THE EFFECTS OF VITAMIN A TOXICITY ON CALCIUM AND LIPID METABOLISM IN CHRONIC RENAL FAILURE

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Summary

Serum vitamin A levels were high in haemodialysis patients, and were found to correlate with plasma calcium, triglyceride, cholesterol and insulin levels. Vitamin A containing multivitamin supplements were found to contribute to increased serum vitamin A levels, and their withdrawal in seven patients caused a significant decrease in serum vitamin A and calcium levels, with no effect on lipid levels. Vitamin A containing preparations should therefore be prescribed with caution in these patients.

Introduction

Serum vitamin A levels are elevated in chronic renal failure [1]. Hypervitaminosis A has been shown to cause hypercalcaemia in normal patients [2], and may contribute to the abnormalities in skeletal and lipid metabolism common in haemodialysis patients [3]. We wanted to assess the contribution of hypervitaminosis A to these abnormalities in our patients. We therefore examined the relationships between their serum vitamin A levels and biochemical parameters of bone disease and hyperlipidaemia. As many of our patients were taking multivitamin preparations containing vitamin A their contribution to hypervitaminosis A was investigated. More importantly, the withdrawal of vitamin A supplements in seven of these patients provided an opportunity to study the effects of hypervitaminosis A on skeletal and lipid metabolism more directly.

Patients and methods

Serum vitamin A levels were measured in 71 chronic renal failure patients receiving regular haemodialysis (mean age, 39.7 ± 13.4 SD years, mean duration of dialysis, 66.7 ± 52.3 SD months). Forty of these patients were taking a multivitamin preparation (Multivite Pellets, Duncan Flockhart Co Ltd) containing
2500 IU vitamin A per tablet, at up to six per day. Vitamin A was measured in 28 normal controls (mean age, 29.5 ± 8.4 SD years) to establish a normal range.

Thirty-eight of the 71 who were not being treated with vitamin D metabolites or analogues and had not had a parathyroidectomy had plasma calcium, phosphate and alkaline phosphatase measured (by standard autoanalyser methods). Plasma hydroxyproline was measured in 30 patients and immuno-reactive parathyroid hormone (i-PTH) in 20 (both by methods previously described [4]). Vitamin A was measured by the macro-method of Neeld and Pearson [5].

In 50 of the patients plasma triglyceride and cholesterol were measured (by standard autoanalyser methods). Insulin was measured in 22 (RIA kit – Amersham International).

Seven patients on ‘Multivite Pellets’ had these withdrawn. Blood samples were taken at baseline and monthly for 3 months, and assayed for all the parameters above, except insulin.

All samples in this study were taken after overnight fasting and at least 36 hours after dialysis. Vitamin A samples were protected from light at all times. Statistical methods used were Students t-test, linear regression and the Wilcoxon rank sum test, where appropriate.

Figure 1. Vitamin A concentrations in 28 controls, 71 patients on haemodialysis and the 20 normocalcaemic and 18 hypercalcaemic patients of the calcium study.
Figure 2. Biochemical changes in 7 haemodialysis patients after withdrawal of vitamin A supplements. Bars indicate standard error of mean.
Results

In 71 chronic renal failure patients the mean vitamin A level (147 ± 53µg/100ml) was found to be significantly higher (p < 0.001) than in the controls (52 ± 12µg/100ml) (Figure 1). There was a significant difference (p < 0.01) in mean vitamin A levels between those taking (161 ± 30µg/100ml) and not taking ‘Multivite Pellets’ (130 ± 24µg/100ml). Vitamin A levels did not correlate with age or duration of dialysis.

There was a significant correlation between serum vitamin A levels and plasma calcium levels (p < 0.05). Vitamin A levels did not correlate with phosphate, alkaline phosphatase, hydroxyproline or i-PTH. Eighteen of these patients were hypercalcaemic. These had a significantly higher (p < 0.005) mean serum vitamin A (161 ± 59µg/100ml) than the 20 normocalcaemics (114 ± 36µg/100ml) (Figure 1). There was no significant difference in mean i-PTH levels in these two groups, nor were any significant differences in vitamin A levels to be found by dividing the patients according to levels of alkaline phosphatase, hydroxyproline or i-PTH.

There was a significant correlation between vitamin A and triglyceride (p < 0.005), cholesterol (p < 0.05) and insulin (p < 0.05).

The biochemical changes in seven patients after vitamin A withdrawal may be seen in Figure 2. Serum vitamin A fell dramatically and was significantly lower than baseline at 2 and 3 months (p < 0.01). Six of the patients were originally hypercalcaemic, but only two remained so after 3 months. There was a fall in alkaline phosphatase, significant at 2 months (p < 0.01). Plasma phosphate, hydroxyproline, i-PTH, triglyceride and cholesterol did not change significantly.

Discussion

Elevated serum levels of vitamin A were found in chronic renal failure patients on haemodialysis. Possible causative factors are the decreased metabolism of retinol to retinoic acid (a function of the kidney) and the increased levels of retinol-binding protein found in chronic renal failure [1]. We found that serum vitamin A levels were significantly higher in patients taking vitamin A supplements, and that there was a large fall in vitamin A levels after their withdrawal in seven patients. This indicates a significant contribution to the hypervitaminosis A by these supplements. Obviously care must be exercised in prescribing vitamin A containing preparations to patients with impaired renal function.

That hypercalcaemia can be a result of hypervitaminosis A can be seen from the positive correlation between serum vitamin A and plasma calcium levels, the significantly higher levels of vitamin A in the hypercalcaemic subgroup, and by the significant reduction of calcium levels after withdrawal of vitamin A supplements. In case reports of hypervitaminosis A [2] hypercalcaemia was associated with serum vitamin A levels similar to those found in this study. ‘Multivite Pellets’ contain vitamin D2 (250 IU/tablet) but it is very unlikely that this amount was sufficient to contribute to hypercalcaemia in chronic renal failure patients.

Vitamin A may cause hypercalcaemia either by a direct effect on bone, on the parathyroids or both [6]. In tissue culture vitamin A has been shown to cause osteolysis and potentiate the osteolytic effect of parathyroid extract [7]. In rats
hypervitaminosis A causes increased bone resorption and may inhibit osteoblastic activity. This osteolytic effect may be due to the action of vitamin A on lysosomal membranes. Vitamin A has been shown to stimulate PTH secretion in bovine parathyroid tissue and in man [8]. The drop in alkaline phosphatase after vitamin A withdrawal suggests that hypervitaminosis A was affecting bone metabolism, though plasma hydroxyproline remained unchanged. No change in i-PTH was seen after withdrawal, although the lowering of calcium would be expected to cause a rebound rise in i-PTH.

It has long been known that excess oral vitamin A can increase plasma lipids in children, and that excess vitamin A fed to experimental animals can have a striking effect on lipid metabolism [3]. We found significant correlations between vitamin A and triglyceride and cholesterol, but no significant changes were seen after withdrawal of vitamin A. These correlations may therefore be fortuitous, hyperlipidaemia, especially hypertriglyceridaemia being common in chronic renal failure. Vitamin A, being fat soluble, is found associated with lipoproteins so hyperlipidaemia may increase the vitamin A carrying potential of the plasma. In vitro work has shown that vitamin A at different levels may have a varying effect on insulin secretion [9]. We demonstrated a significant correlation between vitamin A and plasma insulin levels.

In conclusion, it may be that hypervitaminosis A has some toxic effects, manifested particularly as hypercalcaemia, probably caused by a direct or indirect effect on bone metabolism. Whether vitamin A has a role in the complex aetiology of hyperlipidaemia in chronic renal failure has yet to be determined.

References
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9 Chertow BS, Buschmann RJ, Kaplan RL. Diabetes 1979; 28: 754

Open Discussion

O'HARE (Cork) Did the multivitamin preparation contain any calcium carbonate?

SWENY No, it contained a very small amount of Vitamin D₂; 250 international units.

PARSONS (London) Did you notice any difference in the condition of the skin, because Vitamin A is handed out in increasing amounts by the dermatologists for various forms of pruritus?
SWENY We did not notice that and obviously we hope that no one else will be prescribing Vitamin A.

PARSONS You are absolutely against it now unless it is measured.

SWENY Yes, I do not think it is necessary and it can lead to confusion as to the presence or absence of tertiary hyperparathyroidism.

DRÜEKE (Paris) Is there any experimental evidence that Vitamin A might directly interfere with lipid metabolism or could it be that the effect on parathyroid gland secretion explains the toxicity in these patients?

SWENY I do not know of any experimental evidence. We have attributed the initial positive correlation to the fact that Vitamin A is a lipid soluble vitamin, and the fact that the triglyceride and cholesterol levels did not fall when we withdrew Vitamin A probably implies that it is not important.

RITZ (Heidelberg) And there is good evidence for this from secondary hyperlipidaemia such as hypothyroidism etc, that it partitions into the lipid fraction.

SCHRÄGER (Heidelberg) Vitamin A is also known to be nephrotoxic. Did you find any improvement of residual renal function in your dialysed patients after omission of the vitamin A preparation?

SWENY All these patients had been on dialysis a long time and we were not checking renal function.

WILL (Leeds) Can you comment on the influence of the length of time on dialysis? If your hypercalcaemic patients had been longer on treatment there might be a multiple correlation with Vitamin A. Secondly, did you say that the fall in serum phosphate on stopping the supplements was or was not significant, because that would obviously have a bearing on your conclusions?

SWENY There was no difference in the duration of dialysis between the patients in the two groups, those taking Vitamin A and not taking Vitamin A, although I realise they had both been on dialysis a long time and there was not a significant fall in phosphate after withdrawal of Vitamin A.

SCHULTZ (Bamberg) Have you measured Vitamin A binding proteins?

SWENY No.

SCHULTZ They are elevated, parallel to Vitamin A, and that is a problem of metabolism in the kidney.