Original Research Article

Title: An Open Label, Single Arm Multi-Centric Study to Assess the Safety and Efficacy of Sodium Feredetate (Fedate syrup) within 21 days in Patients with Iron Deficiency Anemia in Ivory coast

Abstract:

Introduction: Iron deficiency anemia is a common disease prevalent mostly in developing countries Replenishing iron stores via oral route supplementation takes longer time, however for safety reasons it is considered as the most convenient route. There is always search of better oral iron supplement which can replenish the iron deficiency at short duration of time.

Objectives: A post-marketing surveillance study to assess the safety and efficacy of Fedate syrup (Sodium Feredetate) within 21 days in clinical practice.

Materials and methods: A total 40 patients visiting 2 gynaecologists, who had a hemoglobin (Hb) level of < 10gm/dl, and had a body mass index (BMI) of < 24 kg /m^2 were included in the study. All patients were prescribed either 10-15 ml Fedate syrup once or twice a day. Clinical effectiveness was assessed over a period of 21 days. Treatment response was recorded as responders or non-responders based on a minimum 1 gm/dl increase in Hb levels.

Results: A total of 33 patients (82.5%) responded to the treatment within 21 days as compared to 7 patients (17.5%) who did not respond to the treatment. There was significant difference in global efficacy and assessment of tolerability which was recorded on a scale of poor to excellent. The drug was tolerated well in all patients responding either as "good" or "excellent" to the treatment. Global efficacy was "poor" in 6 patients (15%) and "excellent" in 20 (50%). The paired student's T-test score for increase in hemoglobin from baseline to 21^{st} day was 5.4995 (P<0.0001).

Conclusions: We conclude that Sodium Feredetate is an effective compound as Fedate syrup in improving the symptoms of anemia in majority of the patients.

Keywords: Iron Deficiency Anemia, Sodium Feredetate, Hemoglobin, and oral iron

Introduction:

Anemia continues to be a major public health problem worldwide, particularly among females of reproductive age in developing country settings. Anemia impairs health and wellbeing in women and increases the risk of maternal and neonatal adverse outcomes. It affects half a billion women of reproductive age worldwide. In 2011, 29% (496 million) of non-pregnant women and 38% (32.4 million) of pregnant women aged 15–49 years were anemic. [1] The Sub-Saharan Africa is one of the most affected regions - with more than half (53.8%) of children under - 5 years old suffering from anemia and in Africa, 57.1% of pregnant women are anaemic. [2] In Kenya, the prevalence of anemia among pregnant women is 55.1%. [2] When the prevalence of anemia among pregnant women is 40.0% or more, it is considered as a severe public health problem. [2] Prevalence data of iron deficiency anemia among women among of reproductive age (15 – 49) in Ivory Coast was reported at 52.9% in 2016 and among pregnant women was reported at 59.3% thereby resulting in higher prevalence of anemia among children below 5 years of age, which was reported at 73.4%. [3]

While there are regional differences, prevalence rates across the states are remarkably similar, reflecting underlying determinants that include diets low in heme-iron and high in phytates, high levels of malaria and other infectious diseases, and frequent reproductive cycling that decreases iron stores. [1]

Severe anemia can have serious consequences and therefore needs urgent treatment. Guidelines in the management of anemia recommend measurement of the serum ferritin level to diagnose iron deficiency anemia. It also recommends, screening of all pregnant women for iron deficiency anemia. Adult men and postmenopausal women with iron deficiency anemia are recommended to be screened for gastrointestinal malignancy. Treatment should involve attending to any diagnosed underlying cause. The aim of the treatment should be to restore Hb concentrations and red cell indices to normal, and replenish iron stores either by oral route or parenteral route. If this cannot be achieved, consideration should be given to further evaluation. [4, 5]

Replenishing iron stores via oral route supplementation takes longer time, however for safety reasons it is considered as the most convenient route. Some people are non-responders to oral iron therapy due to longer durations of supplementation, which is

probably why they need to be shifted to parenteral iron therapy. However, it is difficult for the physicians to decide when to make the shift as no clear guidelines are present stating the same. Various iron preparations with different elemental iron content are available in the market. [4] However, most of them are associated with problems like poor oral bioavailability, interaction with food and poor gastrointestinal tolerance. Attempts have been made to overcome the above problems by making complex iron preparations like iron sodium feredetate. [4] Sodium feredetate (sodium iron ethylene diamine tetraacetic acid) is a ferric iron chelate which is shown to have no food interaction and good bioavailability. [7] It contains iron that is combined with a chemical called EDTA to make sodium feredetate. This is a unionised form of iron and not an iron salt. Sodium feredetate breaks down in the gut and releases the iron, which is then absorbed by the body. This unionised form of iron is less likely to cause stomach upsets or discolour teeth that iron supplements that contain iron salts, like ferrous sulphate and was therefore the chosen molecule for this study. [8] Therefore, given the above mentioned supporting data, we chose to conduct our study using sodium feredetate over the more commonly prescribed ferrous sulphate.

Iron EDTA [sodium iron (Fe3+) ethylenediaminetetraacetic acid (EDTA)], shown to have a significant beneficial effect on iron status by increasing iron bioavailability in human diets, Iron EDTA, like other EDTA–metal complexes, dissociates in the gastrointestinal tract to form iron, which is bioavailable, and an EDTA salt; absorption of the metal ion and EDTA are independent. They have a low degree of acute oral toxicity. EDTA compounds are not reproductive or developmental toxicants when fed with a nutrient-sufficient diet or minimal diets supplemented with zinc. In chronic toxicity studies, diets containing as much as 5% EDTA were without adverse effects. An upper-bound estimated daily intake (EDI) of EDTA from iron EDTA (1.15 mg/kg bw/day for the US population) is less than half the acceptable daily intake (ADI) for EDTA of 2.5 mg/kg bw/day established by JECFA. [7]

Fedate syrup containing Sodium Feredetate manufactured by Ajanta Pharmaceutical Limited claims visible improvement an increase of minimum 1gm/dl hemoglobin (Hb) within 21 days of treatment. The company suggests shifting to parenteral therapy if levels are not raised within 21 days of treatment.

Materials and Methodology:

This prospective interventional study on Fedate syrup was carried out in two institutional clinics; Chef de Service Gynecologie and Hospital general d'Abobo located in Ivory Coast.

Data was collected from two practicing gynaecologists, where the patients had visited the doctor either complaining of pelvic pain or as a part of their routine antenatal checkup. A total of 40 female patients were included in the study that were between the ages of 18-40, had a hemoglobin level of < 10gm/dl, and had a body mass index (BMI) of < 24 kg /m^2. Patients over the ages of 40 with baseline Hb > 10 gm/dl, and BMI > 24 kg /m^2 were excluded in order to specifically treat moderate anemia in the short treatment time. Patients with any chronic illness and history of oral or Intravenous (IV)/ Intramuscular (IM) iron therapy in last two months were also excluded from the study. Patients were informed about the study and were prescribed either 10-15 ml Fedate syrup to be taken once or twice a day post informed consent procedures. Previous studies have indicated adults should take one 5ml spoonful of sodium feredetate oral solution three times a day, gradually increasing to two 5ml spoonfuls (10ml) three times a day. [8] Our study suggested the use of 10-15ml of Fedate syrup prescribed per the physician's discretion to be taken at least once daily along with meals which would suffice the initial increase of 1gm/dl in Hb levels.

Clinical features of the patients, diagnosis, duration of illness, concomitant medication, were recorded through case report forms prepared by the gynaecologists at their respective institutional clinics. Baseline Hb at day 0 and day 21 were recorded through a simple blood test capturing the complete blood cell count. Clinical effectiveness was assessed over a period of 21 days and patients were classified as responders or non-responders based on Hb increase of more or less than 1.0 g/dl at day 21 respectively. Investigators also gave an overall assessment of tolerability based on a 4-point scale ranging from excellent to poor. Incidence of adverse events was also recorded to evaluate safety of the given treatment.

Statistical analysis:

Data were presented as numbers and percentages for clinical features, treatment recommendation, effectiveness of the medicine and adverse events. Paired Student's T- test was performed to examine the increase in hemoglobin from baseline to 21st day of treatment. P value less than 0.05 was considered statistically significant. All analyses were performed in IBM SPSS statistics version 23 (IBM Corp, USA).

Results:

The most common clinical feature among the patients visiting the gynecologists were pregnancy with anemia (37.5%). Other clinical feature were post-surgical anemia (30%), anemia with infertility (7.5%) and anemia due to malaria (7.5%). For all patients, Fedate

syrup was recommended. Fedate alone was prescribed in 15 patients whereas concomitant medications were prescribed in 25 patients along with Fedate. Concomitant medications prescribed are shown in Table 1.

Table 1: Common Clinical feature with concomitant medication

Common Clinical feature	Concomitant medication
Infertility with anemia (7.5%)	Primlout N ,Acfol,Oroperidys
Pelvic pain, irregular menstruation with anemia (12.5%)	Lutenyl,Acfol.Ccal sachets
Pregnancy with anemia (37.5%)	Duphaston,Profenid suppositories
Vaginal infection with anemia (5%)	Antiinflammtory ,antibiotics ,vitamin C
Gynaecological surgery due to myoma ,fibroid, ectopic pregnancy (30%)	Doxy 200, Yodocefol,paracetamol
Anemia due to malaria (7.5%)	Artefan 80/480,Efferalgan,Vitamin C

The baseline Hb levels of all patients were grouped into two sections and the baseline Hb levels at day 0 and day 21 were tabulated. The average increase in each group is calculated and represented below in Table2. There was 1.85 gm /dl and 1.68 gm /dl increase in Hb level in patient group who had baseline Hb below 9 gm /dl and above 9gm/dl respectively.

Table 2: Baseline Hb level and average increase in Hb levels after 21 days

Baseline Hb level (gm/dl)	Number of patient on day 0	Number of patient on day 21	Average Increase of hemoglobin
< 9	12	1	1.85
9-10	28	6	1.68

All patients were prescribed 10-15 ml of Fedate. 50% Patient taken 10 ml and another 50% patient taken 15 ml fedate syrup orally per day for 21 days. Table 3 represents the patient's dosage.

Table 3: Fedate Dosages

Fedate dosage	N (%)
10 ml	20 (50%)
15 ml	20 (50%)

Treatment response was recorded as responders or non-responders. Patients with a minimum of 1gm/dl increase in baseline hemoglobin level were categorized as responders and patients whose baseline hemoglobin did not raise 1gm/dl were categorized as non-responders. A total of 33 patients (82.5%) responded to the treatment within 21 days as compared to 7 patients (17.5%) who did not respond to the treatment. Most of the patients who did not respond to the treatment were pregnant (n=4/7). Our understanding is that the systemic nutritional requirements of these pregnant women were probably a hindrance in increasing their Hb levels. We assume that these patients were complaint with the treatment protocols per conversation with the gynecologists at their follow-ups. Unfortunately, we did not have any further means to ensure the same. However, all patients who did not respond to the treatment were shifted to IV iron as per the objectives of the study and were followed up through their treatment schedules.The paired student's T - test score for increase in hemoglobin from baseline to 21st day was 5.4995 (P<0.0001).

There was significant difference in global efficacy and assessment of tolerability which was measured as "poor" (Severe or serious adverse event(s), which necessitated stoppage of study medication), "Fair" (without medication and did not necessitate stoppage of study medication), "Good" (Mild adverse event(s) reported which subsided with or without medication and did not necessitate stoppage of study medication), and "Excellent" (No adverse events reported). The drug was tolerated well in all patients responding either as "good" or "excellent" to the treatment. Global efficacy was "poor" in 6 patients (15%) and "excellent" in 20 (50%). Figure 1 represents the global efficacy and assessment of tolerability in all patients.

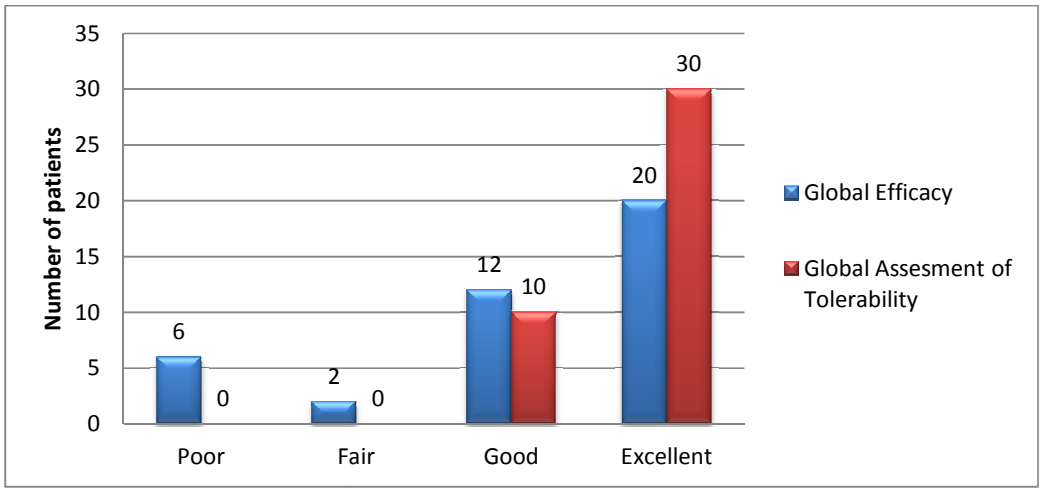

Figure 1: Global efficacy and Global Assessment of Tolerability

We also grouped patients in two age groups (18–30 and 30–40) and demonstrated the increase in Hb after 21 days of Fedate syrup in each patient in **figure 2**

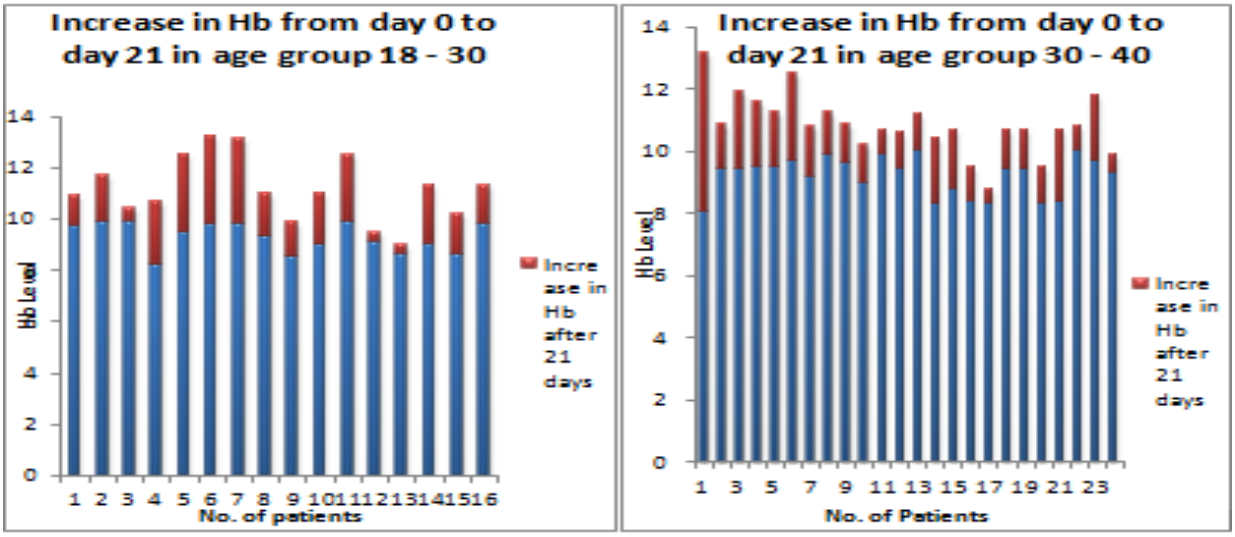

Figure 2: **Increase in Hb after 21 days of Fedate syrup in age groups 18-30 and 30-40**

Safety:

Adverse events were reported by 10 patients (25%) predominantly in the responder group. Most common adverse events were abdominal pain and slight vertigo reported in 2 patients (5%). Other adverse events are shown in table 4. None of the patients reported any serious adverse events and all the reported events are considered negligible given the overall positive response to the treatment.

Table 4: Adverse Events

Adverse Event	N (%)
Abdominal pain	2 (5%)
Constipation	1 (2.5%)
Pelvic pain	1 (2.5%)
Lack of energy with excessive sleepiness	1 (2.5%)
Diarrhea	1 (2.5%)
Vertigo	2 (5%)
Fatigue	1 (2.5%)
Nausea	1 (2.5%)

Discussion:

The present study assessed the safety and efficacy of Fedate syrup within 21 days in patients with iron deficiency anemia. Similar observations have been made by other studies. Sarkate P et al. conducted a randomized study to compare efficacy of sodium feredetate Vs ferrous fumarate in improving hemoglobin profile in 48 pregnant anemic women. Low doses of sodium feredetate produced comparable results as higher dose of ferrous fumarate and no adverse effects were reported with sodium feredetate. Revankar et al conducted another randomized study comparing the efficacy of Sodium Feredetate with Ferrous Sulphate in treatment of iron deficiency anemia in 74 pregnant women. Sodium feredetate (Na Fe EDTA) in iron deficiency anemia led to a significant and rapid rise in hemoglobin levels than that with ferrous sulphate in the study. Singhal et al. compared various iron salts in treating iron deficiency anemia in 250 pregnant women. The study found that Sodium feredetate had minimum side effects as compared to any other iron salts. In our study 33 out 40 patients responded to the treatment with minimal side effects. [11, 12, 13]

Currently there aren't any guidelines discussing clinical determinants and timelines to switch patients from oral to parenteral iron supplementation. Okam et al suggested that Hb measurements taken 14 days after initiation of oral iron therapy can reliably predict overall response in Hb to oral iron therapy. Accordingly, day 14 Hb may be a useful tool for clinicians in determining when to switch patients from oral to parenteral/IV iron. Our study found that a 1gm/dl increase over a period of 21 days in hemoglobin can be a clinically

significant determinant of successful oral therapy. We suggest that patients in whom hemoglobin does not increase by 1gm/dl within 21 days can be suggested parenteral iron therapy. [14]

Limitations:

This was a multi centre, single arm, interventional study design, with a clinical diagnosis followed by limited period of follow up. The single arm focus, small subject population, and short period of follow up are some of the limitations of this study. Given, the short duration of this study, we were unable to record patient compliance through phone calls, or other sophisticated compliance measures. We also were unable to address or monitor any additional nutritional components that would've attributed to iron supplementation. Further studies with multiple arms and long-term follow up are required to find out the efficacy of Fedate syrup in large sets of populations.

Conclusion:

Sodium Feredetate is an effective compound as Fedate syrup in improving the symptoms if anemia in majority of the patients. There was no difference in the effectiveness when treatment was given alone or along with other concomitant medications. Treatment was tolerated well without clinically significant adverse events.

Acknowledgement:

We thank all patients for participating in this study. Special thanks to Ramkumar Subramanian and Dayan Dang for acquisition of funding and general supervision of this study. Thanks to Siddhesh Sharma and Sanvritti Manjrekar for helping technical editing, language editing, and proofreading.

Consent:

Patients were treated by physicians in their routine practice. Patient confidentiality was maintained at all points of drafting this manuscript. All treatments were explained thoroughly to the patients and informed consent was obtained for the same.

Ethical approval:

Ethical approvals were taken from appropriate ethical institutions.

Competing interest:

This trial was sponsored by Ajanta Pharma Limited

Abbreviation:

ADI: Acceptable Daily Intake

BMI: Body Mass Index

EDTA: EthyleneDiamineTetraacetic Acid

EDI: Estimated Daily Intake

Hb: Hemoglobin,

IV: Intravenous

IM: Intramuscular

IDA: Iron Deficiency Anemia

JECFA: The Joint FAO/WHO Expert Committee on Food Additives

References:

1) World health organization. Global Nutrition Targets 2025: Anemia policy brief. Available at: https://www.who.int/nutrition/publications/globaltargets2025_policybrief_anemia/en/. Last accessed on: 17-12-2018
2) Legason ID, Atiku A, Ssenyonga R, Olupot-Olupot P, Barugahare JB. Prevalence of Anemia and Associated Risk Factors among Children in North-western Uganda: A Cross Sectional Study. BMC Hematol. 2017;17:10. Published 2017 Jul 3. doi:10.1186/s12878-017-0081-0
3) Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in hemoglobin concentration and prevalence of total and severe anemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. The Lancet Global Health 2013; 1(1): e16-e25.
4) Goddard AF, James MW, McIntyre AS, et al. Guidelines for the management of iron deficiency anemia. Gut 2011;60:1309-1316.
5) Matthew w. et al. Iron Deficiency Anemia: Evaluation and Management. Am Fam Physician. 2013 ;87(2):98-104.
6) Davidsson, L., Kastenmayer, P., & Hurrell, R. F. Sodium iron EDTA [NaFe(III)EDTA] as a food fortificant: the effect on the absorption and retention of zinc and calcium in women. The American Journal of Clinical Nutrition,1994; 60(2), 231–237.
7) Heimbach, J., Rieth, S., Mohamedshah, F., Slesinski, R., Samuel-Fernando, P., Sheehan, T., Borzelleca, J. Safety assessment of iron EDTA [sodium iron (Fe3+ethylenediaminetetraacetic acid]: summary of toxicological, fortification and exposure data. Food and Chemical Toxicology, 2000;38(1), 99–111.
8) https://www.medicines.org.uk. [Online].; 2017 [cited 2018 December 24. Available from: https://www.medicines.org.uk/emc/files/pil.8791.pdf
9) Nicholas J. Kassebaum, Rashmi Jasrasaria, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood ;2014 123:615-624; doi: 10.1182/blood-2013-06-508325
10) Taner CE, Ekin A, Solmaz U, et al. Prevalence and risk factors of anemia among pregnant women attending a high-volume tertiary care center for delivery. J Turk Ger Gynecol Assoc. 2015;16(4):231-6. Published 2015 Nov 2. doi:10.5152/jtgga.2015.15071
11) Sarkate P, Patil A, Parulekar S, Rege NN, Samant BD, Lokhande J, Gupta A, Kulkarni K. A randomised double-blind study comparing sodium feredetate with ferrous fumarate in anemia in pregnancy. J Indian Med Assoc. 2007 May; 105(5): 278, 280-1, 284.

12) Revankar et al. efficacy of Sodium Feredetate with Ferrous Sulfate in treatment of iron deficiency anemia in pregnant women. International Journal of Reproduction, Contraception, Obstetrics and Gynecology Revankar VM et al. Int J Reprod Contracept Obstet Gynecol. 2017 May;6(5):1978-1981 www.ijrcog.org pISSN 2320-1770 | eISSN 2320-178
13) Singhal et al. Comparison of Various Oral Iron Salts in the Treatment of Iron Deficiency Anemia in Pregnancy. doi: 10.5958/2394-2754.2015.00005.3
14) Maureen Okam, Todd Koch and Minh Ha Tran. Clinical Criteria for Transitioning from Oral to IV Iron Replacement Therapy in Patients with Iron Deficiency Anemia. Blood 2014 124:211