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The Effect of Steroid Therapy on Serum Trace Metal Levels in Sub-Fertile Males

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Summary. The effect of 96 mg methylprednisolone on trace metals and hormone levels was measured in 13 males with sub-fertility associated with an antibody problem. Over a period of 5 days the serum zinc was significantly reduced ($p < 0.05$) as was the serum testosterone ($p < 0.01$). By contrast the luteinising hormone levels rose ($p < 0.01$) within 3 days of administration of the steroid. The lability of serum zinc to the administration of steroids is further demonstrated by its significant fall ($p < 0.01$) after 3 days of therapy. These results suggest an adreno-cortical control of zinc in serum.

Key words: Methyl-prednisolone, Male sub-fertility, Trace metals.

Introduction

Steroid therapy may be valuable in the management of male subfertility to suppress endogenous anti-sperm antibodies [15]. However, steroids have major effects on the adrenal glands. There is relatively little appreciation of the effect of steroids on trace metal metabolism, in particular zinc and magnesium.

Materials and Methods

Thirteen males (mean age 32.0 years) were investigated at the male subfertility clinic. Their ages and the results of two sperm counts, MAR test and Kibrick test are shown in Table 1. On the basis of these results they were considered suitable for steroid treatment.

The patients were admitted to the ward and given methylprednisolone 96 mg for one week as recommended by Shulman [15]. A 24 h urine collection was made on day 1 before commencement of therapy. Similar collections were made on days 3 and 5 of their hospital stay. Serum samples were also collected on days 1, 3 and 5 and all were analysed in the routine laboratories in the Department of Biochemistry. Measurements undertaken included serum calcium, magnesium and zinc levels together with Luteinising Hormone (LH), Follicle Stimulating Hormone (FSH) and testosterone measurements. Urine was analysed for calcium, magnesium and zinc by atomic adsorption spectro-photometry. Patients continued on a normal hospital diet during their admission.

Table 1. Age, sperm counts, MAR and Kibrick tests in 13 subfertile males

No.	Age (years)	Sperm counts (million/ml)		MAR test	Kibrick test
		1	2		
1	38	30	2	positive	1/128
2	33	31.5	1.4	positive	1/128
3	29	6	20	positive	1/64
4	30	92	55	positive	1/32
5	26	5	3	positive	1/32
6	32	100	24	positive	1/16
7	27	56	85	positive	1/16
8	30	36	61	positive	1/256
9	38	320	193	positive	negative
10	34	11	32	positive	negative
11	39	41	100	positive	negative
12	30	25	83	positive	1/256
13	31	14	27	positive	1/64

Results

Trace Metals

The results of serum analyses are given in Table 2 and demonstrate (Wilcoxon signed rank test) a significant fall in the median serum zinc concentration on both days 3 ($p < 0.01$) and 5 ($p < 0.05$) following the commencement of steroid therapy. A significant fall ($p < 0.01$) in the median urine magnesium occurred between days 1 and 5 (Table 3). No other changes either in serum or urine could be demonstrated.

Table 2. Median serum results in male infertility subjects treated with steroids (n: 13)

	Day 1 (pre-treatment)	Day 3 (on treatment)	Day 5 (on treatment)
Calcium (m mol/l) normal range 2.2–2.6	2.48	2.40	2.40
Magnesium (m mol/l) normal range 0.7–1.0	0.82	0.79	0.83
Zinc (μmol/l) normal range 12–18	13.5	11.5[b]	12.3[a]
LH (U/L) normal range <2.0–8.6	6.1	8.2[a]	7.5
FSH (U/L) normal range <1.0–4.5	3.0	3.1	2.5
Testosterone (n mol/l) normal range 11–36	15.2	11.2[b]	10.2[b]

Statistical analyses: Wilcoxon Signed Rank Test (Day 1 pre-treatment versus Day 3 and Day 1 versus Day 5 on treatment)

[a] significant $p < 0.05$
[b] significant $p < 0.01$

Table 3. Median urine results (m mol/24 h) in male subfertile subjects treated with steroids (n:13)

	Day 1 (pre-treatment)	Day 3 (on-treatment)	Day 5 (on treatment)
Calcium normal range 3.0–6.0 m mol/24 h	3.75	3.10	2.70
Magnesium normal range 2–11 m mol/24 h	2.40	2.40	1.65[a]
Zinc normal range 5–11 μmol/24 h	10.0	16.0	8.5

Statistical analyses: Wilcoxon Signed Rank test (Day 1 pre-treatment versus Day 3 and Day 1 versus Day 5 on treatment)

[a] significant $p < 0.01$

Hormones

The LH values rose significantly from day 1 to day 3 ($p < 0.05$) (Table 2) but there was no significant difference from day 1 to day 5. By contrast, the serum testosterone values fell from day 1 to day 5 ($p < 0.01$).

Discussion

Zinc has for some time been recognised as being important in the physiology of the prostate, epididymis and testis. Early work confirmed that in the castrated rat there is a direct relationship between the uptake of zinc by the dorsolateral prostate and interstitial cell stimulating hormone activity, indicating a possible hormonal control of zinc metabolism in the rat prostate [7]. By contrast, the ventral lobe of the prostate, which does not appear to be influenced by hormonal control, has a very small but stable zinc content. It has also been demonstrated that the addition of exogenous androgen reduces the uptake of zinc by the intact rat gland [6]. It is clear that there is a complex and poorly understood interaction between zinc and the various hormones influencing the reproductive system [10].

In man it is recognised that zinc deficiency may be associated with hypogonadal dwarfism [10, 13, 14]. Apart from chronic deficiency of zinc which is probably dietary in origin, low levels of serum zinc occur in a variety of different diseases such as alcoholic cirrhosis and other more chonic conditions [9]. In alcoholic cirrhosis detoxification of the male hormone is abnormal and although this has long been recognised, it has never been speculated that zinc abnormalities may be a factor involved in the metabolism of the hormone.

A state of relative zinc deficiency is probably more common than is generally realised. To surgeons this may be of practical concern since such deficient states may be responsible for delayed healing in varicose ulcers or surgical wounds [4, 5, 8]. Further evidence that zinc deficiency could be implicated in wound healing was afforded in a study which confirmed that the addition of zinc supplements to patients on long-term cortico-steroid therapy resulted in an improved rate of wound healing [4]. This observation followed the realisation that there was a rapid depletion of serum zinc associated with the administration of large doses of cortico-steroids [3].

The plasma zinc fraction represents less than 1% of the total body pool [12], but nevertheless is a very mobile part of the total zinc content. It can be affected by starvation [11] as is demonstrated by a rapid excretion of zinc as a response to injury [2].

That there is a little understood relationship between zinc and the sex hormones in humans is demonstrated by the rise in testosterone levels found by administering zinc to men with uraemic impotence [1]. In these uraemic subjects, it was shown that the administration of zinc caused the expected rise in plasma zinc but interestingly a fall in plasma LH. By contrast in our study, a fall in serum zinc levels was accompanied by a rise in LH levels. This indicates the close relationship between zinc and LH in serum. The present study has also shown reduction in testosterone values which is the reverse of the trend in uraemic subjects.

Our study, undertaken in men who are normal apart from sub-fertility associated with an antibody problem, confirms that serum zinc levels, LH and testosterone are closely interrelated and that serum zinc is rapidly reduced by the administration of large doses of steroids. This confirms, as did Flynn et al. [3], that the adreno-cortico

steroid axis is important in regulating the level of plasma or serum zinc and that significant changes in these levels occur within 48 h. Although a short-term course of steroids has other implications with respect to the effects of stress including anaesthesia, it is more than likely that, when long-term steroids are given, they could significantly interfere with the most mobile fraction of the total body zinc. This could well explain the delayed wound healing common in subjects on long-term steroids.

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