NICE APPRAISAL FOR CINACALCET

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PROJECT TITLE
THE EFFECTIVENESS AND COST-EFFECTIVENESS OF CINACALCET FOR THE TREATMENT OF HYPERPARATHYROIDISM SECONDARY TO IMPAIRED RENAL FUNCTION

Secondary hyperparathyroidism

Secondary hyperparathyroidism is a common complication of chronic kidney disease and begins early in the progression of disease as glomerular filtration falls. Three major factors contribute to secondary hyperparathyroidism. These are:

a) low calcium

b) decreased formation of calcitriol (the active form of Vitamin D)

c) elevated levels of phosphate within the blood.

This condition is called ‘Secondary hyperparathyroidism’ and is present in the vast majority of patients receiving renal replacement therapy. The technology assessment incorrectly states that 40% of patients on renal replacement therapy have secondary hyperparathyroidism (reference 4). The majority of patients will have biochemical evidence of secondary hyperparathyroidism, or be on therapy for secondary hyperparathyroidism.

In a proportion of such patients this may develop into tertiary hyperparathyroidism, as parathyroid glands no longer adequately respond to plasma calcium levels. One or more dominant adenomata may develop within the glands, secreting parathyroid hormone (PTH), with relative or absolute insensitivity to serum calcium levels.

Clinical effects

The principle classical effect of second hyperparathyroidism is osteitis fibrosa, one form of renal bone disease. In this condition bone turn over is rapidly increased. This can lead to symptoms such as fractures and bone pain. Histological data would suggest 20-30% of patients have osteitis fibrosa (e.g. Kidney Int Suppl 2003 Jun;(85):S73-80). In addition, high turnover bone disease can release further phosphate into the circulation, exacerbating the dysfunctional production of PTH and risking further metastatic calcification. Severe hyperparathyroidism is also associated with a reduction in the efficacy of erythropoietin, muscle weakness and itching.

Metastatic calcification
The second aspect of increased parathyroid hormones secretion can be the accumulation of calcium phosphate product with precipitation into arteries, joints and soft tissues. A severe form (called calcific uraemic arteriopathy) is associated with tissue death and a high mortality rate. Current therapies have had little or no impact on this complication once it occurs. Once ulceration occurs the mortality rate is >80%. (Kidney International 2002 June Issue 2210-07)

Current treatment for hyperparathyroidism

Treatment of secondary and tertiary hyperparathyroidism in chronic renal failure involves therapeutic strategies to lowering serum phosphate, maintain normal serum calcium levels, and restore parathyroid hormone levels towards normal values.

Reduction of serum phosphate levels

Dietary phosphate intake

Dietary phosphate intake may be restricted in patients but only at the cost of limiting protein intake. A large proportion of dialysed patients have a borderline malnutrition. Protein supplementation is there for required in that group. Dietary phosphate restriction consequently is only achievable in a small minority of patients.

Phosphate binders

The majority of patients with chronic renal failure and receiving renal replacement therapy require phosphate binders. These act by limiting the absorption of dietary phosphate. A variety of drugs have been used for this purpose.

A decade ago aluminium hydroxide was the main stay of therapy, but in the United Kingdom calcium containing phosphate binders had become the norm. These have limited efficacy, can be poorly tolerated, and cause a range of side effects, particularly hypercalcaemia.

Alternative agents have been developed and in the UK sevelamer (Renagel) has been introduced. This is a non-calcemic phosphate binder. The main problems associated with this agent are those of cost, gastrointestinal tolerance and limited efficacy. Lanthanum carbonate is licensed in the US and other countries but there is limited experience in the United Kingdom.

Vitamin D analogues

One aspect of the pathogenesis of secondary hyperparathyroidism is the inability to activate Vitamin D as the kidneys become damaged. The kidneys hydroxylate Vitamin D in a healthy person, but as they become damaged this enzyme is no longer available to sufficiently produce activated Vitamin D. Consequently any patients are often prescribed Vitamin D analogues. This may potentially lower parathyroid hormones levels by two mechanisms

1. Elevating serum calcium which acts via the calcium sensing receptor on the parathyroid glands and

2. Suppressing PTH gene transcription and therefore the production of PTH, (in other words changing the set point for any given calcium)

Side effects of such therapy are common. Severe hypercalcaemia can result in hospitalisation of patients with confusion and other generalised side effects. Hypercalcaemia is more common if patients are receiving calcium containing phosphate binders.

Parathyroidectomy

Despite the above therapies, patients may require surgery to deal with refractory hyperparathyroidism.
Surgical approaches include sub total parathyroidectomy, total parathyroidectomy with auto transplantation and total parathyroidectomy.

**Subtotal parathyroidectomy** involves the removal of all parathyroid tissue identified at operation except for a proportion of the least enlarged gland. Drawbacks are that there is a higher rate of recurrent disease and further surgery then becomes more complicated.

An alternative approach is to remove all the glands but to implant some portion of a gland into the forearm (total parathyroidectomy with auto transplantation). However recurrent disease also occurs in this group and removal of the auto grafted nodule can be extremely difficult.

Finally **total parathyroidectomy** without auto transplantation does minimise the chance of persistent or recurrent disease by virtually removing all parathyroid tissue. However patients can develop low turn over bone disease with osteomalacia. There maybe impaired bone healing because of the absence of the parathyroid hormone and consequence increased fracture rate. Despite surgery a small portion of patients once again develop tertiary hyperparathyroidism. This maybe due to missed glands or maybe development of parathyroid secreting tissue within other areas pf the body such as within the mediastinum.

**Clinical implications**

The clinical and dietetic workload required to manipulate the biochemical triad of calcium, phosphate and parathyroid hormone is currently very intensive. Patients are regularly subjected to changes in medication and suffer both from the consequences of the side effects of the medication and inadequate control of the underlying problem. The UK Renal Registry report 2004 indicates that only 61% of dialysis patients achieve serum phosphate concentrations of <1.8µmol/L (current Renal Association target). Calcium control is achieved in only 63% of patients and similarly only 66% of dialysis patients achieved the association standard (ranging from 46-87%).

Cinacalcet is the first group of agents called the calcimimetics. It acts by increasing the sensitivity to the calcium sensing receptor in the parathyroid gland to the serum calcium level. Consequently it lowers parathyroid hormone level. The studies to date have indicated that it results in significant reductions in parathyroid hormone levels, calcium and phosphate levels. The US it has been licensed for use in the dialysis population but not in pre-dialysis population. However it is generally safe and well tolerated. The most frequent side effects have been nausea, vomiting. Occasionally low serum calcium levels have been observed. These can be adjusted by chances in either calcium supplementation or Vitamin D analogues.

Current therapeutic strategies to treat both hyperphosphataemia and hyperparathyroidism are complex, erratic and unsatisfactory. Few patients achieve adequate control in all areas on a consistent basis, due to the ‘competing interests’ of calcium, phosphate, PTH and their therapies. Each potential therapy can destabilise control in another area. This is borne out in the poor attainment of agreed national standards across the United Kingdom.

Consequently Cinacalcet offers a benefit in achieving biochemical targets as lay down by the Renal Association and indorsed within the Renal National Service Framework, since it can act on a single part of the bone and mineral triad. It would appear to have the prospect of rationalising therapy within this difficult area. From a patient’s perspective, not only does it reduce the need for surgery but potentially reduce symptoms related to secondary and tertiary hyperparathyroidism. Whilst data on hard end points such as mortality and morbidity, evidence is available for the achievement of biochemical variable targets.

**Conclusion**

Whilst cinacalcet is a new medication, it offers an important therapeutic tool to modulate bone and mineral metabolism in patients with end stage renal failure. End point data for mortality is not available, but data does support its efficacy in hyperparathyroidism, and indirectly the control of hyperphosphatemia. This will allow the achievement of evidence-based targets (already endorsed by the Renal Association) in a greater proportion of patients.