A CLINICAL STUDY OF THE POSTULATED ANTAGONISM BETWEEN GLUCOCORTICOIDS AND VITAMIN D

By

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ABSTRACT

Present knowledge and theory concerning the postulated antagonism between the glucocorticoids and vitamin D is first considered. Attempts at assessment of cortisone/calciferol antagonism were made in 3 groups of subjects. First, the effect of cortisone was observed in 4 normal volunteers who were taking large doses of calciferol. Then calciferol, in doses ranging from 100,000 units to 400,000 units daily, was given to hypoadrenal subjects and to sufferers from hypercortisolism (Cushing's syndrome), in order to observe whether dysadrenalism would alter the sensitivity to the vitamin.

Results indicate that cortisone did not appear to counteract the observed effects of calciferol while the vitamin was being taken concurrently. Hypoadrenal subjects were not more sensitive to the vitamin, nor were hyperadrenal subjects less sensitive than normal.

Finally, the expression of the "incomplete antagonism" between cortisone and vitamin D is summarised.

Cortisone and its analogues can reduce both the hypercalcaemia and the hypercalciuria that occur in sarcoidosis, and as these derangements of calcium metabolism are probably caused by hypersensitivity to vitamin D it has been suggested that cortisone might be a vitamin D antagonist (Shulman et al. 1952; Anderson et al. 1954; Scholtz 1959). Hypercalcaemia caused by administration of excessive amounts of vitamin D to metabolically normal subjects can also be lowered by cortisone (Verner et al. 1958). However, the concomitant administration of cortisone and vitamin D to rats did not lessen vitamin D-induced hypercalcaemia (Thomas & Morgan 1959) or renal calcification (Cruikshank & Kodicek 1956). The histological changes in the bones...
of these rats showed the combined effect of both compounds, suggesting that vitamin and cortisone acted independently rather than competitively on bone. On the other hand, Williams et al. (1961), using an in vitro technique involving gut sacs from vitamin D-deficient rats, demonstrated that cortisone decreased the active transport of calcium through the gastrointestinal wall. This effect, which opposed the action of vitamin D, was confined to the upper portion of the small intestine. Cortisone administration has also lowered the plasma phosphorus in sarcoidosis and in normal subjects (Hennemann et al. 1956; Scholtz 1959; Anderson & Foster 1959). This effect is the opposite of that produced by vitamin D.

Cortisol in Vitamin D Deficiency States
Discussion regarding vitamin D/cortisone antagonism has mostly centred around vitamin D in pharmacological dosage. Harrison et al. (1957) conducted experiments on rats to discover whether cortisol (hydrocortisone) was antagonistic to the physiological effects of the small amounts of vitamin D required to heal rickets. Some of their results, which appear to be conclusive, are summarised as follows:

1. In rats rendered rachitic by vitamin D and phosphorus deprivation, cortisol was without effect on the level of the serum calcium, but caused a further lowering of the serum phosphorus level, without any phosphorus appearing in the urine. The authors point out that the cortisol must have produced a shift of phosphorus into the cells.

2. Cortisol did not prevent the normal healing of rickets in those rachitic rats given vitamin D, nor the usual rise in serum calcium and phosphorus levels. It did, however, prevent the expected rise in the level of serum citrate from occurring.

Hypo- and Hyper-Adrenocortical States
If cortisone/vitamin D antagonism exists, subjects suffering from hypercortisolism (Cushing's syndrome or glucocorticoid administration) might be resistant to the effects of vitamin D, while hypoadrenal subjects might be unduly sensitive to the vitamin. In adrenal insufficiency hypercalcaemia has been reported, with levels up to 15 mg per 100 ml (Taylor & Graven 1927; Loeb 1932; Sprague et al. 1953 and Leeksma et al. 1957), but there is no evidence that this was produced by unusual sensitivity to vitamin D. Leeksma et al. stress that the hypercalcaemia occurred during manifest or imminent adrenal crisis. The serum phosphorus levels were also elevated in their patients.

Hypercalcaemia may occur immediately after subtotal adrenalectomy for Cushing's syndrome (Kepler et al. 1948) but has apparently not been found after an adrenalectomy for any other reason. Presumably a sudden fall of glucocorticoids from abnormally high levels is a necessary factor.
Bone atrophy is common in Cushing’s syndrome (Plotz et al. 1952; Carter et al. 1954), and the serum inorganic phosphate is frequently low. However no definite evidence of vitamin D deficiency has been reported in this condition. Albright & Reifenstein (1948) found that the levels of the serum, urinary and faecal calcium were normal in two patients with Cushing’s syndrome who underwent metabolic balance studies. Slight elevation of serum calcium levels have been reported in some cases (Mellinger & Smith 1956; Molinatti et al. 1960). Parathyroid overactivity and disordered renal function have been suggested as possible causes for this hypercalcaemia (Robinson 1954; Mellinger & Smith 1956; Grollman 1954). Hypercalciuria was present in 10 out of 17 cases investigated by Molinatti et al. (1960). The urinary calcium output returned to normal levels after adrenalectomy. Increased faecal calcium in Cushing’s syndrome, a possible anti-vitamin D effect, was noted by Freyberg & Grant (1936) and Soffer (1952), but was not confirmed by Henneman et al. (1956). It is possible that a degree of vitamin D antagonism is present in Cushing’s syndrome which is insufficient to cause a vitamin deficiency state, but might prevent the effects of moderate overdosage with vitamin D. The response to administered vitamin D might provide a more sensitive index in assessing antagonism.

**OUTLINE OF PROCEDURE**

The possibility of cortisone/vitamin D antagonism was investigated in four male adult volunteer Bantu subjects, who appeared to be metabolically normal. All these individuals underwent metabolic balance studies.

Calciferol was administered to these subjects until an effect on calcium metabolism was observed, after which cortisone or cortisol, in doses up to and including 300 mg daily, was taken in addition to the continuation of calciferol. Details differed in each case and have been previously reported (Jackson & Dancaster 1962).

In order to assess sensitivity or resistance to vitamin D in patients with adrenal dysfunction it was necessary to select a suitable dose. Several metabolically normal control subjects (including the four mentioned above) and a few patients with hypoparathyroidism had received between 300 000 to 400 000 units of vitamin D daily for 5 to 10 days. Hypercalciuria was produced in every case except one and the level of the serum calcium rose in most of the subjects who had received the vitamin at this dosage for 10 days. It therefore appeared that this amount of vitamin D would usually result in either hypercalciuria or hypercalcaemia or both within 10 days.

Changes in phosphate metabolism were less obvious, but of similar type. Hypoparathyroid patients have been maintained on 50 000 to 100 000 units of vitamin D daily for many years without ill effects and 200 000 units for shorter periods. In normal adults also we have not seen evidence of overdosage from 200 000 units given daily for short periods.

Based on the foregoing results, we gave 5 patients with Cushing’s syndrome
3-400,000 units of calciferol daily orally for 10 days with daily estimation of urinary and serum levels of calcium and phosphorus. Two of these patients were studied by full metabolic balance technique. Changes in serum and urinary calcium and phosphorus were also studied in 9 patients suffering from hypoadrenalism caused by either Addison’s disease or hypopituitarism. Five received 200,000 units or less of vitamin D daily. When this dose was found to be ineffective in causing any changes, four further patients were given 300,000 or 400,000 units daily for 7 days or longer. In all cases a normal ward diet (approximately 800 mg of calcium and 1000 mg phosphorus daily) was eaten. No patient had impairment of renal function.

In expressing the results below, the mean figures for the first 4 days of observation (immediately prior to vitamin D administration) are termed »first mean«, and the mean figures for the last 4 days on vitamin D are termed »second mean«. In the case of serum calcium and phosphorus the figures refer to mg per 100 ml and in the case of urinary calcium and phosphorus they refer to mg per 24 hour period.

Methods of chemical analyses are those previously described by us (Jackson & Dancaster 1959). The calciferol used was »Ostelin forte«, tablets, supplied by Glaxo laboratories.

Methods used:
Serum calcium: Greenblatt & Hartman (1951).
Serum and urinary inorganic phosphate: King (1951).
Urinary calcium: Jackson & Irwin (1957).
Urinary 17-ketosteroids: Norymberski et al. (1953).
Urinary 17-hydroxycorticoids: Appleby et al. (1955).
Plasma cortisol: Peterson et al. (1957).

RESULTS

Normal Adults
Full balance studies with discussion have been published previously (Jackson & Dancaster 1962). In brief review:

Case 1. W. M. Vitamin D caused a rapid increase in urinary calcium output, further enhanced during administration of cortisol. Faecal calcium fell slightly after 10 days of calciferol and this diminution was maintained when cortisol was given. The serum calcium level rose slightly during calciferol therapy and did not change markedly with cortisol.

Case 2. A. M. Vitamin D (300,000 units per day) produced an immediate increase in urinary calcium and in serum and urinary phosphorus levels. There was actually a decrease in net intestinal absorption, i.e. an increase in faecal levels. The serum calcium level remained within the normal range. Cortisone, given while the calciferol was being continued, appeared to have no effect on any parameter, except that there was a slight fall in the concentration of serum phosphorus.
Case 3. J. M. Calciferol produced an increase in urinary calcium and a later rise in serum calcium level. When cortisone was added the urinary calcium increased and the serum calcium did not change until the dosage of calciferol had been dropped. The combination of cortisone and calciferol was accompanied by a rise in faecal calcium and phosphorus.

Case 4. H. M. Calciferol caused an increase in serum and urinary calcium, but the highest levels of serum calcium and phosphorus were reached when cortisone and calciferol were being taken concurrently. The faecal calcium fell markedly at this time.

Cushing’s Syndrome

Case 5. J. P., a white girl aged 17, had typical features of Cushing’s syndrome with high 17-hydroxycorticoid (17-OHCS) levels in the urine (26 mg per day, elevated to 180 after ACTH stimulation). At laparotomy, bilateral hyperplastic adrenal glands were removed, after which her appearance reverted to normal.

She received 400 000 units of vitamin D daily for 10 days prior to the operation, during the course of four 5-day balance periods. There was a slight increase in mean serum calcium level during calciferol administration (first mean = 10.4, second mean = 11.0), while the urinary calcium output was almost doubled (control periods: 90 and 87 mg per day, calciferol periods: 152 and 159 mg). A marked drop in faecal calcium and phosphorus, however, brought about a distinctly positive balance of these minerals during calciferol administration.

Case 6. M. Wr., a white woman of 40, had clinical features of Cushing’s syndrome. Diagnosis was confirmed by the finding of elevated urinary 17-hydroxycorticoid levels (30 mg in 24 hours) and an adrenal adenoma was removed at operation. Daily administration of 400 000 units calciferol was accompanied by a slight but inconclusive rise in serum calcium (first mean = 9.6; second mean = 10.2) and urinary calcium (first mean = 137, second mean = 154). Serum phosphorus (mean = 3.8 mg/l) and urinary phosphorus levels showed no change.

Case 7. P. C., a white lad of 18 with typical features of Cushing’s syndrome including widespread purple striae. Resting urinary 17-OHCS output was 51 mg per 24 hours. Bilateral adrenal hyperplasia was confirmed at operation.

Calciferol given for 10 days, 300 000 units daily, did not alter serum calcium or phosphorus levels. A slight rise of urinary calcium output occurred, of doubtful significance. (Urinary calcium, first mean = 205, second mean = 270).

Case 8. M. We., a white woman of 32 with features of Cushing’s syndrome, and a resting urinary 17-OHCS output of 42 mg per day. A single adrenal cortical adenoma was found at operation.

She received 400 000 units of calciferol daily for 9 days. The serum calcium remained virtually unchanged (first mean = 10.2; second mean = 10.4). The urinary calcium output doubled (first mean = 132, second mean = 266).

Case 9. P. o., a white woman of 35 with typical features of Cushing’s syndrome, confirmed by urinary 17-OHCS excretion of 42 mg per day. Bilateral adrenal hyperplasia was found at laparotomy.

This patient was studied during three 5-day balance periods; in the middle period she received 400 000 units of calciferol daily. Serum levels of calcium and phosphorus did not change, but the urine calcium output rose from 180 mg daily in the first period to 336 mg in the second, and 514 in the third. Calcium balance became negative during the last period. Urinary phosphorus rose slightly in the last period. Faecal calcium remained constant; i.e. no change in gastrointestinal absorption was found.
Hypoadrenal Subjects (Daily calciferol dosage 200 000 units or less.)

Case 10. K. W., a white man aged 43, complained of lassitude and darkening of the skin. He had hypotension, excessive buccal pigmentation and low-normal levels of urinary 17-ketosteroid (17-KS) and 17-OHCS which were unchanged by 2 days of intravenous ACTH stimulation.

There was no alteration of either serum or urinary calcium following 5 days of vitamin D administration (50 000 units for the first 2 days, thereafter 100 000 units).

Case 11. C. L., a white man aged 27, was a merchant seaman and had often been incapacitated by severe diarrhoea and weakness when passing through the tropics. He had an insatiable hunger for salt and liquorice, especially at these times. His skin was dark and there was abnormal buccal pigmentation. Low urinary 17-KS and 17-OHCS levels did not rise after ACTH stimulation.

Vitamin D administration over 6 days (100 000 units for the first 3 days and thereafter 200 000 units daily) failed to alter the serum calcium (first mean = 9.6; second mean = 9.6) or urinary levels (first mean = 61, second mean = 57).

Case 12. J. R., a white male aged 40, had noticed increasing skin pigmentation and was easily fatigued. Buccal and nipple pigmentation were excessive and Addison's disease was confirmed by the finding of negligible urinary 17-KS and 17-OHCS. Both adrenal glands were calcified.

200 000 units of vitamin D were administered daily for 10 days without affecting the serum calcium level.

Case 13. M. B., a coloured man aged 53 with hypopituitary myxoedema. 131I uptake rose from 14 %/o to 43 %/o after 4 days of stimulation with thyroid-stimulating-hormone. Water diuresis was impaired, and normalized by cortisone. Daily urinary output of 17-KS was 0.5 mg.

Calcium and phosphorus levels in serum and urine were unchanged after 8 days of calciferol, at 200 000 units per day.

Case 14. M. C., a coloured female aged 39 with Sheehan's syndrome of 8 years duration following a concealed accidental haemorrhage. Symptoms were typical; blood pressure 80/60, 24-hour urinary 17-KS output 0.3 mg and urinary gonadotrophins too low to be detected.

She was given 200 000 units of calciferol for 10 days. Different serum specimens were, by error, analysed in different laboratories so that the results cannot be evaluated. The urinary calcium output appeared to rise (first mean = 82, second mean = 202).

Hypoadrenal Subjects (Daily calciferol dosage 300 000 units or more)

Case 15. E. S., a white woman 58 years old who had undergone operative removal of a parapituitary ganglioglioma one year previously. She had become clinically hypothyroid and this was confirmed by a very low 131I thyroidal uptake. There were no overt features of hypoadrenalinism; the 17-KS and 17-OHCS urinary output were each between 8 and 9 mg per day and plasma cortisol level (Porter-Silber) was 14.4 µg per 100 ml. Metopirone given later caused no rise in urinary 17-OHCS output.

While she was taking 300 000 units of vitamin D, the serum calcium level rose from 9.1 to 10.4 mg per 100 ml (first mean = 9.4, second mean = 10.1) and the serum phosphorus from 4.0 to 5.2 mg. The urinary calcium output rose several fold (first mean = 105; second mean = 350); the urinary phosphorus also rose (first mean = 240, second mean = 600).

Case 16. R. P., a coloured boy aged 15, developed Addisonian features following subtotal adrenalectomy for Cushing's disease. Symptoms included nausea and vomiting.
with hypotension. Low urinary 17-KS and 17-OHCS excretion confirmed the diagnosis. He was maintained on 0.1 mg of flurhydrocortisone during the test period.

The serum and urinary calcium levels remained unaltered after 9 days of vitamin D administration, 400 000 units daily. (Serum calcium, first mean = 10.4; second mean = 10.6; urinary calcium, first mean = 138, second mean = 124). The phosphorus figures were also unaltered.

Case 17. J. L., a white woman with classical features of Sheehan's syndrome following severe post-partum haemorrhage 9 years earlier. The 24-hour urinary 17-KS excretion was 2.3 mg and 17-OHCS excretion 3.4 mg. Water diuresis was very grossly impaired.

Vitamin D was given for 7 days, 400 000 units daily. The serum calcium was unaltered (first mean = 9.5, second mean = 9.6); the urinary calcium output rose somewhat (first mean = 53, second mean = 100). Phosphorus levels did not alter.

Case 18. Y. N. A coloured woman suffering from Sheehan's syndrome, and very similar to the preceding case, with urinary 24-hour 17-OHCS output of 2.9 mg.

Calciferol was given for 10 days, at 400 000 units daily. Serum calcium and phosphorus remained unchanged. Urinary calcium output rose insignificantly (first mean = 38, second mean = 55).

**DISCUSSION**

In our normal subjects calciferol caused a rise in the urinary calcium output, with or without elevation of the serum calcium level and with or without

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**SERUM CALCIUM LEVELS AFTER CALCIFEROL**

![Graph showing serum calcium levels after calciferol](image)

*Fig. 1.*

All serum calcium levels are means as described in the text. In the sarcoid and myeloma cases the dose of calciferol was only 150 000 units daily.
URINARY CALCIUM OUTPUT AFTER CALCIFEROL

![Graph showing urinary calcium output after calciferol](image)

**Fig. 2.**
Same remarks apply to urine calcium output as to serum calcium levels shown in Fig. 1.

similar changes in phosphorus metabolism. Cortisone did not appear to block these effects while the vitamin was still being administered.

The hypoadrenal subjects were completely insensitive to calciferol in doses which did not exceed 200,000 units daily for short periods, except for a rise in urinary calcium in case no. 14. Among the 3 groups of subjects tested, normal, hypoadrenal and hyperadrenal, there was little or no difference in the response to larger doses of calciferol, with regard to serum calcium and phosphorus levels and urinary calcium and phosphorus excretions (Figs. 1 and 2 summarise the relevant calcium levels).

In no person did the serum calcium rise above 11 mg per 100 ml.

The greatest rise in urinary calcium output among the hypopituitary cases was seen in No. 15, in which there was the least evidence of secondary hypoadrenalism.

In contrast to our 3 groups of subjects, a really vitamin D-sensitive patient will respond with immediate and large increases in both serum and urinary calcium levels when given 200,000 units of vitamin D per day, or less. This is illustrated in Figs. 1 and 2 with examples from normocalcaemic sufferers from sarcoidosis and myelomatosis.

We therefore conclude that human states of hypo- and hyper-cortisolism
do not alter the normal degree of sensitivity to large doses of vitamin D. (We must admit, however, that more severely ill patients with, for instance impending hypoadrenal crisis have not been investigated).

We attempt to summarise the present evidence regarding vitamin D/cortisol antagonism as follows:

<table>
<thead>
<tr>
<th>VITAMIN D</th>
<th>CORTISOL</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous sensitivity (e.g. sarcoidosis, infantile hypercalcaemia)</td>
<td>exogenous</td>
<td>antagonism</td>
</tr>
<tr>
<td>Vitamin-lack (low phosphorus rickets in rats) + administered therapeutic D</td>
<td>exogenous</td>
<td>no antagonism (except to citrate effect)</td>
</tr>
<tr>
<td>Exogenous excess</td>
<td>exogenous</td>
<td>no antagonism (except after discontinuation of vitamin)</td>
</tr>
<tr>
<td>Exogenous excess</td>
<td>endogenous deficiency</td>
<td>no increased sensitivity to D.</td>
</tr>
<tr>
<td>Exogenous excess</td>
<td>endogenous excess (Cushing’s syndrome)</td>
<td>no increased resistance to D.</td>
</tr>
</tbody>
</table>

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REFERENCES


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