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Iron Integration in Anaemias and New Pharmaceutical Technologies Correlation between Pharmaceutical Iron Technology and the Effectiveness of Supplements

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Abstract

Iron is one of the most important elements for humans because it plays an essential role in many metabolic processes. However, it is also recognized to be dangerous for its detrimental effect inside human cells, where, in the absence of homeostatic balance, it can induce free radicals formation.

Moreover, an excessive accumulation of iron in tissues can produce iron overloading, a condition incompatible with life. The use of liposomes as carriers can represent an interesting iron therapy to improve iron bioavailability and reduce its negative effects, in particular during pregnancy.

In this study, we present the results of Post Marketing Surveillance on an iron-sulfate in liposomes based product plus B-complex vitamins (Iron-folic) in the years 2017-2018.

Keywords: Iron; Elements; Metabolic; Therapy; Vitamins

Introduction

Substitution treatment of iron presents one of the great challenges of medicine for overcoming the many difficulties inherent of iron in effectively and safely way. The limits of iron supplementation are low absorption, metallic taste, gastrointestinal disorders, nausea, constipation or diarrhea, and oxidative stress.

Although iron is one of the essential trace elements for living organisms, including man, since it performs multiple metabolic and biological synthesis functions, on the other hand, it presents a reduced tolerance for the important risks associated with its intake. In fact, in all living organisms, the ionic iron Fe++ or Fe+++ never exists in free form but it is always carried by complex molecular structures that ensure transport and use in total safety.

This is because the iron in ionic form produces harmful effects on cells and in the absence of homeostatic control; it generates the production of free radicals, according to the famous Felton reaction. Moreover, its excessive accumulation causes irreversible damage to cellular structures.

To overcome this problem, technological research has made available various transport systems (carriers) for drugs and active ingredients, to improve their absorption and tolerability.

In the biomedical field, in particular, delivery systems are intensively studied to optimize the results obtained in the diagnosis and treatment of the most common pathologies.

Among the several delivery systems used in the biomedical field are liposomes, nanospheres, nanocapsules, micelles, etc.

A recent review of nanotechnologies and delivery systems used in the biomedical field was the subject of a conference held in Rome on 19th and 20th June at the Istituto Superiore di Sanità and abstracts are published in “European journal of histochemistry” [1].

Nowadays the most widespread and used technology is represented by liposomes, for the ease of their production and versatility in their use. Liposomes consist of a double layer of phospholipids with an internal cavity that can contain and transport various substances in solution such as drugs or active substances (Figure 1).

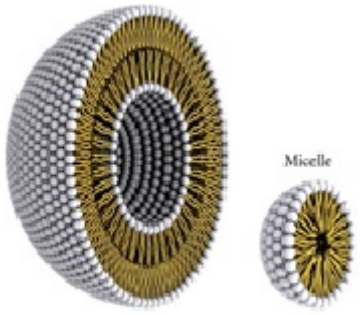


Figure 1: Liposomes and micelles.

The use of liposomes as carriers is particularly suitable for those substances that have a low therapeutic index (such as some anti-cancers, antibiotics, etc) because they reduce drug concentration and improve bioavailability with reduced side effects [2].

The adoption of liposomal technology allows the overcoming also the disadvantages of the martial therapy mentioned above.

Recently a particular iron in liposomes has been introduced on the market, patented with the name of BIOFER of production of Lipotech's company [3].

It is iron sulfate plus vitamin C enclosed in liposomes and dehydrated in powder.

The effectiveness and safety of BIOFER has been documented in numerous clinical studies [4-9] and has been adopted for the fortification of several different foods by major food companies since 1994 till today.

In 2016 the use of BIOFER liposomal iron and other vitamins associated with it was introduced on the Italian market as a supplement to treat various forms of anemia

The choice of BIOFER and Iron sulphate is based on two valid reasons:

- Iron sulphate is a low molecular weight molecule with the highest solubility and bioavailability compared to all other iron salts, in particular compared to pyrophosphate iron [3]
- The iron sulphate in liposomes BIOFER, besides having documented effectiveness and safety in the above studies, is the only one on the market as a supplement; all the others are made of pyrophosphate iron

The liposomal nature of the BIOFER and the capacity of assimilation on cell cultures in the absence of cytotoxicity have been verified by research carried out by the University of Urbino and the results have been subsequently published [10].

Two years after the introduction of the new integrator on the market, a survey by Post Marketing Surveillance (PMS) was carried out to ascertain its long-term effectiveness and safety.

Materials and Methods

This multi-center study brings together "observational results" from a population of over 11,000 patients treated during the years 2017-2018.

The design of the study is "open-label" in the Post Marketing Surveillance and follows the guidelines Ministry of Health and other important institutions [11].

Post-Marketing Surveillance (PMS) studies include monitoring procedures for patients undergoing treatment with drugs or supplements used in clinical practice. Unlike pre-marketing clinical trial procedures in which strictly controlled methodological conditions are essential, in post-marketing surveillance is required fidelity in data collection to monitor over time the safety of use of the tested products. However, PMS studies can provide valuable information on the use of the products sold, in special patients with special problems, which are not easily obtainable or predictable during pre-marketing studies.

Drawing of the work

The aim of this work is to evaluate the effectiveness and tolerability of a supplement based on iron and B complex vitamins, in adults to prevent and/or treat deficiencies from insufficient intake of these nutrients.

Simple open-label works with control of haematological parameters (Data on reserved files)

Questionnaire and registration: Administration of a questionnaire for an anamnestic survey. The first part of the questionnaire relates to personal history, with regard to predisposing diseases.

Other collected data: Age, ethnicity, smoking, physical activity, BMI, food (Confidential data)

Criteria for inclusion: Patients 18 years or more of age; of both sexes who have been asked for informed written consent; Patients enrolled with various degrees of anaemia were checked with routine examinations at the beginning and end of treatment by physicians with the following parameters: hematocrit, hemoglobin, ferremia (sideremia), and ferritin.

The values of the parameters under consideration for inclusion were haemoglobin 12 g/dl; ferritin 100 ng/ml or ferritin between 100 and 300 ng/ml with transferrin saturation (TSAT) 25%.

Patients with a tendency to develop anaemia and previous treatments were ineffective have been included too.

Criteria for exclusion: Excluded patient with infectious diseases of any nature, blood transfusions, treatment with iron intravenous or oral route for the last three months

Duration of treatment: Patients were treated for at least three months, or until normal values were restored, if they had no intolerance problems.

Interruption of treatment: Patients who did not respond to treatment after two months were excluded by work.

Patients who had important side effects during treatment, which were certainly attributable to the treatment itself and not to other concomitant therapies, were excluded and reported side effects.

During the study period, no changes were made to the current therapy, and the diet of patients was not changed.

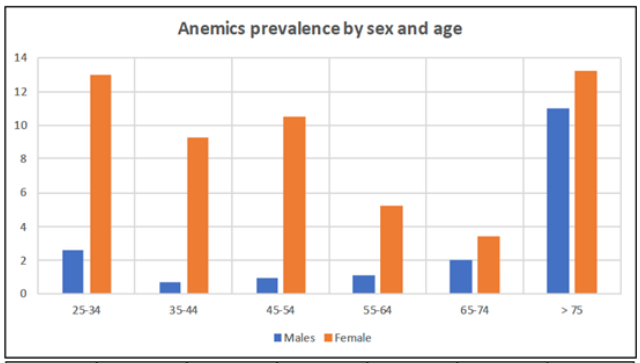
Case Study

The treatment of patients was recruited in various Italian regions, with a particular concentration in Sicily, Emilia,

Triveneto where Iron-folic is more widespread (Data on file: copyright imshealth years 2017-2018) **(Table 1 and Figure 2)**.

Table 1: Geographical distribution of enrolled patients.

Region	Enrolled Patients	Percentage
Abruzzo	39	0.3
Basilicata	73	0.6
Calabria	121	1
Campania	453	3.6
Emilia	2373	18.6
Lazio	110	0.9
Liguria	0	0
Lombardia	218	1.7
Marche	125	1
Molise	0	0
Piemonte	12	0.1
Puglia	98	0.8
Sardegna	316	2.5
Sicilia	6728	53.2
Toscana	1974	15.6
Umbria	11	0.1
Valle Dáosta	0	0
Total	12651	100



Age	25-34	35-44	45-54	55-64	65-74	> 75
Males	2,6	0,7	0,9	1,1	2	11
Female	13	9,3	10,5	5,2	3,4	13,2

Figure 2: Geographical distribution of treated patients and prevalence of anaemia by gender and age.

Some patients (12% of the total) previously treated with other forms of iron, drugs or supplements, from which they had not achieved improvements, were also included in the case studies.

For the treatment of patients, we used the product notified to Health Ministry in 2016: Iron-Folic by Nutragenetech Srl- with number 87465, formulated with BIOFER plus three vitamins of B complex in vegetable capsules.

The association with BIOFER of three B-complex vitamins: Folic acid, Vitamin B6 and Vitamin B12, finds its rationale in the fact that these vitamins play an essential role in the synthesis of many substances essential for the well-being and in particular for erythropoiesis.

Patients were treated with 1 capsule per day of this product.

All patients were asked for informed consent by physicians, who also had adverse events and any intolerances found during treatment **(Table 2)**.

The results are given in the following table:

Table 2: Result shows treated patients after treatment; (1)Time to reach normal values (days); (2)Number of patients who reached normal values; Percentage of patients reaching normal values.

	Hematocrit (%)	Hemoglobin (g/di)	Ferraemia (%)	Ferritin (ng/ml)	Side Effects
Initial (I)	33 ± 1,9	10,1 ± 0,9	37,2 ± 16,1	12,7 ± 1,3	
Final (F)	38,5 ± 2,3	12,6 ± 0,7	132,6 ± 47,3	28,5 ± 26,4	
Δ (I-F)	5,5 ± 23,5	2,6 ± 1,2	95,4 ± 48,1	15,8 ± 26,8	
Tn (1)	51,1 ± 23,5	50,7 ± 19,2	46,6 ± 26,2	46,7 ± 16,8	0,20%
Pn (2)	100%	100%	100%	80%	
P%	100%	100%	100%	50%	0,20%

Conclusion

As shown in the table, the product was effective in all treated patients. The results showed that hemoglobin, hematocrit, ferraemia and ferritin values increased significantly ($p<0.05$). During treatment adverse events were reported in 0.20% of patients and were not necessary, under any circumstances, discontinue treatment. These results encourage the use of the product IRON-FOLIC in other similar situations but require further investigation with clinical studies better structured from a methodological point of view, and comparison with other preparations, to confirm therapeutic validation.

Declaration

This report records the epidemiological follow-up data derived from the use of the IRON FOLIC nutritional supplement registered by the Healthy Minister with the N° 87465 and it is configured as a survey of Postmarketing Surveillance (PMS).

So it is not intended to affirm as a "therapeutic solution" a supplement that statement should not be understood as a substitute for a varied diet but should be used within a healthy and balanced lifestyle.

The present survey is only one " Non-interventional experimentation or observational study" a study in which food is taken according to the usual quantities/modes of use and not according to a predefined test protocol.

No additional monitoring procedure applies to the subjects and epidemiological methods are used for the analysis of the collected data; Healthy Minister; Guidelines on studies to assess food safety and properties review June 2015. Moreover, in this case, it's about supplements based on minerals and vitamins, the effectiveness and safety of which has been widely documented by numerous clinical trials published in international journals cited in the bibliography. NB To ensure the impartiality of the results, clinicians have participated in the survey in an anonymous and voluntary manner.

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