage recovery rate of the patients was 29% on 30th day, 62% on 60th day, 93% on 90th day and 100% on 105th day of treatment.

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