Research & Reviews: Pharmacy & Pharmaceutical Sciences

e-ISSN: 2320-1215
p-ISSN: 2322-0112
www.rroij.com

FERALGINE®A New Oral Iron Therapy for Iron Deficiency Anemia: Preliminary Clinical Results on A Case Series of 12 Anemic Patients

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Rec date: Dec 02, 2016; **Acc date:** Dec 19, 2016; **Pub date:** Dec 23, 2016

Research Article

ABSTRACT

Iron deficiency (ID) represents the most common nutritional disorders worldwide accounting for approximately one-half of anemia cases. Oral iron therapy seems to be the first-choice approach to treat iron deficiency anemia (IDA) also if Gastrointestinal adverse effects such us nausea, epigastric discomfort, constipation, and diarrhea could represent a barrier to patient's adherence to treatment protocol. Ferrous Bysglicinate Chelate has demonstrated an interesting profile in terms of efficacy and safety after oral administration because of its chemicals properties. To improve patient's adherence to oral iron, therapy a new co-processed compound between Ferrous bysglicinate Chelate and Alginic Acid (FERALGINE®) obtained by using Spray drying technique has been developed. 12 adult consecutive patients affected by iron deficiency anemia (IDA)) has been treated with FERALGINE® (1 caps/day containing 30 mg of elemental iron) for a period between 35 and 60 days: at the end of the study every patient statistically significant improved its Hb, Red Blood Cells, HCT, MCV, Plasma Iron concentration and Ferritin values without Gastrointestinal adverse effects. FERALGINE®, a new co-processed compound, seems to be useful in iron deficiency anemia (IDA) domiciliary management because of its pharmacodynamic profile that allows to patients a good domiciliary compliance to oral iron therapy.

KEY WORDS:

Iron Deficiency (ID), Iron Deficiency Anemia (IDA), FERALGINE®, Gastrointestinal Adverse effects

INTRODUCTION

Iron deficiency (ID) is one of the most common disorders all over the world and iron deficiency anemia (IDA) continues to represent a major public health problem [1] . Iron deficiency in adults could recognized almost four big subgroups of causes: a) increased iron loss; b) Decreased Iron from Diet; c) Decreased Iron Absorption and d) Increased Iron Requirements **(Table 1)** [1]. Despite the well-recognized pathology, the prevalence of the iron deficient anemia remains enormous even in the developed world [1]. Over three million of females in U.S. continue to manifest iron deficiency anemia suggests that generic therapeutic approaches remain suboptimal [2]. Diagnosis is usually made in primary practice, but successful therapy is frequently hampered by the high frequency of side effects as well as patient noncompliance [1]. Adherence to oral iron therapy can be a barrier to treatment because of Gastrointestinal adverse effects that could be reduced when iron is taken with meals, but, in this case, absorption may decrease by 40% [3]. Medications like PPIs (Proton Pump Inhibitors) and factors that induce gastric acid hypo secretion (chronic atrophic gastritis, recent gastrectomy or vagotomy) are associated with reduced absorption of dietary iron and iron tablets [4-8]. During the last decade Ferrous Bysglicinate Chelate, a new iron complex between bivalent iron and two molecules of glycine has been developed and used in clinical practice [5-15]because of its particular pharmacodynamic properties (intact absorption of ferrous bysglicinate chelate directly into the mucosal cells of the intestine) that makes this oral iron preparation more bioavailable, tasteful and with less Gastrointestinal adverse effects if confronted with the other oral iron salts available [5,11,12]. Nevertheless, also Ferrous Bysglicinate Chelate treatment alone results in several adverse effects that limit, also if at less extent that other iron salts, the patient's domiciliary compliance to oral iron therapy [6]. To ameliorate even more iron bioavailability, tolerability and taste of Ferrous Bysglicinate Chelate a new compound named "FERALGINE® has been developed [16]. FERALGINE® "a co-processed compound" between two well Known substances: Ferrous Bysglicinate Chelate and Alginic Acid [16]. Alginic Acid salts have usually been used as "gastroprotection" for

e-ISSN: 2320-1215
p-ISSN: 2322-0112

patients affected by G.E.R.D (Gastro Esophageal Reflux Disease), by Gastric Hyperacidity and by Pyrosis [17,18]. Both these substances have been defined like G.R.A.S. (Generally Recognized as Safe) by F.D.A. [16]. The new of this intriguing compound is the methodology that has been used to prepare this new co-processed compound: by using Spray Drying Technology to a solution of Ferrous Bysglicinate Chelate and Alginic Acid has been obtained a new co-processed compound in which alginic acid and Ferrous Bysglicinate Chelate occur in a 1 to 1 ratio and in which every little particle of the final powder possess the same morphology and quantity of the two different co-processed substances [16] **(Figure 1).**

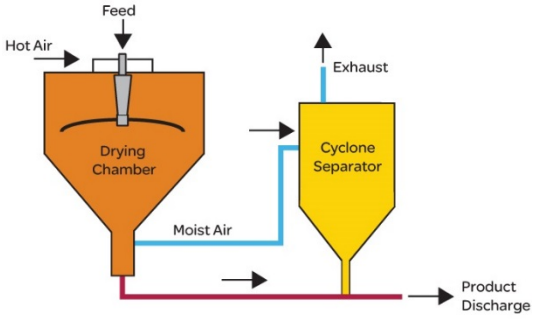

Figure 1. Spray drying techniques

Spray Drying is one of the most exciting technologies for the pharmaceutical industry, being "an ideal process" where the product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density, and morphology [16].

Considering the unique profile of FERALGINE, we wish to test this new compound for clinical use in patients affected by Iron Deficiency anemia to understand if the efficacy and safety of this new co-processed compound could be useful in the global management of these patients.

MATERIALS AND METHODS

Twelve consecutive patients affected by iron deficiency anemia (IDA) have been enrolled in this open prospective uncontrolled pivotal clinical trial during 2016 in the Service of Internal Medicine, Hematology Department, of Sperino Hospital in Turin. All the patients enrolled in the trial (9 women and 4 men) had Hb levels under 12 g/dl at enrollment time and present Iron Deficiency Anemia (IDA) with different causes: 4 patients present multifactorial anemia, 2 hypermenorrhea-related anemia, 2 cancer-related anemia, 2 increased-iron loss anemia, 1 Post Transplantation anemia, 1 hypo-regenerative anemia. All the patients are over eighteen years old (medium age 63.83 +/- 20.94 years) and used FERALGINE®capsules (TECNOFER Plus) (30 mg of elemental iron/cps) daily for a period lasting from 35 days to 60 days. Every patient presented history of chronic fatigue and/or asthenia at enrollment. Values of Haemoglobin (Hb), Red blood cells, Hematocrit (Ht), Mean Corpuscular Volume (MCV), Plasma Iron Concentration and Ferritin have been collected at the beginning of the trial (T0 time) and have been repeated at the end of the trial (T1 time). The adverse events have been reported by the patients to the clinical Investigator during the trial. Primary end-point of the trial was the statistically significant increase of Hb between T0 time and T1 time together with an absence of adverse events for every patient (optimal domiciliary adherence to oral iron therapy). Secondary end points were the statistically significant increase of Red Blood Cells, Ht, MCV, Plasma Iron Concentration and Ferritin between T0 time and T1 time. Also, the control of the symptoms chronic fatigue and asthenia will be referred by patients at the end of the trial and confronted with T0 time. Statistical Analysis was performed by using IBM Statistics 24 for MAC, 2016. Repeated misures analysis of variance (ANOVA) have been performed for Hb, red blood cells, Hematocrit (Ht), Mean Corpuscular Volume (MCV), Plasma Iron Concentration and Ferritin values confronting T0 data (beginning of FERALGINE® therapy) versus T1 (end of FERALGINE® therapy). P value less than 0.05 have been reported like "statistically significant".

RESULTS

Single values for every patient at enrollment time (T0) were reported in **Table 1.**

Table 1. (T0 Time – Hb, red blood cells, Ht; Plasma Iron and Ferritin values for single patient)

T0						
S. no.	**Red Blood Cells (n)**	**Hb (g/100ml)**	**Ht (%)**	**MCV µm3(fL)**	**Plasma Iron (µg/100ml)**	**Ferritin (ng/ml)**
1	4,59*106	10,2	33	68	27	16

e-ISSN: 2320-1215
p-ISSN: 2322-0112

2	3,67*106	8,9	28	73	13	38
3	4,89*106	11,9	37	84	37	19
4	3,45*106	8,3	27	67	15	4
5	4,21*106	9,1	32	71	22	13
6	4,59*106	11,7	36	77	31	20
7	4,38*106	11,9	35	78	34	18
8	3,78*106	7,8	26	71	22	15
9	3,54*106	11,1	31	88	39	18
10	4,49*106	11,5	33	76	29	42
11	3,98*106	11,9	38	79	34	89
12	3,97*106	11,6	33	74	32	21
MEAN	4,12*106	10,49	32,4	75,5	27,9	26

Medium red blood cells and Hb values was, respectively, 4.12*106 and 10.49 g/dl while medium Plasma Iron values and Ferritin values were, respectively, 27.9 µg/dl and 26 ng/ml. After a treatment period from 35 to 60 days (medium period = 46.25 days) (T1 time, end of the study) the same values have been modified for every single patient as reported in **Table 2.**

Table 2. (T1 Time – Hb, red blood cells, Ht; Plasma Iron and Ferritin values for single patient)

T1						
S. no.	**Red Blood Cells (n)**	**Hb (g/100ml)**	**Ht (%)**	**MCV µm3(fL)**	**Plasma Iron (µg/100ml)**	**Ferritin (ng/ml)**
1	5,01*106	11,4	41	86	39	18
2	4,31*106	9,7	37	83	34	43
3	5,26*106	12,8	41	88	62	34
4	4,02*106	9,2	34	78	44	9
5	4,92*106	10,1	39	80	38	19
6	4,98*106	12,6	40	82	56	27
7	4,86*106	13,1	39	87	65	30
8	4,36*106	8,9	36	81	41	15
9	4,25*106	12,2	38	89	27	42
10	5,01*106	13,9	42	82	56	47
11	4,59*106	12,7	41	85	68	94
12	4,38*106	12,7	39	89	57	43
MEAN	4,66*106	11,6	38,9	84,2	48,9	35

Medium red blood cells values were 4.66*106, medium Hb values was 11.6 g/dl, medium Plasma Iron values was 48.9 µg/dl) and medium Ferritin values was 35 mg/ml.

Repeated misures analysis of variance (ANOVA test) between T0 and T1 values were calculated for every single parameter: primary end values (Hb) were statistically improved using FERALGINE® (Hb T1 = 11,608 versus Hb T0=10.492: $p<0.0001$) **(Figure 2).**

e-ISSN: 2320-1215
p-ISSN: 2322-0112

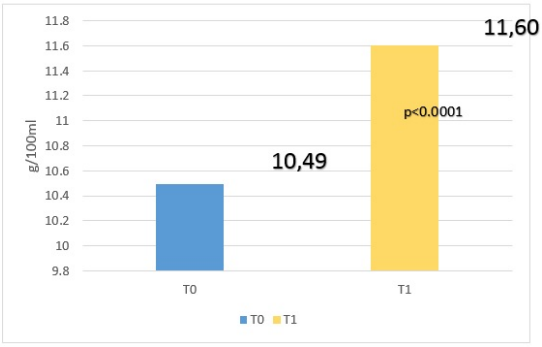

Figure 2. Repeated misures analysis of variance (ANOVA test) for Haemoglobin (Hb) between T0 and T1.

No FERALGINE®adverse events or therapy interruption have been happened during the trial so that also the second primary end-point of the study has been reached.

Referring to the secondary end-points (red blood cells, Ht, MCV, Plasma Iron and Ferritin), repeated misures analysis of variance between T0 and T1 shown a statistically significant improvement (p<0.0001) between T0 and T1 for every value **(Figure 3-7).**

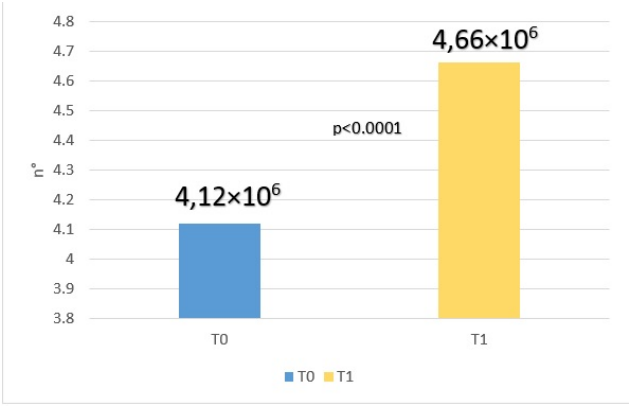

Figure 3. Repeated misures analysis of variance (ANOVA test) for red blood cells between T0 and T1.

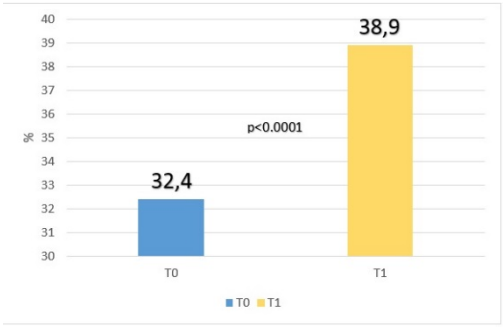

Figure 4. Repeated misures analysis of variance (ANOVA TEST) for Haematocrit (Ht) between T0 and T1

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p-ISSN: 2322-0112

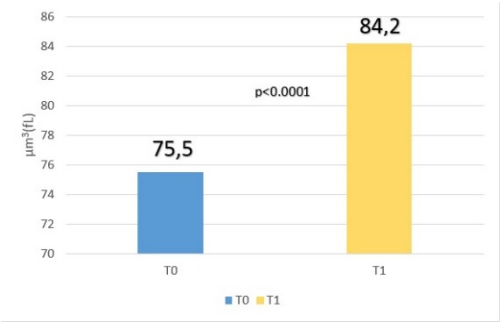

Figure 5. Repeated misures analysis of variance (ANOVA test) for Mean Corpuscular Volume between T0 and T1

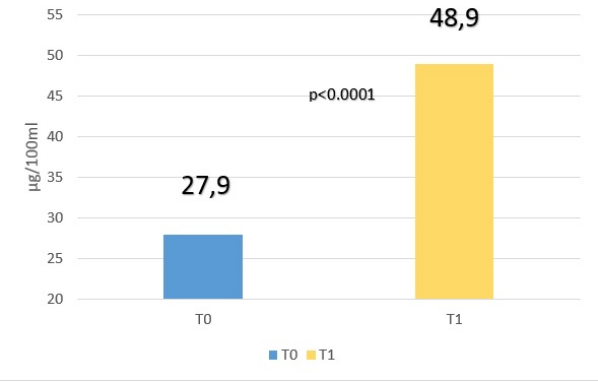

Figure 6. Repeated misures analysis of variance (ANOVA test) for Plasma Iron between T0 and T1.

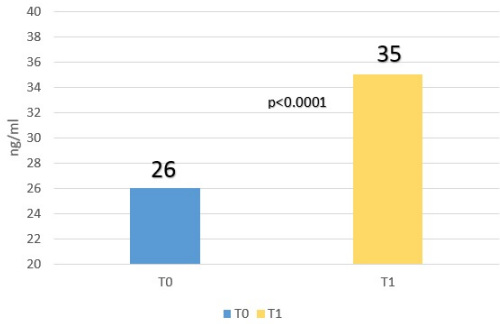

Figure 7. Repeated misures analysis of variance (ANOVA test) for Ferritin between T0 and T1.

Also, the ANOVA test intra subject measured for every primary and secondary end-points resulted statistically significant improved ($p<0.0001$) confirming the previous data and the effectiveness of FERALGINE® in terms of efficacy. Interesting, at the end of the trial all the patients referred a clinical improvement of the symptoms chronic fatigue and/or asthenia when confronted with the beginning of the study.

DISCUSSION

Up to 20% of patients experience some type of gastrointestinal discomfort taking oral iron salts preparation [1] and, unfortunately, 30% of patient may self-discontinue the medication without talking with medical Doctor [1]. Major obstacles toward successful oral iron therapy are dose-related, upper gastro-intestinal side effects such as nausea and epigastric discomfort which occur approximately one hour after ingestion [1]. Ferrous Bysglicinate Chelate, a product consisting of one molecules of ferrous iron bond to two molecules of glycine to form two heterocyclic rings, possesses a typical pharmacodynamic and pharmacokinetic profile that allows to this source of iron a better domiciliary compliance when compared with other iron salts [5-15], has been successfully used in IDA treatment with a less extend of gastrointestinal adverse events after oral administration [5-15]. To ameliorate even more oral iron bioavailability, tolerability, and taste of Ferrous Bysglicinate Chelate, a new compound named FERALGINE®has been developed [16]. FERALGINE® is a “co-processed compound” between two well-Known substances: Ferrous Bysglicinate Chelate and Alginic Acid, two substances defined like G.R.A.S (Generally Recognizes as Safe) by F.D.A. (Food and Drug Administration): by using spray drying technology the two active principles have been “co-processed” in a new one, patent pending

e-ISSN: 2320-1215
p-ISSN: 2322-0112

compound [16]. The spray drying technology applied to this new "co-processed compound" allows to iron powder an increased of superficial area with a "great" uniformity of the single particles (Figure 8) thank to these characteristics FERALGINE® shown a quick and more extensive iron absorption together with an increase in gastrointestinal protection and an increased in tasteful of the final iron product [16].

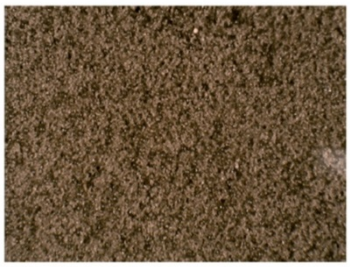

Figure 8. Feralgine powder (picture making by stereomicroscopy Wild Heerbrugg Makroskop M420 linked to an OPTIKAM MICROSCOPY DIGITAL USB CAMERA) [16].

The results obtained in our study are surprising because of "the total absence of adverse events" together with "a statistical significant increase" ($p<0.0001$ – ANOVA between subject and intra-subject) for every primary (Hb) and secondary (Red blood cells, Ht, MCV, Plasma Iron Concentration and Ferritin) end points evaluated. The value of the medium increase in Hb values in the medium treatment time (1.2 g/dl for 46.25 days of treatment) is in accord with the international guidelines that describe like "success" of an oral iron therapy in IDA "an increase in Haemoglobin of 1 g/dl after one month of treatment". The fact that this results have been obtained by using a very low dosage of elemental iron per day (30 mg of elemental iron containing in 1 caps of FERALGINE®) confirms the high bioavailability of the new co-processed compound. A period between 35 days and 60 days of therapy restored Hb values, and RBC, MCV, Ht, Plasma Iron Concentration and Ferritin in IDA patients without adverse events. No one of the patients treated stopped oral iron therapy during domiciliary therapy because of adverse events confirming the excellent safety profile of the new co-processed compound obtained thank to the uniform distribution of the gastroprotection alginic acid on the iron powder [16]. Also, the clinical evaluation of chronic fatigue and asthenia, referred from the patients during the first visit, has been disappeared at the end of the trial, per the laboratory data improvements. Limitations of this study include the open-label, non-blinded, uncontrolled design, which is, obviously, a potential source of bias and the small sample size of the patients enrolled in the trial that limit as "pivotal" the trial results and interpretation. Nevertheless, the absence of adverse events together with the objective results (increased of the values in Laboratory data) in terms of efficacy allow to FERALGINE® treatment an interesting profile that, if confirmed in Randomized, Controlled, double blind clinical trial with an adequate sample size of patients, could ascribe to this new co-processed compound a "key role" in oral iron therapy.

CONCLUSIONS

Oral iron therapy containing ferrous ion is the first line-treatment for patients affected by IDA: using available iron salts, almost 30% of the patients stopped domiciliary therapy without talking with medical doctor because of gastrointestinal adverse effects. In these patients, an alternative to typical oral iron preparation available on the market is required to effectively manage and treat IDA. FERALGINE®, a new patent-pending "co-processed" substance between Ferrous Bysglicinate Chelate and Alginic Acid obtained by spray drying technology, seems to be an interesting alternative option to treat IDA by oral route. In this pilot, clinical trial the effectiveness of 30 mg of elemental iron containing in FERALGINE®has been tested in IDA patients showing an ability in control IDA laboratory data such as Hb, RBC, MCV, Ht, Plasma Iron Concentration and Ferritin without gastrointestinal adverse events. Also, the clinical IDA-related symptomatology such as Chronic fatigue and asthenia have been controlled by a 46 days' time course of FERALGINE® therapy. Surprisingly, only a little quantity of elemental iron belonging to FERALGINE® (30mg daily) has been able to reverse Hb value decrease according to the increase requires by international guidelines (1 g/dl Hb increase for month) [19] confirming the high bioavailability of this new compound. Taking together these observations seems to support the use of FERALGINE® as first-line treatment for patients affected by IDA in order to avoid therapy discontinuation and, consequently, all the associated adverse health and Quality of Life related issues including impaired cognitive development and performance, reduced work capacity, lower resistance to infections, increased morbidity and mortality related to childbearing, restricted infant and child growth and impaired endocrine function [20]. If this pilot and pivotal data will be confirmed by RCT with an adequate sample size this new "co-processed compound" could become "a gold standard" for IDA patients all around the world.

e-ISSN: 2320-1215
p-ISSN: 2322-0112

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