Use non-invasive dark adaptometry to screen children and adolescents

EDITOR,—N J Watson and colleagues remind readers of the possibility of vitamin A deficiency in patients with gastrointestinal or liver disease.¹ I am surprised, however, that they do not also mention its possibility in cystic fibrosis.^{2,3} They suggest measurement of serum vitamin A concentrations and cytological examination of conjunctival specimens, presumably as a screening technique in people at risk. I suggest that dark adaptometry, which is non-invasive, might be more appropriate, particularly in children and adolescents.³

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Effect of alfacalcidol on renal bone disease in mild to moderate renal failure

Monitoring the calcium-phosphate product is important

EDITOR,—In Neveen A T Hamdy and colleagues' study of alfacalcidol in chronic renal failure, treatment with phosphate binding agents (other than 500 mg elemental calcium daily) was started only if the serum phosphate concentration was >2.2 mmol/l.¹ We believe that the threshold for starting phosphate binding agents should be lower, particularly when alfacalcidol is being given to "maintain serum calcium concentration at the upper limit of the normal laboratory reference range" (2.63 mmol/l).

Metastatic calcification has long been recognised as a complication of chronic renal failure with serious vascular and other consequences, and it was suggested many years ago that the main determinant of metastatic calcification was the solubility product of calcium and phosphate in vivo.² Subsequent estimates of this product have varied widely. Herbert *et al* estimated that a calcium-phosphate product >6 mmol²/l² would result in precipitation, on the basis of in vitro data, and showed that 15 of 17 patients with metastatic calcification had a product exceeding this value.³ Hebert *et al* suggested that calcium and phosphate would precipitate at 4.6 mmol²/l² on the basis of an extrapolation of in vivo data from 12 patients.⁴ The study that was perhaps most relevant clinically showed progression of vascular calcification in 15 patients with chronic renal failure with a mean calcium-phosphate product of 4.93 mmol²/l² and no progression at 4.10 mmol²/l² (20 patients); the authors advocated a target of <4.2 mmol²/l².⁵

In Hamdy and colleagues' study, however, a calcium-phosphate product of up to 5.8 mmol²/l² would have been regarded as acceptable.¹ While most of their patients clearly did not have a high calcium-phosphate product (mean serum calcium concentration 2.36 (SD 0.15) mmol/l rising by 0.07 (0.02) mmol/l at two years, mean serum phosphate concentration 1.29 (0.28) mmol/l rising by 0.13 (0.05) mmol/l), their protocol could result in metastatic calcification because of inadequate control of phosphate concentration. A raised serum phosphate concentration may in addition explain why parathyroid hormone concentrations

had started to rise again in the treated group at two years despite normal serum calcium concentrations. We recommend that serum phosphate concentration should be kept below 1.7 mmol/l, as is our practice, with a maximum calcium-phosphate product of 4.2 mmol²/l², which would allow a serum calcium concentration of up to only 2.47 mmol/l. If these target maximum values are used metastatic calcification should be avoided. The effect of better control of phosphate concentration with a serum calcium concentration in the lower normal range on renal bone disease is as yet unknown.

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Questions remain over alfacalcidol's efficacy in preventing secondary hyperparathyroidism

EDITOR,—Nveen A T Hamdy and colleagues report a placebo controlled trial of alfacalcidol in patients with mild to moderate renal failure.¹ They conclude that alfacalcidol might be used more widely in these patients. Before we accept their conclusion we would appreciate answers to the following points.

Firstly, since the conclusions are based on histomorphometric data on bone we would like to know the normal ranges for these histomorphometric variables, the criteria used to show that the number of osteoclasts and osteoblasts was increased, and the significance of the difference in the number of bone cells between the two groups at the end of the trial.

Secondly, were the final plasma concentrations of parathyroid hormone significantly different between the two groups? Why was the suppression of secretion of the hormone with alfacalcidol only transient? Might not this escape in the control of secretion of parathyroid hormone lead to a reversal of the improvement in hyperparathyroid bone disease? This improvement was moderate since the difference in bone formation rate between the two groups was not significant.

Thirdly, as the administration of calcitriol in children has been reported to increase the risk of metastatic calcification,² did the authors look for this?

Fourthly, was the daily intake of calcium and native vitamin D in the placebo group optimal according to the recommended daily allowance? What were the plasma concentrations of 25-hydroxycholecalciferol in the placebo group? This is important since in patients with renal insufficiency the plasma concentrations of 1,25-dihydroxycholecalciferol depend directly on the plasma concentrations of 25-hydroxycholecalciferol, which are often low in northern countries,³ and physiological doses of native vitamin D have been found to heal osteomalacia in uraemic patients⁴ and to decrease the risk of hip fracture in elderly women.¹

Fifthly, is alfacalcidol the most logical treatment for renal osteodystrophy? Its suppressive effect

on the synthesis and secretion of parathyroid hormone by increasing plasma concentrations of 1,25-dihydroxycholecalciferol and calcium is finally counteracted by the increase in plasma phosphate concentration. Indeed, whereas the plasma phosphate concentration fell in the placebo group, it increased by 0.3 mmol/l with alfacalcidol, probably because of the stimulation of intestinal absorption of phosphate; hyperphosphataemia is recognised as an independent stimulating factor of synthesis of parathyroid hormone.⁵ Would it not be more logical to use the alternative approach of native vitamin D repletion associated with dietary phosphate restriction reinforced by giving oral calcium before meals as a phosphate binder?⁶ This approach has been proved to be effective and safe,⁴ especially in more advanced renal failure (glomerular filtration rate <15 ml/min)⁷ since the hazards of hyperphosphataemia and hypercalcaemia are less likely to occur than with alfacalcidol (alfacalcidol induced hypercalcaemia in 11% of the patients, although their final mean creatinine clearance was still 25 ml/min). A controlled comparison of these two approaches would be necessary to resolve this issue.

Finally, what is the optimal range of plasma concentrations of intact parathyroid hormone for various degrees of renal insufficiency in order to maintain a normal rate of formation of bone and decrease the risk of hypercalcaemia? The resistance of uraemic bone to the remodelling effect of parathyroid hormone increases with the severity of renal insufficiency.³

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Authors' reply

EDITOR,—Mark S McGregor and colleagues suggest that the threshold for serum phosphate concentration above which phosphate binding agents might be given should be lower than 2.2 mmol/l. We accept this point for patients before they receive dialysis, but in patients receiving dialysis the serum phosphate concentration that best balances the risk of extraskeletal calcification and osteomalacia is probably the value that we quoted.¹ If McGregor and colleagues' suggestion of 1.7 mmol/l for serum phosphate concentration is used as the threshold then a higher proportion of patients treated with placebo (18%) than with alfacalcidol (15%) developed hyperphosphataemia. Thus the regimen that we gave is safe in this regard.

Constraints of space did not permit us to report our radiographic findings, but we found no evidence of extraskeletal calcification. Incidentally, the use of the calcium phosphate product is neither practically nor theoretically justifiable in the absence of hypercalcaemia, since variations in serum calcium concentration contribute fourfold less to the product than does phosphate itself.

A Fournier and colleagues raise several points