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The Effects of Treatment on the Hypercalciuria of Chronic Cadmium Poisoning

R. Scott*, P. J. Paterson, R. Burns, G. S. Fell and J. M. Ottoway

Departments of Urology and Biochemistry, Royal Infirmary, Glasgow, and University of Strathclyde, Glasgow, Scotland

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Summary. Cadmium induces a variety of effects on kidney tubules including hypercalciuria. This is accompanied by hyperzincuria. The present work shows that both of these biochemical abnormalities can be corrected but where a state of cadmium-induced-anaemia exists urine zinc and calcium excretion do not follow the expected parallel course in response to iron therapy as they do with bendrofluazide.

Key words: Cadmium, Iron, Bendrofluazide, Hypercalciuria Hyperzincuria, Treatment.

INTRODUCTION

Chronic cadmium poisoning has been recognised for several years (12). Most authors have tended to concentrate on making the diagnosis of the condition (3, 12) but few have attempted to correct the abnormalities which have been recognised as part of the effects of cadmium. The reasons for such hesitancy are related to the complexity of the interaction between cadmium and other elements and the simple fact is that no known safe chelating agent exists. The present study relates the effects of a thiazide diuretic and of iron on the urinary calcium and zinc levels in men who suffer from chronic cadmium poisoning.

MATERIAL AND METHODS

Investigation of a group of workers confirmed a high prevalence of stone disease (18.5%) in a group of 27 coppersmiths who had been exposed to cadmium fume (15).

As a result of the above investigation 24 of the 27 workers were intensively investigated and the following cadmium induced abnormalities of renal function were observed: –

Renal tubular acidosis	(15 of 24)
Hypercalciuria	(19 of 24)
Proteinuria	(7 of 24)
Hyperzincuria	(19 of 24)
Glycosuria	(6 of 24)
Phosphaturia	(7 of 23)

In addition a full haematological screen was undertaken and this confirmed that, when compared with a normal population (14), 7 of the men had a low serum iron associated with a low haemoglobin value i.e. a haemoglobin value of less than 14 G/dl. Apart from the haematological abnormality in these 7 men, they exhibited a variety of abnormal biochemical measurements including hypercalciuria. 7 other subjects had haemoglobin values greater than 14 G/dl but less than 15.1 G/dl which was the mean haemoglobin value found in a group who worked in the factory but were not directly exposed to cadmium fume.

Hypercalciuria was found in 4 men who had normal haematological measurements and 2 men had radiological evidence of kidney stones.

Two different therapeutic regimes were undertaken viz: –

(a) Those men with a basic haematological problem received
   (i) 47 mg iron as ferrous sulphate (Feospan SKF) 5 days per week for 6 months.
   (ii) 60 mg iron as ferrous sulphate with copper (Ferrous sulphate BP) 5 days per week for 6 months.

*Please address requests for reprints to R. Scott

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Table 1. Effect of iron on urine calcium and zinc; haemoglobin <14 G/dl

Subject no.	Urine calcium u mol/24 hr initial	12 months	Urine zinc u mol/24 hr initial	12 months	Known failure to take iron (expressed as iron equivalents in mg) Fe SO_4 S	FE SO_4 Cu
1	9.90	7.80	15.4	5.74	47	180
2	10.90	9.43	19.0	12.20	+	+
3	7.80	9.50	15.3	6.35	47	180
4	7.30	6.60	12.0	7.40	94	120
5	9.80	7.80	19.6	10.40	705	120
7	8.50	14.30	14.8	10.80	47	60
	$\bar{x}$ 9.70	$\bar{x}$9.70	$\bar{x}$15.41	$\bar{x}$ 9.65		

Table 2. Effect of iron on urine calcium and zinc; haemoglobin >14 G/dl

Subject no.	Urine calcium u mol/24 hr initial	12 months	Urine zinc u mol/24 hr initial	12 months	Known failure to take iron (expressed as iron equivalents in mg) Fe SO_4 S	FE SO_4 Cu
1	2.60	12.90	13.90	11.10	141	840
2	3.70	6.60	15.10	15.60	47	180
3	9.80	4.05	15.10	9.40	235	300
4	2.90	9.25	14.80	14.30	658	840
5	9.20	7.60	7.60	9.20	188	60
6	11.80	9.10	16.10	8.70	47	60
7	12.10	6.66	10.70	5.00	329	60
	$\bar{x}$7.44	$\bar{x}$8.00	$\bar{x}$ 13.32	$\bar{x}$ 10.47		

(b) Men with normal haemoglobins, but with hypercalciuria or who had stones present in kidneys received Bendrofluazide 2.5 mg (Neonaclex-K-Glaxo) on 5 days per week.

The drugs were administered by the factory nurse under supervision and recorded. There were very few occasions when individuals failed to take their appropriate therapy. Apart from recognised holidays, the known failure of compliance expressed as mg iron are given in Tables 1 and 2. Subject No 2 of the low haemoglobin group (Table 1) was made redundant 3 months before the one year completion date of the study and is therefore ommitted with respect to total compliance. The same applies to subject No 6 on the thiazide regime (Table 3).

RESULTS

Therapy – Compliance

The overall compliance to both formes of therapy is good (see Tables). Subject No 5 in the low haemoglobin group has a known cardiac history and was frequently absent from work because of this condition. Subjects 4 and 5 in the second group (Table 2) with haematological problems tended to work variable shifts both day and night. In the same group subject No 7 was initially off work following a cholecystectomy.

In the thiazide treated group subject No 1 refused to take this therapy for one month for no apparent reason. Apart from these special subjects the regularity of any drug taken was remark-

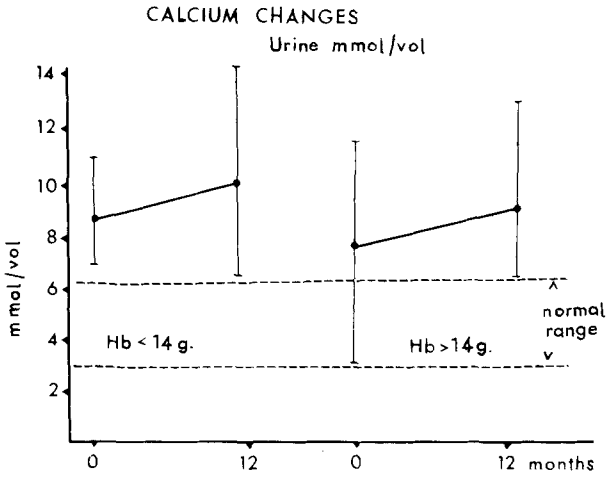

Fig. 1. Calcium changes in iron treated subjects

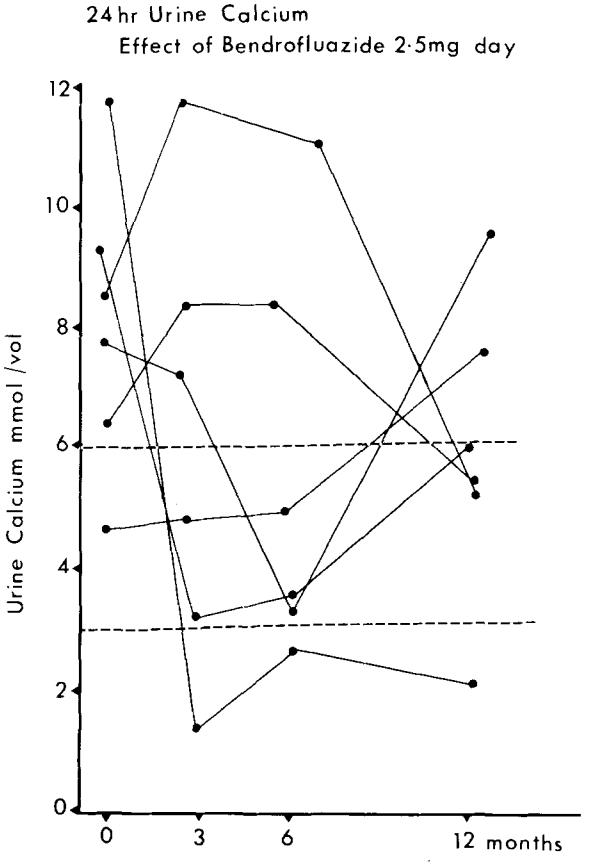

Fig. 2. Urine calcium changes in subjects treated with diuretics

ably good and ommissions from the regimes were insignificant.

Effects of Regimes

(1) Urine Calcium. Those subjects treated solely with iron (Tables 1 and 2) showed initially that

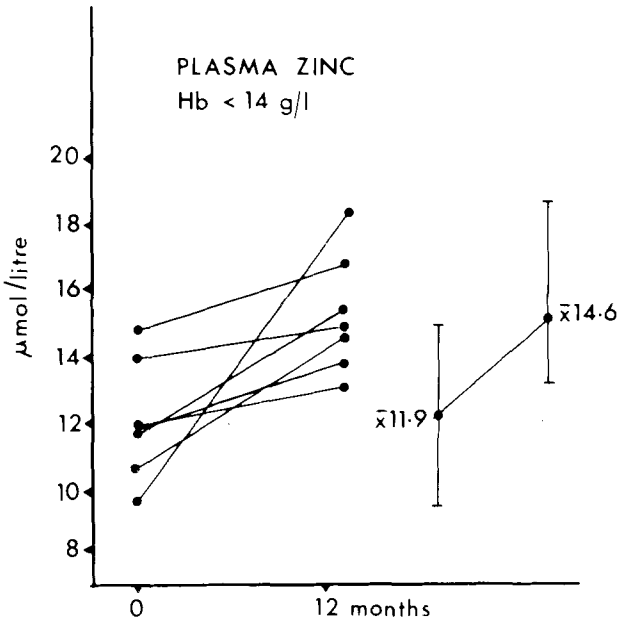

Fig. 3. Plasma zinc changes in iron treated subjects – haemoglobin less than 14G

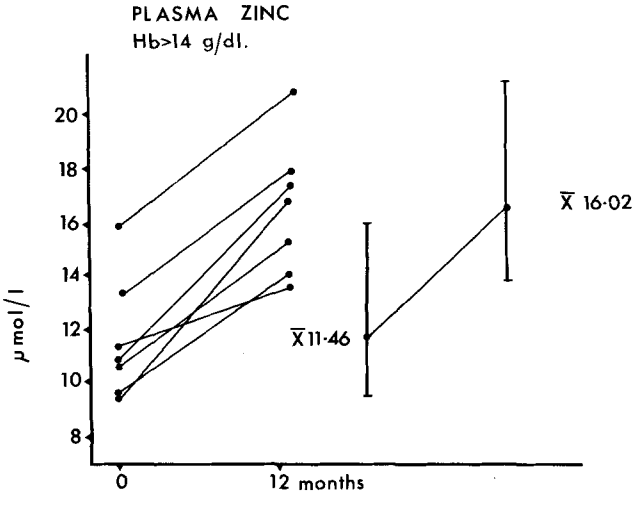

Fig. 4. Plasma zinc changes in iron treated subjects – haemoglobin more than 14G

all those in the low haemoglobin group had urine calcium values above the 'normal' accepted range in the hospital laboratory (3 - 6 mmol/24 hours) and that after one year's therapy the mean value for the group was higher ($\bar{x}$ 9.15 - $\bar{x}$ 9.70); a similar situation existed in those with the higher haemoglobin values ($\bar{x}$ 7.44 - $\bar{x}$ 8.00) (Fig. 1). By contrast, in the group treated with the agent known to reduce urine calcium (Table 3) the expected fall in urine calcium occurred ($\bar{x}$ 8.00 - $\bar{x}$ 5.91) (Fig. 2). It should be noted that in the group with the lowest haemoglobin values the mean urine calcium output per 24 hours was

Table 3. Effects of bendrofluazide on urine calcium and zinc

Subject no.	Urine calcium u mol/24 hr initial	12 months	Urine zinc u mol/24 hr initial	12 months	Known failure to take diuretic (expressed as mg bendrofluazide
1	7.74	9.31	4.5	6.0	245
2	9.10	5.80	17.8	7.0	10
3	8.50	5.30	14.1	7.5	15
4	11.70	2.40	19.8	6.8	65
5	6.40	5.40	11.6	9.7	110
6	4.60	7.30	5.2	9.0	+
	$\bar{x}$8.00	$\bar{x}$5.91	$\bar{x}$ 12.26	$\bar{x}$7.6	

higher than those with normal haematological findings but who had hypercalciuria or existent stones ($\bar{x}$ 9.15 v $\bar{x}$ 8.00).

(2) Urine Zinc Values. The mean urine zinc values fell in both the iron treated sub groups ($\bar{x}$ 15.41 - $\bar{x}$ 9.65 and $\bar{x}$ 13.32 - $\bar{x}$ 10.47) and also in the thiazide treated group ($\bar{x}$ 12.26 - $\bar{x}$ 7.6).

(3) Plasma Zinc Values. In both of the iron treated groups the mean of the plasma zinc values rose ($\bar{x}$ 11.9 - $\bar{x}$ 14.6 and $\bar{x}$ 11.46 - $\bar{x}$ 16.02) (Figs. 3, 4) in contrast to the fall in urine zinc values.

DISCUSSION

There are obviously good arguments which suggest that a casually found biochemical abnormality should be left untreated. However when such a finding is part of a group of abnormalities associated with a particular poison, then such arguments are less tenable especially if the long term effects of the toxic substance could prove to be serious e.g. osteomalacia (7). In the case of the non-essential toxic metal cadmium there is no recognised therapy used in the treatment of chronic poisoning despite the fact that the metal is known to have a biochemical half life of 20 - 30 years (2) and is associated with chronic effects on lungs (1) kidneys (16) and bones (7).

The present studies have been undertaken to ascertain whether cadmium induced biochemical abnormalities can be corrected and if so what changes might occur in other associated elements known to be affected in chronic cadmium poisoning. In the case of hypercalciuria it is generally assumed that when urine calcium rises, urine zinc does likewise (6). It would be expected therefore that when urine calcium falls urine zinc would follow in parallel and in those subjects given orthodox therapy (10) to reduce the urine calcium excretion, there has been a corresponding reduction in the urine zinc output.

To emphasize the complexity of the reactions between trace elements it is observed in the present study that when iron is used to treat subjects with a cadmium induced anaemia there is a rise in urine calcium output. What is very interesting however is that the rise in urine calcium is accompanied by a fall in urine zinc with an associated rise in plasma zinc.

In order to understand these apparent anomalies it has to be remembered that zinc deficiency is associated with anaemia (5). Zinc is present in erythrocyte carbonic anhydrase (13) and it has been suggested that haemoglobin may be able to bind zinc (4). It is postulated therefore that in the iron treated subjects plasma zinc, rising because of the reduction in environmental cadmium contamination, will be assimilated in the red cells and in the haemoglobin molecules resulting in less zinc being available for excretion either by the bowel or in the urine. By contrast however the calcium excretion in these individuals is a reflection of the tubular damage induced by cadmium (9) due possibly to altered Vit D metabolism in the kidney tubules and this may be even further complicated by failure of tubular conversion of Vit D to its active metabolite (8).

The results of the present study confirm that it is possible to correct biochemical abnormalities induced by cadmium. It must be remembered however that interactions between trace elements are very complex.

The justification for treating chronic cadmium poisoning is that the element has a long biochemical half-life and can produce effects many years after its initial ingestion. It has been shown that lack of calcium enhances the effects of cadmium

(11) and similarly some measure of protection can be obtained with zinc. Using both iron and bendrofluazide it has been possible to reduce the output of both zinc and calcium and it is hoped that by reducing excretion of these two antagonists some protection against cellular damage can be obtained.

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Mr. R. Scott
Department of Urology
Royal Infirmary
Glasgow
Scotland