



## Subcutaneous bolus injection of deferoxamine in adult patients affected by onco-hematologic diseases and iron overload

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### Abstract

**Background and Objective.** Chelation therapy is often necessary for patients who undergo chronic transfusion therapy for myelodysplastic syndromes. In these patients, deferoxamine, the most widely used chelating agent, has been reported to be effective in reducing the iron burden and the transfusion requirement. Unfortunately, compliance with the drug, that is usually administered by slow subcutaneous infusion via a battery operated pump, is often poor, especially in elderly patients.

**Design and Methods.** To verify efficacy and tolerability of deferoxamine by subcutaneous bolus injection as compared to the conventional pump-driven slow infusion, eleven patients affected by onco-hematologic diseases were given 2 g of deferoxamine diluted in 10 mL of distilled water over twelve hours by continuous infusion, or by bolus injection in two divided doses.

**Results.** Mean urinary excretion was comparable with the two methods, being  $9,183 \pm 4,349 \mu\text{g}/48\text{h}$  after two daily subcutaneous bolus injections and  $8,291 \pm 3,970 \mu\text{g}/48\text{h}$  with the slow infusion. The bolus injection was preferred by all eleven patients, who chose to continue chelation therapy by this method.

**Interpretation and Conclusions.** The iron excretion induced by bolus injection is not statistically different from that induced by subcutaneous infusion. The side effects are acceptable. Subcutaneous bolus injection of deferoxamine is an acceptable alternative to slow, pump-driven infusion.

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Key words: deferoxamine, chelation, iron overload, bolus injection, myelofibrosis

Chronically transfused patients develop iron overload which in time becomes responsible for variable degrees of organ damage and dysfunction. Chelation therapy is therefore neces-

sary to prevent or decrease the iron burden. The almost universally used chelating drug is deferoxamine (DF) that needs to be infused parenterally and that, because of its short half-life, is usually administered subcutaneously over 8 to 12 hours by means of a battery-operated portable pump.<sup>1</sup> In addition to its chelating effects, DF has been reported to be effective in reducing the transfusion requirement.<sup>2,3</sup> However, compliance with this treatment is often poor, especially in adult or elderly patients with hematologic and myeloproliferative disorders. Recently it has been reported in a group of thalassemic patients<sup>4</sup> that the administration of deferoxamine by subcutaneous bolus administration twice a day is as effective as the slow subcutaneous infusion. We tested the efficacy and tolerability of this new therapeutic modality in a population of adult patients undergoing transfusional therapy for chronic onco-hematologic disorders.

### Materials and Methods

Eleven patients, 51 to 77 years of age (median age 63 years) were enrolled in this prospective study. All patients were affected by onco-hematologic diseases and were regularly transfused (two units of concentrated erythrocytes every 2 to 3 weeks) at the Transfusion Center of the University of Verona. Informed consent was obtained from all patients before enrollment in this study.

Patients' characteristics are reported in Table 1.

Patients were enrolled alternatively to start with continuous infusion or bolus injection in two divided doses. Any previous chelation therapy (by continuous infusion in all but one patient) was discontinued 48 hours before the test.

### Continuous infusion

Each patient self administered 2 g of DF diluted in 10 mL of distilled water over twelve hours, subcutaneously in the abdominal wall in two consecutive nights and collected urine, at home, from the beginning of the first infusion and for 48 hours. Since there is a high variability in iron excretion in each patient, 24 hr collections were not considered adequate.

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**Table 1. Patients' characteristics and iron excretion.**

Pt	Diagnosis*	Sex	Age (years)	Ferritin (mg/L)	48-h urinary iron excretion after s.c. bolus injection (mg/48h)	48-h urinary iron excretion after s.c. pump infusion (mg/48h)
1	MFI	F	61	1,705	8,450	6,870
2	MDS, RA	F	54	1,400	8,728	10,218
3	MDS, RAEB	M	77	2,236	17,640	14,510
4	MFI	M	61	2,100	7,880	11,530
5	MDS, RAEB-t	M	77	3,140	4,243	2,556
6	CML, CF	F	48	1,670	13,000	11,390
7	NHL, LG	F	77	1,130	4,144	3,737
8	MDS, RA	F	51	685	7,703	6,790
9	MDS, RAEB	F	76	1,186	10,990	8,262
10	MFI	M	66	660	4,360	3,400
11	EA	F	69	6,400	13,885	3,400

\*MFI = idiopathic myelofibrosis; MDS = myelodysplastic syndrome; RA = refractory anemia; RAEB = refractory anemia with excess of blast cells; RAEB-t = refractory anemia with excess of blast cells in transformation to acute myeloid leukemia; CML = chronic myelogenous leukemia; CF = chronic phase; NHL = non Hodgkin's lymphoma; LG = low grade; EA = erythroid aplasia.

### Bolus injection

The same daily amount of DF was administered in two divided doses, twelve hours apart, each diluted in 10 mL of distilled water. The injection was done by means of a 25 gauge scalp needle at the rate of about 1 mL/min, as tolerated. Particular attention was given to avoiding direct injection of the product into a vessel. Urine was again collected for 48 hours, at home, starting with the first bolus injection. Both continuous and bolus infusions were performed in the 48 hours preceding transfusion. The two tests were carried out two weeks apart, in different transfusion cycles. Vitamin C supplementation was not given. Urinary iron excretion was measured by atomic absorption spectrophotometry. Side effects were recorded by all patients on a specifically prepared form.

Comparison of iron excretion was performed by paired t test analysis.

### Results

The mean 48-hour deferoxamine-induced urinary iron excretion was  $9,183 \pm 4,349$   $\mu\text{g}/48\text{h}$  (range 4,144 to 17,640) after two daily subcutaneous bolus injections and  $8,291 \pm 3,970$   $\mu\text{g}/48\text{h}$  (range 2,556 to 14,510) after subcutaneous infusion. The 48-hour urinary iron excretion for each patient is reported in the table. Nine patients had a higher 48-hour urinary iron excretion after subcutaneous bolus injection than after subcutaneous infusion of DF. The difference between the two methods of drug administration was not statistically significant ( $p = 0.2$  by paired t test). There was no difference in whether the bolus or the pump was administered first. Side effects were mild local swellings and were of similar intensity with

both methods. One patient complained of reddening and pain during the first bolus injection. The symptoms did not reappear during the subsequent injections. At the end of the study all eleven patients chose to continue chelation therapy by the bolus method.

### Discussion

Compliance with slow subcutaneous infusion of deferoxamine by means of a portable pump is often poor. Therefore, the search for new chelators, or improved methods of administration of the old one, is ongoing. Following a preliminary report by Jensen *et al.*,<sup>3</sup> it has recently been shown that DF administered as a bolus injection is effective and well tolerated in young patients with thalassemia.<sup>4</sup> Similar data were later duplicated by others.<sup>5</sup> The toxicity of the oral chelator deferiprone is at present under scrutiny.<sup>6</sup> In addition, a phase I trial to assess the tolerability of a modified form of DF, that should be injected as a daily bolus of a small amount of product has just been completed.<sup>7</sup> However, until such or other products are available for widespread use, the bolus administration of DF might be a valid alternative, as confirmed by the findings in the present study, especially for elderly patients with acquired blood disorders, who tolerate poorly the burden of pump-driven subcutaneous infusion. All of our adult patients, in fact, chose to continue chelation therapy by bolus injection. However, the level of iron loading in these patients was relatively low and therefore the potential efficiency of chelation may be less with the repeated bolus injection if dose response curves with the two approaches were determined. Since there is a high variability in iron excretion in each

patient, even 48 hr collections could be inadequate, although our results are very similar to those of previous studies. A word of warning is needed regarding the risk of allergy that, according to recent reports<sup>8,9</sup> could be increased by pulsatile injections, as compared to slow infusion, of DF. In addition, a study is ongoing to evaluate the levels of non-transferrin bound iron maintained by the DF bolus. On the other hand, intravenous and/or continuous delivery of DF may involve the risk of developing lung injury.<sup>10</sup> Larger long-term trials will be necessary for establishing long-term efficacy and safety of this method to treat hemosiderosis.

### Contributions and Acknowledgments

CB-P was responsible for study design (with MF and GA) and for writing the paper; MF and GA were also responsible for data handling and statistical analysis; GG was responsible for recruitment of the patients and discussion of the project; AV and MDG organized the urine collection and measured the study parameters.

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### Disclosures

Conflict of interest: none.

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### Manuscript processing

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