Zinc concentration in patients with iron overload receiving oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one or desferrioxamine

F N Al-Refaie, B Wonke, D G Wickens, Y Aydinok, A Fielding, A V Hoffbrand

Abstract

***Aims*—To determine the changes in serum zinc concentration and the extent of urinary zinc excretion in patients with iron overload receiving the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L_1) or desferrioxamine (DFX), and to correlate these results with blood glucose concentration.**

***Methods*—Serum zinc and ferritin concentrations, urinary zinc and iron excretion were regularly assayed in 39 patients and the glucose tolerance test (GTT) was performed in each patient. Patients were segregated according to their GTT into normal, diabetic, and those with an abnormal GTT. The mean of L_1- or DFX associated urinary zinc excretion for each group was determined and compared with the other two groups and with normal value. L_1 associated urinary zinc excretion was also compared with L_1 dose, serum ferritin values, and urinary iron excretion.**

***Results*—Both DFX and L_1 were associated with a significantly increased urinary zinc excretion (15·1 (7·3) μmol/24 hours, 11·1 (6·0) μmol/24 hours, respectively) compared with normal subjects. In patients receiving DFX this increase only occurred in patients with diabetes mellitus. Both diabetic and non-diabetic patients receiving L_1 treatment excreted more zinc than normal. Diabetic patients receiving L_1 or DFX excreted more zinc than non-diabetics receiving the same treatment. No correlation was found between urinary zinc excretion and L_1 dose or patients' serum ferritin concentrations. In seven patients receiving long term L_1 treatment a fall in serum zinc was observed from an initial 13·6 (1·6) μmol/l to a final 9·6 (0·8) μmol/l. In one patient this was associated with symptoms of dry skin and itchy skin patches requiring treatment with oral zinc sulphate.**

***Conclusions*—In contrast to DFX, L_1 treatment is associated with increased zinc loss. This, however, is modest and does not lead in most patients to subnormal serum zinc concentrations. In a few patients whose negative zinc balance may give rise to symptoms, zinc supplementation rapidly corrects the deficit.**

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Department of Haematology, Royal Free Hospital, Pond Street, London NW3 2QG
F N Al-Refaie
A V Hoffbrand

Department of Haematology, Whittington Hospital, London
B Wonke
Y Aydinok
A Fielding

Department of Chemical Pathology, Whittington Hospital, London
D G Wickens

Correspondence to:
Dr F N Al-Refaie

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Zinc is an essential trace metal for the normal function of many enzymes involved in cell division and DNA and protein synthesis in mankind.[1] Zinc deficiency is associated with several clinical manifestations, such as growth retardation, delayed wound healing, skin changes, hypogonadism, glucose intolerance, anaemia and abnormal leucocyte function.[2] Patients with diabetes mellitus and particularly those with insulin-dependent diabetes mellitus (IDDM) are at risk of developing zinc deficiency.[3 4] Although these patients excrete more zinc in their urine than normal,[3 5 6] serum zinc concentrations may be normal, increased, or decreased.[7] Furthermore, only a few patients with diabetes mellitus develop clinical manifestations of zinc deficiency.

Although several mechanisms for hyperzincuria in diabetic patients have been suggested, such as a non-osmotic process mediated by glucose and changes in gastrointestinal absorption of zinc,[3 8] the exact mechanism remains obscure. The low incidence of zinc deficiency among patients with hyperzincuria is probably due to an adequate intake or compensatory increased absorption of zinc. Furthermore, the estimation of serum zinc has its technical and interpretive limitations,[9] so patients with normal serum zinc concentrations can be zinc deficient. On the other hand, a subnormal serum zinc concentration is suggestive, but alone not diagnostic, of zinc deficiency.[2]

Patients with thalassaemia major not receiving regular chelation treatment or blood transfusions also have serum zinc values below normal, and they have increased urinary zinc excretion (Cavdar A, paper presented to 6th meeting of the Mediterranean Blood Club, Milan, Italy, 1991). It is not clear, however, whether these findings are due to diabetes mellitus in these patients.

The effect of iron chelation treatment on trace metals in patients with iron overload depends on the affinity of the chelator to these metals. DFX has now been used for many years with no report, as far as we are aware, of an associated zinc deficiency. This contrasts with the well known severe zinc loss associated with the iron chelator diethyltriamine penta-acetic acid (DTPA),[10 11] necessitating substantial oral supplements of zinc.

The oral iron chelator L_1 has now been given to many patients worldwide—for over three years in some centres.[12] None of the earlier short and long term trials reported a change in serum zinc concentrations or increased urinary zinc excretion. Recently, however, we found increased urinary zinc excretion in eight patients receiving regular chelation treatment with L_1 for up to one year and subnormal serum zinc values in four associated with symptoms of dry, itchy, skin patches which resolved with zinc supplementation in two patients.[13]

In our current long term trial of L_1 treatment in patients with iron overload we have monitored zinc values closely and correlated them with the presence of diabetes mellitus or more subtle biochemical abnormalities of glucose metabolism. A preliminary abstract of this work has been published.[14]

Methods

DFX was obtained from Ciba Geigy and L_1 was synthesised, as described before.[15] Serum ferritin was estimated using an enzyme linked immunosorbent assay (ELISA) technique.[16] Urinary iron and zinc and serum zinc were measured using atomic absorption spectrophotometry.[17] Oral glucose tolerance tests were performed by administering 75 g of glucose after overnight fasting and sampling blood every 30 minutes for two hours.

Significance was evaluated using Student's *t* test. Data were expressed as mean (SD).

This study had the approval of the Ethical Committee of the Royal Free Hospital.

Thirty nine patients (24 males, 15 females) were studied. Their ages ranged from 13 to 60(27·1 (11·0)years). Initial serum ferritin ranged between 733 and 9060 μg/l (3551 (2123) μg/l). Thirty one patients had β thalassaemia major, two sickle cell disease, two congenital sideroblastic anaemia, one myelodysplastic syndrome, one pyruvate kinase deficiency, one haemoglobin E/β-thalassaemia and one sickle/β-thalassaemia. Serum zinc was assayed initially and two monthly thereafter. Two to four 24 hour urine collections were obtained from each patient while receiving subcutaneous infusion of DFX at an approximate dose of 50 mg/kg/day, and four or more collections of urine were obtained during L_1 therapy (50–100 mg/kg/day). These urine samples were analysed for both the total iron and zinc contents. Normal values for serum zinc concentration and 24 hour urinary zinc excretion are 11·5–17·0 μmol/l and 4·5–9·0 μmol/24 hours, respectively, in our laboratory.

Results

Twenty four hour urinary zinc excretion in 39 patients receiving L_1 treatment was 15·1 (7·3) μmol (range, 4·4–34·2 μmol), significantly higher than that associated with DFX treatment (11·1 (6·0) μmol; range 2·6–26·5; $p = 0·01$), and both were significantly higher than the normal range for urinary zinc excretion ($p < 0·001$, $p = 0·04$, respectively). There was a significant correlation between L_1 and DFX associated urinary zinc excretion ($r = 0·74$; $p < 0·001$). Different regimens of L_1 administration (twice or four times a day) showed no significant difference in their effect on urinary zinc excretion in the 19 patients

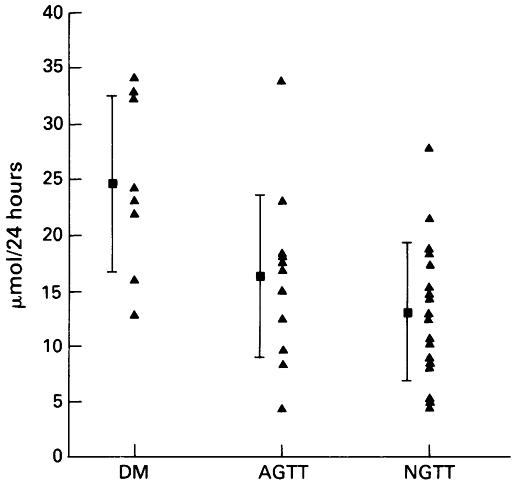

Figure 1 Urinary zinc excretion in 39 patients with iron overload receiving L_1 segregated into three groups: diabetes mellitus (DM, n = 8), abnormal glucose tolerance test (AGTT, n = 13), and normal glucose tolerance test (NGTT, n = 18). X (SD) for each group is shown.

studied nor did the co-administration of vitamin C. Nor did taking L_1 with food or fasting significantly alter urinary zinc excretion. No correlation was found between urinary zinc excretion and L_1 dose ($p = 0·11$) or urine iron excretion ($p = 0·1$) or between urinary zinc excretion and serum ferritin values ($p = 0·92$).

Urinary zinc excretion was significantly higher in patients with diabetes mellitus receiving L_1 (24·6 (7·9), n = 8) than patients with a normal glucose tolerance test (13·1 (6·2), n = 18; $p = 0·0006$) or those without diabetes mellitus but with an abnormal glucose tolerance test (16·3 (7·3), n = 13; $p = 0·02$). No significant difference was observed between the latter two groups of patients ($p = 0·2$) (fig 1). Comparable results were observed with DFX. Patients with diabetes mellitus receiving DFX (n = 7) excreted

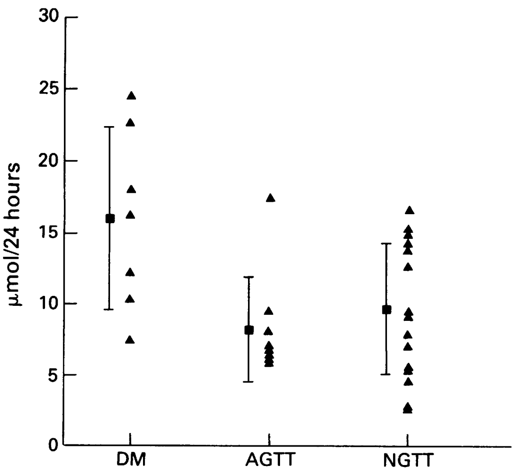

Figure 2 Urinary zinc excretion in 33 patients with iron overload receiving DFX segregated into three groups: diabetes mellitus (DM, n = 7), abnormal glucose tolerance test (AGTT, n = 9), and normal glucose tolerance test (NGTT, n = 17). X (SD) for each group is shown.

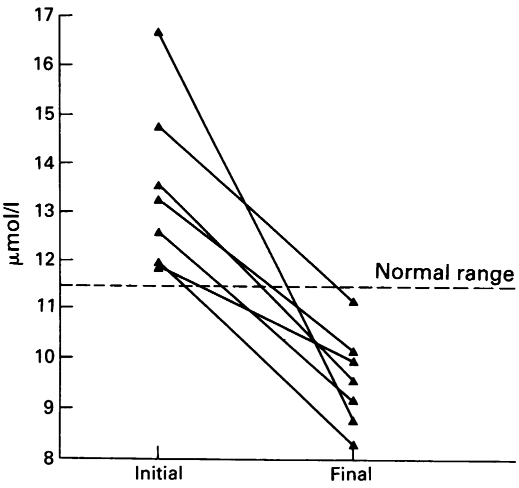

Figure 3 Fall in serum zinc concentrations in seven of 35 patients receiving long term L_1 treatment at a dose of 50–100 mg/kg/day.

more zinc than non-diabetics (n = 17) or those with abnormal glucose tolerance test (n = 9) (16 (6·4) *v* 9·7 (4·6) (p = 0·01), 8·2 (3·7) (p = 0·008), respectively) (fig 2). Again no significant difference was found between the latter two groups of patients (p = 0·59).

There were significant differences between the urinary zinc excretion of patients with diabetes mellitus or an abnormal glucose tolerance test receiving L_1 treatment and corresponding patients receiving DFX (p = 0·04 and 0·03, respectively), but no significant difference was observed between normal glucose tolerance test patients receiving L_1 and those receiving DFX (p = 0·59). However, when the paired *t* test was used to compare the excretion of zinc in the individual patients in the latter two groups, the difference was significant (p = 0·003). All three groups of patients receiving L_1 treatment had significantly increased urinary zinc excretion compared with normal (diabetes mellitus: p = 0·0009; abnormal glucose tolerance test: p = 0·0036; normal glucose tolerance test: p = 0·01). Among patients receiving DFX only those with diabetes mellitus had significantly increased urinary zinc excretion compared with normal (p = 0·03).

In seven of 35 patients receiving long term L_1 treatment serum zinc concentrations fell over a period of six to 12 months from a mean initial value of 13·6 (1·7) μmol/l (11·9–16·7 μmol) to a mean final concentration of 9·6 (1·0) μmol/l (8·3–11·2 μmol) (fig 3). The urinary zinc excretion in these patients was increased at 20·2 (9·4) μmol/24 hours (range 4·4–32·3 μmol/24 hours). This was associated in one patient with symptoms of dry skin and itchy skin patches which rapidly resolved on treatment with zinc sulphate (220 mg/day).

Discussion

In this study we confirm our previous observation that zinc excretion in the urine is increased in patients receiving L_1 treatment. This was significantly higher than the zinc excretion found in patients receiving DFX, although this was also significantly increased compared with normal. Neither the L_1 dose nor iron load of the patients correlated significantly with urinary zinc excretion. The significant correlation observed between L_1 and DFX associated urinary zinc excretion suggests that individual susceptibility for increased zinc excretion is the same with both chelators.

Patients with transfusion dependent refractory anaemias are at risk of developing diabetes mellitus as a result of iron overload. As patients with diabetes mellitus excrete more zinc in their urine than normal subjects it was essential to assess the urinary zinc excretion of patients receiving iron chelation treatment in relation to their blood glucose values. When patients receiving L_1 or DFX were segregated according to their glucose tolerance into normal, diabetes mellitus, and those with abnormal glucose tolerance test, patients with diabetes mellitus excreted significantly more zinc than the others. All three groups of patients receiving L_1 treatment excreted raised amounts of zinc compared with normal. Although the urinary zinc excretion in diabetics receiving L_1 is higher than the mean (18·4 μmol/24 hours) of previously reported values for urinary zinc excretion in patients with IDDM not receiving chelation treatment (21·4 (9·5)[5]; 18·3 (4·1)[6]; 15·4 (5·5)[18]), the difference was not significant (p = 0·06). This may have been due to the small number of patients with diabetes mellitus receiving L_1 treatment studied here. On the other hand, patients receiving DFX with normal or abnormal glucose tolerance tests did not excrete increased amounts of zinc, and in diabetics DFX was not associated with increased urinary zinc excretion compared with diabetics not receiving chelation treatment (p = 0·64). The increase in urinary zinc excretion in patients receiving DFX compared with normal seems to be mainly, if not entirely, due to the presence of diabetes mellitus in some of them.

The lack of a significant difference between the mean urinary zinc excretion of patients treated with L_1 and DFX with a normal glucose tolerance test (13·1 (6·2) *v* 9·7 (4·6); p = 0·59) may also have been due to the small number of patients studied as the difference was significant (p = 0·003) when the paired *t* test was used.

A fall in serum zinc to subnormal values was observed in seven of 35 patients with symptoms of zinc deficiency, necessitating zinc supplementation in one. The incidence of subnormal serum zinc values encountered in our study is comparable with that reported in 20 patients with diabetes mellitus (25%).[3]

In summary, patients with iron overload receiving DFX do not excrete more zinc than normal unless they have diabetes mellitus when their increased zinc excretion is comparable with diabetics not receiving DFX. Patients receiving L_1 treatment excrete more zinc than similar patients receiving DFX or normal subjects. The overall increase in zinc

loss accompanying L_1 treatment is modest and in most patients is presumably balanced by increased absorption of dietary zinc. In a few patients negative zinc balance leads to zinc deficiency. Fortunately, this is easily corrected with zinc supplementation.

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