# Effect of Deferiprone on Urinary Zinc Excretion in Multiply Transfused Children with Thalassemia Major

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*A prospective multi-centric study was conducted to determine if iron-chelating agent deferiprone also chelates zinc. Twenty four-hour urinary zinc levels were compared in multiply transfused children with thalassemia major not receiving any chelation therapy (Group A, n = 28), those receiving deferiprone (Group B, n = 30) and age and sex-matched controls of subjects in Group B (Group C, n = 29) by a colorimetric method. The 24-hour mean urinary excretion of zinc was significantly higher in Group B (1010.8 ± 1248.1 mcg) than in the other two groups (Group A: 547.8 ± 832.9mcg and Group C 459.8 ± 270.3mcg) indicating that deferiprone chelates zinc.*

**Keywords:** *Adverse event, Chelation, Hemosiderosis, Iron.*

BETA thalassemia is one of the most common genetic defects seen in certain populations(1). Thalassemia major represents the life threatening variety of this disorder wherein the child's life depends upon receipt of regular red cell transfusions. Chronic iron overload leading to organ dysfunction involving the heart, liver and endocrine glands is the logical consequence of life-long transfusion therapy(2).

Chelation therapy with desferrioxamine (deferoxamine) helps avert iron overload(3). However, the drug has to be administered as a subcutaneous infusion 5-6 days a week. Cost of therapy and need to administer it as an injection make many families reluctant in initiating chelation therapy. Deferiprone (L1 or 1, 2-dimethyl-3-hydxoxypyridin-4-one), the only oral iron-chelating drug cleared for clinical use, is primarily being prescribed in the developing countries. Although the drug deferiprone offers an affordable option to children with thalassemia major in developing countries, it is imperative that investigators continue to study the drug. Gastrointestinal disturbances, arthralgia, agranulocytosis and raised levels of transaminases in the liver are some of its known side effects(4). Being a chelator of iron, it is possible that the drug may also chelate other metallic ions. Zinc is one of the important elements that play an extensive role in various body functions. However, limited information is available regarding the effect of deferiprone administration on zinc status. Hence, the present study was undertaken to determine the effect of deferiprone therapy on urinary excretion of zinc.

## Subjects and Methods

This prospective study was conducted at two large tertiary care hospitals in Mumbai

over a period of one year. The institutional ethics committee endorsed the study protocol. Multiply transfused children diagnosed to have thalassemia major on the basis of clinical presentation, dependence on blood transfusion and hemoglobin electrophoresis report were enrolled in the study after obtaining an informed consent from the guardians. Those not receiving any chelation therapy were included in Group A while those receiving deferiprone were enrolled in Group B. In addition, the age-and sex-matched children without thalassemia major and not receiving any transfusion therapy were included in the study as controls (Group C) after following a similar procedure for obtaining the consent from the guardians. The controls were also matched for the nutritional status. The data regarding age at diagnosis, duration of transfusion therapy, yearly transfusion requirements (transfusion required in the last 12 months), results of the liver function tests (plasma levels of hepatic transaminases and protein), serum ferritin levels and the dose and duration of deferiprone therapy was collected by review of records. The nutritional status was determined and the grade of malnutrition was judged using the classification provided by the Indian Academy of Pediatrics(5).

Two mL of venous blood was collected from subjects using heparin as anticoagulant. The sample was centrifuged and plasma was separated. Twenty-four hour, urine was collected by patients at home in a zinc-free container. The volume of the urine was measured in the laboratory. Samples of plasma and urine were stored in the refrigerator at 2ºC to 8ºC and determination of zinc levels in these samples was done in batches of five samples. The laboratory technician who performed the assay was unaware of the groups to which the subjects belonged. Zinc level was estimated using a colorimetric method(6) using a kit provided by Randox Laboratories. Comparison of a variable between different groups was determined using Student's "t" test. Correlation of different variables in a single group was done by using coefficient of correlation.

**Results**

Eighty seven subjects (55 boys and 32 girls, M : F = 1.6) were enrolled in the study that included 28 children in Group A, 30 in Group B and 29 in Group C. As shown in *Table I*, the three groups were comparable in terms of age and state of malnutrition. Fifteen (50%) children in Group B were on deferiprone for only 3-6 months, six were receiving the drug for 7-12 months while another 9 (30%) were on chelation therapy for over 12 months. As shown in *Table 1*, the 24-hour urinary excretion of zinc was significantly higher in children receiving deferiprone (Group B, 1010.8 ± 1248.1 mcg) than in the other two groups. Children with thalassemia major who were receiving regular transfusion therapy, but were not receiving any chelation therapy (Group A) did not show significantly high urinary zinc excretion (547.8 ± 832.9 mcg/24 hr) as compared to the controls (Group C, 459.8 ± 270.3; P >0.05).

An attempt was made to determine if the urinary excretion of zinc was related to the duration and dose of deferiprone in the patients belonging to the Group B (*Figs. l* and *2*). As the range of values for 24-hour urinary zinc excretion were too wide, log of these values were compared with the duration and dose of deferiprone therapy. It was noted that there was no correlation between duration ($r = -0.26$, $P < 0.05$) and dose ($r = 0.19$, $P < 0.05$) of deferiprone and (log of) urinary zinc levels. Although plasma zinc levels in Group B were found to be lower than those

**TABLE I**–*Demographic Characteristics, 24-hour Urinary Zinc Excretion and Plasma Zinc Levels.*

| Characteristics | Group A | Group B | Group C |
|---|---|---|---|
| | Children with thalassemia major on Regular transfusion therapy | | Controls |
| | Without chelation therapy | On deferiprone | |
| Age (Mean ± SD; years) | 7.2 ± 2.5* | 7.9 ±3.4* | 7.2 ±2.9* |
| Male: female ratio | 1.3:1 | 2: 1 | 1.9 : 1 |
| Median grade of malnutrition | II | II | II |
| 24-hr urinary zinc excretion (µg/24 hrs) | 547.8 ±832.9** | 1010.8 ±1248.1**# | 459.8 ±270.3# |
| Plasma zinc level (µmol/L) | 8.0 ±5.8 | 7.5 ±6.0 | 9.5 ±3.8 |

*P > 0.05, ** P< 0.01; #: P<0.001.

in other groups, the difference was not statistically significant (P >0.05). However, it is noteworthy that the levels in all the three groups were significantly lower than the reference values(6).

## Discussion

A few studies have indicated that deferiprone may, in addition to iron, chelate zinc as well. This is an important issue since zinc plays an important role in several physiological functions; protein synthesis, gene expression, immunity, wound healing amd maintenance of integrity of intra-cellular organelles(7). In addition, it has been recently noted that deferiprone therapy is associated with zinc depletion in thymocytes(8).

The present study demonstrated that urinary zinc levels in children on deferiprone were significantly higher than those in controls as well as in children with thalassemia who were not receiving deferiprone. This unequivocally proves that the drug chelates zinc and it is not the "thalassemic

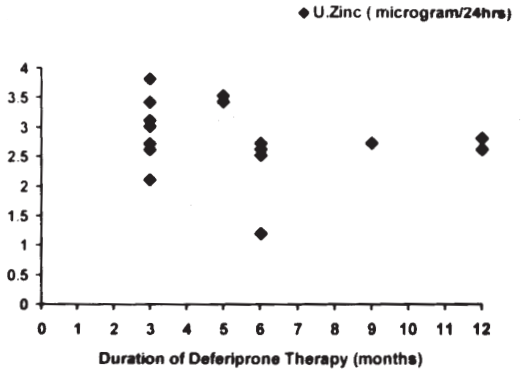


*Fig. 1. Relationship between the duration of deferiprone therapy and urinary zinc excretion.*

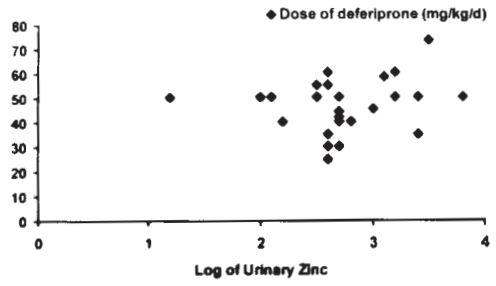


*Fig. 2. Relationship between the dose of deferiprone and urinary zinc excretion.*

## Key Messages

- Administration of deferiprone is associated with an increase in the urinary excretion of zinc.
- Further research is warranted on the need to provide zinc supplementation to children receiving deferiprone for a longer duration.

state" that is responsible for excessive zinc excretion. The study did not demonstrate any significant relationship between dose of deferiprone and duration of chelation therapy and urinary zinc excretion. Al Refaie, *et al.*(9) also did not find correlation between the dose of deferiprone and the extent of urinary zinc excretion. It is possible that long-term deferiprone therapy depletes total body zinc and therefore, urinary zinc excretion may not increase any further or may, in fact, show a decline from the baseline when the body zinc stores have been significantly depleted.

The failure of the present study to demonstrate this relationship may be due to the fact that up to 50% of our subjects in Group B were receiving deferiprone for a short period of 3-6 months. This may also account for the inability of the study to demonstrate significantly lower plasma levelsof zinc in patients receiving deferiprone.

Despite certain limitations, the findings obtained from the study have definite implications. Deferiprone chelates zinc and hence, with long-term use is likely to result in depletion of body zinc. Cohen, *et al.*(4) and Al-Refaie, *et al.*(9) have already shown that deferi-prone therapy results in low zinc levels in the blood. Therefore, it may be prudent to start zinc supplementation to avoid the occurrence of negative zinc balance. This is probably more relevant in Indian children as they are known to have zinc levels that are lower than reference values(10).

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