

IRON - POLYMALTOSE



“Boy Holding a Basket of Fruit”, oil on canvas, c.1592. Michelangelo Merisi da Caravaggio. Galleria Borghese, Rome.

...This last, it is recorded, entered into a competition with Zeuxis, who produced a picture of grapes so successfully represented that birds flew up to the stage buildings; whereupon Parrhasius himself produced such a realistic picture of a curtain that Zeuxis, proud of the verdict of the birds, requested that the curtain should now be drawn and the picture displayed; and when he realized his mistake, with a modesty that did him honour he yielded up the prize, saying that whereas he had deceived birds Parrhasius had deceived him, an artist. It is said that Zeuxis also subsequently painted a Child Carrying Grapes, and when birds flew to the fruit with the same frankness as before he strode up to the picture in anger with it and said, "I have painted the grapes better than the child, as if I had made a success of that as well, the birds would inevitably been afraid of it".

*Pliny the Elder, "The Natural Histories", Bk XXXV, 62
77-79 A.D*

The period historians today call the Renaissance, represented one of the most astonishing periods of the cultural development of the West. Following the fall of the Western Roman Empire in 476 A.D, the West entered a protracted "Dark Age", where little scientific or cultural progress seemed to occur, all intellectual development held in relative stasis for close on eight centuries, by religious dogma and superstition. Although the term "Dark Ages" is today considered "politically incorrect", it is nonetheless entirely appropriate at least in relative terms. As William Manchester, wrote in his magisterial "A World Lit only by Fire".... "Modern historians have abandoned that phrase, one of them writes, "because of the unacceptable value judgment it implies." Yet there are no survivors to be offended. Nor is the term necessarily pejorative. Very little is clear about that dim era. Intellectual life had vanished from Europe. Even Charlemagne, the first Holy Roman Emperor and the greatest of all medieval rulers, was illiterate..."

Around the Fourteenth century, the ancient knowledge, persevered largely in inaccessible form (to the West at least) at Constantinople and in the Islamic world began to be restored to the West, which took to its rediscovery with an insatiable thirst and an ungoverned curiosity. Over the next centuries the new learning would equal and then far surpass the ancients. This astonishing relearning would see its culmination in the Seventeenth century, as the "Age of Reason", or the great "Enlightenment"; and the birth of the age of science as we know it today. By the Fourteenth century very little had survived. It was not simply the fall of Rome, there were many other factors, such as the disastrous loss of the great Library of Alexandria to fire and the rise of extreme religious dogma and oppression that contributed to the catastrophic collective loss of memory of the classical age. Records were fragmentary in the extreme - apart from a few great works which survived almost complete. Among these it was the works of the extraordinary Roman polymath and military commander, Pliny the Elder, (c.23- 79 A.D) that stand out as the greatest jewel in the crown of lost knowledge from a remote but fabulous age.

Pliny wrote three monumental works, each veritable encyclopedias that summarized virtually all knowledge in their fields. Tragically the first two works did not survive the early middle ages, 31 volumes on the History of Rome and 21 volumes dedicated specifically to the history of the early wars Rome fought in Germania. Fortunately his best work has survived, "The Natural History"; 37 priceless volumes. The only Roman

“encyclopedia” of the natural world to survive to the present day, is rich in fascinating anecdotes which bring Pliny’s times to vivid life. What is less well known about Pliny’s work of “science” however is that ironically the last five volumes give us our only written record of Greek and Roman Art! Pliny describes the geology of the world not in dry terms of locations of mines or amounts of precious metals produced, but rather the uses to which these were put to in the Arts - most fascinating of all he gives rich descriptions not only of fabulous works of Art which were produced from the natural products of the earth, but of the Artists themselves, very famous in their day, and who without Pliny’s work we would remain in complete ignorance of their existence. The greatest Artists of the early and high Renaissance studied Pliny’s books on Art intensely, they laboured mightily to emulate the ancient world’s achievements and above all to regain the lost prestige and exalted position that Art and the Artists themselves had once enjoyed, but had totally lost during the long ages of darkness, that came after the fall of Imperial Rome in the West.

One famous anecdote of Pliny tells of the great rivalry between Zeuxis and Parrhasius. As part of a theatre stage backdrop Zeuxis had painted a still-life of grapes, so convincing in its reality that birds flew up to it and began to peck at it. Parrhasius decided to see if he could outdo Zeuxis. He painted a curtain and placed it in front of Zeuxis’ painting. When Zeuxis saw that a “curtain” had been placed in front of his painting he demanded that it be drawn back, as it was obscuring his masterpiece. Suddenly he realized that the curtain was in fact a painting, and then learning that it had been painted by his rival Parrhasius, he graciously conceded that Parrhasius was the superior painter, as he himself had deceived only birds, but Parrhasius had deceived a fellow painter. This story and others struck a powerful chord with Renaissance Artists, whose quest was the achievement of reality through illusion and the idealization of nature. In subsequent centuries the apogee of human recreation of the real world would be achieved and carried on until the mid-Nineteenth century when Art moved on to new and radically different directions.

In the late Sixteenth century the great Baroque master, Michelangelo Merisi da Caravaggio inaugurated in Italy a genre of realist still-life. Two of his paintings, “Boy Holding a Basket of Fruit”, circa 1592 and “The Basket of Fruit”, 1599, recreate the pair of images by Zeuxis; the choice of subjects would not have been lost on educated connoisseurs, who would have known of Pliny’s story. Caravaggio was pitting his genius against that of the ancient Greek masters, Zeuxis and Parrhasius.

In the Art of Medicine, we strive, like ancient and Renaissance masters alike, for perfection. In the treatment of iron deficiency we now have a superior treatment over oral preparations in the form of IV iron preparations. Alas though, true perfection is a mere illusion, as Zeuxis himself would have admitted. Though he could fool the birds with his brilliant still-lives, he could not fool them with his likeness of humans; “I have painted the grapes better than the child, as if I had made a success of that as well, the birds would inevitably be afraid of it”. And so it is with our IV iron formulations, though a significant advance over older oral therapies, they may yet have some not insignificant side effects. The search for iron therapy perfection therefore remains an ongoing quest!

IRON - POLYMALTOSE

Introduction

Iron - Polymaltose (trade name in Australia **Ferrosig** or **Ferrum H**) is one of a range of newer IV iron preparations, that are far safer than the older iron-dextran preparation which is no longer used.

It has very low rates of allergic or adverse reactions.

A “**total-dose**” infusion (i.e. where iron stores can be replenished in a single treatment episode) can be administered with iron polymaltose.

Chemistry

Iron - Polymaltose is iron dextran - (as opposed to the now no longer available dextran)

It consists of a macromolecular sphero-colloidal complex of iron (III) hydroxide and the carbohydrate polymaltose.

Classification

There are 3 IV iron formulations currently available:

1. Iron - polymaltose
2. Iron - carboxymaltose
3. Iron - sucrose

The polymaltose formulation binds iron more tightly than the carboxymaltose and the sucrose formulations. As the carboxymaltose and the sucrose formulations bind iron less tightly there is more potential for free iron to “leach” into the circulation and cause adverse reactions.

For this reason total replenishment dosing should not be attempted as a single dosing with the carboxymaltose or sucrose formulations.

Total replenishment can be achieved in single dosing regimens with the polymaltose formulation however where iron is transferred directly to the body’s iron storage sites, with minimal leaching of free iron.

See Appendix 1 for comparison data.

Preparation

Iron - Polymaltose as:

Ampoule:

- 100 mg/ 2 mls (Ferrum H)

Mechanism of Action

Iron is a vital component of:

1. Haemoglobin:
2. Myoglobin:
3. Cytochromes and other enzymes essential to aerobic cellular metabolism.

Pharmacodynamics

A “total-dose” infusion (i.e. where iron stores can be repleted in a single treatment episode) can be administered with iron polymaltose.

Pharmacokinetics

Administration:

- Iron - Polymaltose is given as an **IV infusion**.
- IM Injection of iron preparations is *not* recommended as it is painful and can cause permanent skin scarring and discolouration.

Metabolism:

- Iron is incorporated into iron depleted haemoglobin, myoglobin and cytochrome molecules.

Body transferrin and ferritin store are also repleted.

Polymaltose is either metabolised or excreted.

Indications

Indications for IV iron therapy in general include:

1. **Rapid** repletion of iron stores is required:
 - Patients who require **blood transfusion**
 - There is a clinical need for a rapid restoration of iron stores for example in patients where the optimisation of erythroid response is important to prevent physiological decompensation and / or transfusion.

It can help avoid significant complications or a blood transfusion (such as before or after major surgery or in late third trimester of pregnancy)

2. Avoidance of blood transfusion in non-urgent situations
 - Blood transfusion carries greater risks than IV iron infusion and so should be avoided unless there is an immediate need to increase the Hb level.

IV iron transfusion offers another option to raise Hb levels, albeit more gradually, whilst avoiding a blood transfusion.
3. Used for those unable to tolerate oral therapy
4. Can be used for patients with malabsorption GIT disease
5. Pregnancy (beyond the first trimester) and postpartum, to avoid imminent decompensation/transfusion (e.g., in women who present late and/or display severe anaemia).
6. In situations of *ongoing* iron blood losses that will likely exceed oral iron absorptive capacity
7. Chronic renal impairment patients who are receiving concomitant erythropoietin-stimulating agent therapy.
8. Useful for patients who are unreliable/ socially disadvantaged, who are unlikely to be compliant and unlikely to present for follow-up

Contraindications/ Precautions

These include:

1. Allergy to a parenteral iron product, means parenteral use is generally contraindicated. However, in certain circumstances, e.g. chronic kidney disease, an alternative formulation may be considered; seek specialist advice.
2. Anaemia **not** due to iron deficiency (contraindicated).
3. Haemochromatosis/ haemosiderosis (contraindicated).

Pregnancy

Intravenous and oral iron supplements are safe to use in correcting iron deficiency during pregnancy

If possible, avoid parenteral iron products, in the **first trimester**, due to risk of hypersensitivity reactions (some manufacturers of parenteral iron contraindicate use in the first trimester).³

Iron - Polymaltose is classified as a **category A** drug with respect to pregnancy.

Category A class drugs are those drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Breast feeding

Intravenous (and oral) iron formulations are safe to use during breastfeeding.

Note that exclusively breastfed infants of women who are iron deficient may require iron supplementation as human milk is a poor source of iron.

Adverse Effects

In general terms the sugars cause the allergic reactions - while “leached free iron” causes the other (“oxidative”) effects.

1. Allergic/ hypersensitivity reactions:

Anaphylactic and anaphylactoid reactions, though significant reactions are uncommon with the newer IV iron agents.

- Fever (CRP tends to be normal).⁴
- Bronchospasm
- Tachycardia, changes hypertension/ hypotension
- Dermatological hypersensitivity skin reactions can also occur

2. Nonspecific constitutional symptoms.

- Malaise
- Nausea, vomiting
- Headache
- Arthralgias/ myalgias

3. Chest muscle pain

4. Hypophosphataemia
5. Permanent skin staining:

IM administration or **para-venous extravasation** of iron preparations can result in long lasting or *permanent* dark brown skin discolouration, inflammation and even tissue necrosis.

In case of para-venous leakage, the infusion must be stopped immediately.

Iron staining has been treated successfully with Nd-YAG laser therapy, resulting in almost complete resolution of staining.

See Appendix 3 below

6. **Delayed reactions:**

It should be noted that acute reactions are **usually mild** and **are uncommon**

Delayed reactions however, can also occur and in fact appear to be relatively more common than acute reactions. This phenomenon has been well documented for Iron - polymaltose, ⁴ but it is also seen with Iron carboxymaltose and Iron sucrose as well.

Reactions tend to be of the *non-specific constitutional type* (as opposed to true allergic reactions).

Delayed reactions occur up to **2 days** after the infusion (in up to 26 % of cases for Iron -polymaltose in one study ⁴) and can last from a little as long as **1 day** to as long as **8 days**, (with a median of **4 days**).

Patients who receive IV iron, should be warned of the possibility of a delayed reaction.

Previous uneventful iron infusions do not guarantee freedom from adverse effects on subsequent infusions.

Alternative parenteral iron preparations should be considered if iron deficiency recurs.

This unexpected frequency of adverse events should not deter clinicians from the use of intravenous iron, as the problems associated with oral iron replacement therapy, including poor compliance, high rate of side effects and slow and inadequate iron repletion, far outweigh the chance of transient, mild, (albeit occasionally severe) adverse effects from a therapy that **reliably ensures** iron repletion.

Dosing

Dose and administration vary according to:

- The formulation being given
- Local protocols
- Specific product information.

Iron infusions should be prescribed on **product-specific forms** designed for local use, as maximum dose per infusion, rate of infusion and dilutions are **not** interchangeable between the various formulations.

Iron polymaltose (Ferrosig or Ferrum H) can be given in a single large dose (“total dose” infusion) or less over a number of hours.

Exact dosing regimens are complex and are based on the **Ganzoni formula** for calculation of total body iron deficit which gives the **total** iron dose in mg for restoration of haemoglobin (Hb) and repletion of body iron stores. **Ideal body weight** is used, (see **Appendix 2 below**).

A reasonable *initial* empiric dosing for iron - polymaltose is:

- **1000 mg for patients > 35 kgs weight**
- **500 mg for patients < 35 kgs weight.**

Dilute in 250 mls of normal saline and infuse over 2 hours

Appendix 1

Formulation	Cost	Initial Empiric Dosing	DILUTION & RATE	Subsequent Dosing to Achieve Total Replenishment
Iron - Polymaltose	Ferrum H \$ 3.42	1000 mg for > 35 kgs 500 mg for < 35 kgs	Give in 250 mls normal saline over 2 hours	Total iron replenishment can be achieved in a single initial dose.
Iron - Carboxymaltose	Ferinject \$ 36.38 (100 mg ampoule) \$ 141.37 (500 mg ampoule)	1000 mg for > 50 kgs 500 mg < 50 kgs	Give in 100 mls normal saline over 30 minutes	Cumulative iron doses greater than 1000 mg must be split into TWO DOSES given AT LEAST ONE WEEK APART
Iron – Sucrose	Venofer \$ 4.62	200 mg for > 35 kgs Consult Haematol for < 35 kg	Give in 100 mls normal saline over 30 minutes	Doses of 200 mg can be repeated every 72 hours to achieve the required iron total.

Appendix 2

The **Ganzoni formula** for the calculation of total body iron deficit:

Total body iron deficit in mg = Iron depot + [weight in kg x 0.24 x (target Hb in g/L – actual Hb in g/L)]

- Use ideal body weight if overweight/obese
- Iron depot (store):
 - >34kg weight = 500mg
 - ≤ 34 kg weight = 15mg/kg body weight (to a maximum of 500mg).
- Target Hb:
 - ♥ > 34 kg weight = 150g/L
 - ♥ ≤ 34 kg weight = 130g/L

Ideal body weight is calculated from the following formula (Australian Medicines Handbook 2012):

- Females: 45.5 kg + 0.9 kg/cm for each cm >152 cm.
- Males: 50 kg + 0.9 kg/cm for each cm >152 cm.

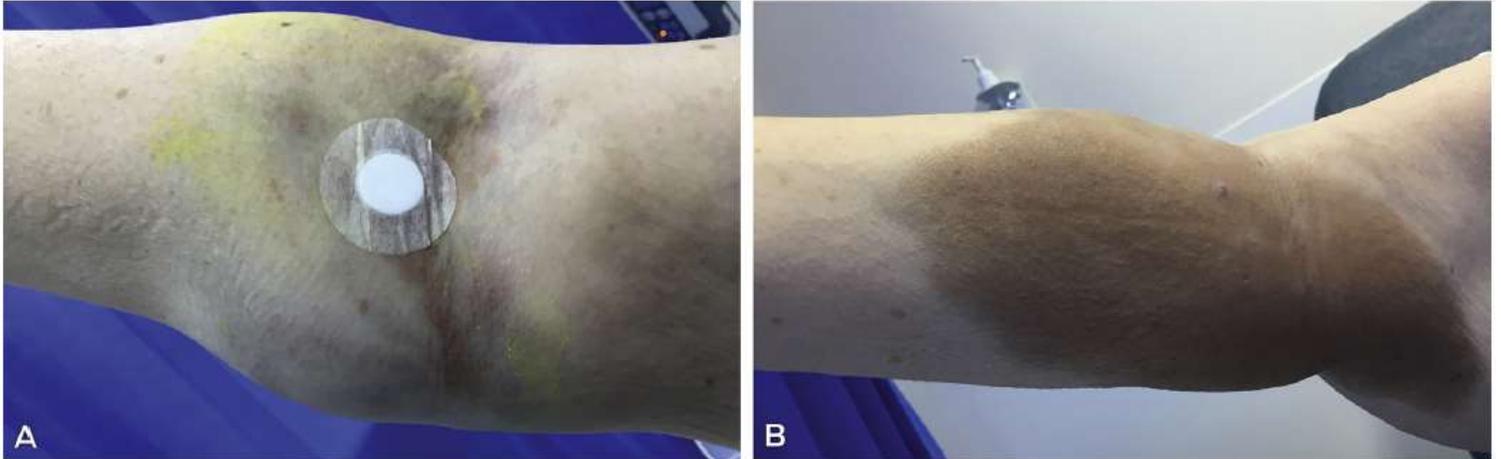
Add 10% for a heavy frame; subtract 10% for a light frame

Alternatively:

A medical calculator is available at:

- <http://www.mdcalc.com/>

Appendix 3



Iron staining secondary to extravasation of IV Iron polymaltose. It was administered via rapid infusion to a patient with iron deficiency anaemia. Staining developed during the infusion, which was stopped immediately. Panel A show the arm 30 after cessation of the infusion. Staining extended to a large part of the arm, and follow up at 21 days revealed no change in size; Panel B.

*This reaction has been reported with multiple iron preparations. One study found an incidence of 1.3%. Iron staining can be successfully treated with **Nd - YAG** laser therapy, resulting in almost complete disappearance. Intravenous infusion sites should be monitored closely for extravasation during administration.*

***Nd - YAG** (neodymium-doped yttrium aluminium garnet; $\text{Nd:Y}_3\text{Al}_5\text{O}_{12}$) is a crystal that is used as a lasing medium for solid-state lasers.*



"Basket of Fruit", oil on canvas, c. 1597, Michelangelo Merisi da Caravaggio.

References:

1. Iron - Polymaltose in MIMs Website 1 May 2014.
2. RWH - Pregnancy and Breastfeeding Guidelines.
3. Iron in Australian Medicines Handbook, Website Accessed May 2016.
4. M. L. Haines, P. R. Gibson; Delayed adverse reactions to total dose intravenous iron polymaltose. *Internal Medicine Journal* 39 (2009) 252 - 255.
5. Martin L Canning et al. Iron stain following an intravenous iron infusion. *MJA* 207 (2) 17 July 2017.
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