

PERSONAL STATEMENT

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Submission to NICE, Health Technology Appraisal

“Cinacalcet HCl for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy”

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Background Information

Secondary hyperparathyroidism, is a common complication of chronic kidney disease, characterized by increased circulating levels of parathyroid hormone (PTH). The most widely recognized complication of secondary hyperparathyroidism is renal osteodystrophy. The accompanying abnormalities in bone metabolism, together with the abnormal mineral metabolism that result from secondary hyperparathyroidism, are *associated* with poor quality of life, fractures, cardiac dysfunction and increased mortality. These associations are largely based on retrospective, cross-sectional studies, the results of which have yet to be confirmed in large scale prospective interventional studies, and therefore one must be circumspect in drawing from them any firm conclusions. Management of bone and mineral metabolism in dialysis patients is a complex and incompletely understood aspect of nephrological practice but the development of new pharmaceutical agents is adding to our understanding. However significant controversy exists in many areas of clinical practice at present.

Current Practice

Hyperparathyroidism is a common occurrence in dialysis patients. Current practice is to try to maintain serum PTH levels below 32 pmol/L pg/ml (normal range < 8 pmol/L). This may be achieved by careful control of serum phosphate and calcium, and the administration of oral (or less commonly IV) vitamin D3. Failure to do this results in 'secondary' hyperparathyroidism, and over a period of months to years the over-stimulated parathyroid glands may undergo adenomatous change resulting in uncontrollable or 'tertiary' hyperparathyroidism. The likelihood of tertiary hyper-parathyroidism increases with time on dialysis, such that surgical parathyroidectomy is required in 10-15% of patients after 10 years, and 20% after 20 years. A recent publication from the USA demonstrated a rate of around 12% per 1000 patient years for all dialysis patients in the study. Unfortunately hyperparathyroidism recurs in between 6 and 13% of patients at 2 years post-parathyroidectomy, presumably as a result of regrowth of incompletely excised glands. Further surgery is much more hazardous than a first procedure.

Mortality from parathyroidectomy is less than 1%, but some complications are well recognised such as hyperkalaemia, hypocalcaemia, and damage to the recurrent laryngeal nerve (10%) which is usually, but not always, temporary.

An alternative approach to surgery is 'percutaneous ethanol ablation' which involves injecting the parathyroid glands with ethanol under ultrasound guidance. However, very few centres in the UK use this approach.

Cinacalcet HCl is an oral calcimimetic agent that acts as an allosteric modulator of the calcium-sensing receptor present on the surface of parathyroid cells. By targeting the calcium-sensing receptor, cinacalcet provides a new means of regulating PTH secretion by amplifying the receptor's sensitivity to extracellular calcium and reducing PTH concentrations. It is the first drug of its kind available for clinical use, and is licensed for "treatment of secondary hyperparathyroidism in dialysis patients". Its use is not currently described in any UK or US CKD mineral metabolism guidelines but its role in bringing serum PTH down to below 32 pmol/L is obvious, and it will certainly be included in the next iteration of such guidelines. UK Renal Registry data shows that at least 36% of patients have serum PTH levels above 32 pmol/L and this is known to be associated with poor long-term outcome. Such patients may benefit from use of cinacalcet although no long-term outcome studies exist to inform this debate, and differences of opinion exist with regard to the precise limit of the 'ideal' range for dialysis patients.

Mild/Moderate secondary hyperparathyroidism

In practice it is difficult to separate the effects of elevated serum phosphate and calcium from those of elevated serum PTH, since all three factors are inextricably linked. Suppressing serum PTH with cinacalcet whilst failing to control serum phosphate and/or calcium might not alter outcomes, whereas controlling serum phosphate and calcium is known to suppress serum PTH in many patients. Similarly, use of vitamin D3 is well known to suppress PTH, but sometimes at the expense of an elevation in both serum calcium and phosphate. Therefore although it is clear that cinacalcet is effective in controlling serum PTH in the majority of patients with secondary hyperparathyroidism, I doubt that anyone would recommend its use until 'standard' treatments have been attempted using existing guidelines. Many patients with serum PTH in the range 32 – 64 pmol/L (mild to moderate secondary hyperparathyroidism) will respond to conventional manoeuvres, but use of

cinacalcet would probably be a much simpler and more direct method of achieving quick and effective suppression of PTH in most patients.

Severe complicated secondary hyperparathyroidism

Whilst there remains some doubt in my mind as to its role in mild/moderate secondary hyperparathyroidism, it is clear that it can be life-saving for certain dialysis patients with severe symptomatic secondary hyperparathyroidism where surgical intervention is not possible (e.g. complicated by cardiovascular disease or other co-morbidity). The following case histories were included in an earlier submission, but relate to patients under my care who I suspect would have died without administration of oral cinacalcet.

Case 1 A 64 year old patient on haemodialysis who suffered partial vocal cord paralysis at the time of previous surgical parathyroidectomy (a well recognised complication), was found to have recurrent hyperparathyroidism some years later (PTH >1500pg/ml). He was significantly symptomatic with bone pain, muscle ache and general malaise. Conventional treatments with phosphate control and vitamin D had been unsuccessful. The likelihood of further damage to the recurrent laryngeal nerve was felt to be too high to risk re-operation and isotope scans had failed to demonstrate active parathyroid tissue. Venous sampling of the neck veins was similarly unhelpful. Cinacalcet was started at 60 – 90mg daily which over the following 6 months reduced the PTH level to a stable figure of around 100pg/ml with complete resolution of symptoms. PTH remains stable at this level.

Case 2 A 30 year old patient who had had renal failure since childhood and two previous parathyroidectomies, now on haemodialysis, was found to have recurrent symptomatic hyperparathyroidism for a third time. He had severe bone pain and proximal muscle weakness. An isotope scan showed multiple small areas of parathyroid tissue throughout his neck, presumably 'seeded' from previous surgery. Surgical removal of these areas was thought to be impossible because of their size and number. Treatment with cinacalcet quickly reduced his PTH to a stable level of between 100 and 200 pg/ml which was sustained until he received a renal transplant in 2003.

Therefore I would strongly recommend its use in such patients, who may require life-long treatment.

Severe 'simple' secondary hyperparathyroidism

This leaves a third group of patients who have severe secondary hyperparathyroidism and are suitable for surgical parathyroidectomy, but who would prefer to take cinacalcet in order to avoid surgery and its associated hazards. The situation is perhaps analogous to the use of proton pump inhibitors in patients who would otherwise require vagotomy and pyloroplasty (except that PPIs are not usually required 'life-long'). It seems to me that cinacalcet is definitely able to offer a 'medical' parathyroidectomy for up to 65-70% of patients. However, the correct course of action in these circumstances is not clear. Obviously the cost-benefit analysis of each approach needs careful scrutiny, and long-term trials are required to provide evidence of outcomes. I am aware that Prof. John Cunningham has undertaken some of these analyses and I am sure will have made a submission to the appraisal process.

One theoretical benefit of avoiding surgical total parathyroidectomy is that long term PTH suppression is also avoided. In patients who undergo successful surgery their PTH levels become unrecordable and they usually enter a state of low bone turnover known as adynamic bone. This may also be associated with less good outcomes (although not as bad as those associated with tertiary hyperparathyroidism) but data is lacking. Cinacalcet treatment offers the prospect of controlling serum PTH to a more physiological level, thereby avoiding a low bone turnover state.

Summary

Management of hyperparathyroidism in dialysis patients is a complex and incompletely understood process. Cinacalcet offers a simple and effective method of suppressing PTH levels in dialysis patients. However, current methods are effective in the majority of cases of mild/moderate secondary hyperparathyroidism, and control of serum phosphate and calcium is important regardless of serum PTH.

In patients with *severe complicated* secondary hyperparathyroidism cinacalcet treatment may be life-saving when surgical parathyroidectomy is not possible. Patients with *severe simple* secondary hyperparathyroidism may prefer to avoid surgery by use of cinacalcet, and this may have longer term benefits for bone metabolism.