Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients

Review information

Review number: 085

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What's new

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History

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Abstract

Background

Objectives

Search methods

Selection criteria

Data collection and analysis

Results

Authors' conclusions

Plain language summary
Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients

**Background**

Abnormalities of calcium and phosphorus metabolism are present in all individuals with chronic kidney disease (CKD). These biochemical changes cause many bone and metabolic disorders, including renal osteodystrophy that is characterized by abnormalities of bone turnover (ranging from high turnover osteitis fibrosa to adynamic bone disease), mineralization defects (osteomalacia) and architectural change. Renal osteodystrophy is associated not only with an increased incidence of fracture, bone and muscular pain and abnormalities of bone and joint morphology, but also with vascular and soft tissue calcification. In addition to causing reduced quality of life, these complications and the associated abnormalities of elevated phosphorus, calcium, the calcium by phosphorus product and levels of parathyroid hormone (PTH) have been associated with increased mortality (Block 2004b; Ganesh 2001; Malluche 2004b; Marco 2003; Martin 2004; Stehman-Breen 2004).

Standard management of patients with CKD, particularly those on dialysis, includes treatment to control levels of calcium, phosphorus and PTH, so as to prevent bone and soft-tissue complications. Based on a number of association studies, (Block 2004b; Ganesh 2001; Kestenbaum 2005; Marco 2003; Stevens 2004) including studies of bone histomorphometry, (Hutchison 1993; Qi 1995; Wang 1995; Zolkowska 2000) optimal ranges for serum phosphorus, calcium, the calcium by phosphorus product and PTH have been suggested (CARI 2005; NKF 2003). However, success in achieving these targets has been limited (Young 2004).

Specific management of secondary hyperparathyroidism (SHPT) in CKD stages 3 and 4 may be accomplished by restriction of dietary phosphorus, calcium supplementation, and/or the use of calcitriol. Once patients have commenced dialysis, standard therapy of SHPT generally includes calcitriol, vitamin D analogues or derivatives, calcium or other phosphate-binding agents and parathyroidectomy (Albaaj 2003; Courant 1993). Recently the use of a novel class of drugs, the calcimimetics, has been proposed as a strategy to reduce PTH secretion and possibly to reduce parathyroid cell proliferation, while decreasing levels of serum calcium, phosphorus and the calcium by phosphorus product (Ott 1998). Use of these agents has been advocated whenever there is inability to control SHPT with other agents. Results of randomised controlled trials (RCTs) testing the efficacy and safety of calcimimetics in patients undergoing dialysis are becoming available. With the aim of preventing complications associated with SHPT, cinacalcet HCl has now been incorporated into many treatment algorithms.

However, several aspects of calcimimetic therapy require further evaluation. In the dialysis population, for which these drugs are approved, the most important question is the degree to which calcimimetics will impact on clinically relevant end-points such as parathyroidectomy rates, fracture, renal osteodystrophy, cardiovascular disease and death, as well as surrogate markers for these conditions, such as abnormalities of serum calcium and phosphorus. Other important questions include the optimal time for commencement of calcimimetic therapy, the influence of calcimimetics on standard treatment regimens and the effectiveness of calcimimetics at different stages of CKD and after transplantation.

This systematic review will review the evidence for benefits and harms of calcimimetic therapy in adults with chronic kidney disease.

**Objectives**

To evaluate the benefits and harms of calcimimetics for the prevention of secondary hyperparathyroid bone disease (including osteitis fibrosa cystica and adynamic bone disease) in patients with CKD.

**Methods**

Criteria for considering studies for this review
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Types of studies
We will include RCTs of any calcimimetic agent, cinacalcet HCl (AMG-073, Sensipar®), NPS R-467 or NPS R-568 administered to patients with CKD for the treatment of SHPT.

Types of participants
Patients with CKD needing treatment for SHPT.

Types of interventions
Any calcimimetic agent (e.g. cinacalcet HCl (AMG-073, Sensipar®), NPS R-467 or NPS R-568).

Types of outcome measures
1. All-cause mortality
2. At least 30% decrease in mean PTH level
3. Fractures
4. Hypocalcaemia (as defined by the authors)
5. Nausea
6. Vomiting
7. Dyspnoea
8. Muscle weakness
9. Hypotension
10. Upper respiratory tract infection
11. Parathyroidectomy
12. Headache
13. Paraesthesia
14. Abdominal pain
15. Diarrhoea
16. Mixed uraemic osteodystrophy
17. Bone histomorphometry
18. End of treatment PTH levels (any measure)
19. End of treatment serum calcium concentrations (mg/dL or mmol/L)
20. End of treatment serum phosphorus concentrations (mg/dL or mmol/L)
21. End of treatment calcium x phosphorus product (mg²/dL²)

Search methods for identification of studies
The literature searching will be performed independently by two authors. Relevant studies will be obtained from the following sources without language restriction (see Table 1 - Electronic search strategies).

1. The Cochrane Renal Group's specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library
2. EMBASE using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 1996) together with a specific search strategy developed with input from the Cochrane Renal Group's Trial Search Co-ordinator.
3. Reference lists of nephrology textbooks, review articles and relevant trials.
4. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous trials.
5. Personal records and citation alerts

The Specialised Register contains studies identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, handsearching of kidney-related journals and proceedings of major conferences, and searches of trials registries using search strategies based on the scope of the Cochrane Renal Group.
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Data collection and analysis

Selection of studies
The results of the electronic searches will be analysed in title and abstract form by two authors according to the inclusion criteria in consultation with a third author. We will consider all randomised controlled trials of any calcimimetic agent (cinacalcet HCl, NPS R-467, or NPS R568) and that report data for adults with CKD (any stage). Reference lists from the identified articles will also be searched and information about unpublished or ongoing trials will be sought from experts in the field and pharmaceutical companies. Trials will be considered without language restriction.

Data extraction and management
Each trial will be assessed independently by two authors. From all included trials, data will be extracted on study sample characteristics, the type of agent, dose, and route of administration, the trial methods and outcomes. Discrepancies in data extraction will be resolved by discussion among the authors, and when data were missing or incomplete, the investigators of the trial will be contacted for clarification.

Assessment of risk of bias in included studies
The methods and quality of included trials will be assessed using standard criteria (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, analysis by intention to treat and completeness of outcome data, selective reporting, and other sources of bias).

Sequence generation
● Low risk: The investigators describe a random component in the sequence generation process
● High risk: The investigators describe a non-random component in the sequence generation process

Allocation concealment
● Low risk: Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
● Unclear risk: Randomisation stated but no information on method used is available
● High risk: Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

Blinding
● Blinding of investigators: Yes/no/not stated
● Blinding of participants: Yes/no/not stated
● Blinding of outcome assessor: Yes/no/not stated
● Blinding of data analysis: Yes/no/not stated

The above are considered not blinded if the treatment group can be identified in > 20% of participants because of the side effects of treatment.

Intention-to-treat
● Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
● Yes: Not stated but confirmed on study assessment
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- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation)
- No: Stated but not confirmed upon study assessment
- Not stated

Incomplete outcome data
- Per cent of participants excluded or lost to follow-up.

Selective reporting
- Low risk: The study protocol is available and all the study's pre-specified outcomes have been reported or the study protocol is not available but it is clear from published reports that all expected outcomes are reported
- High risk: Not all study pre-specified primary outcomes have been reported or the study report fails to include results for a key outcome that would have been expected to have been reported for such a study

Other sources of bias
- Low risk: The study appears to be free of other sources of bias
- High risk: There is at least one important risk of bias

Measures of treatment effect
The estimate of effect of an experimental versus a control intervention on categorical outcomes (e.g. fracture rate, all-cause mortality including sudden death) will be analysed using the risk ratio (RR) measure and its 95% confidence interval (CI) for each trial. For continuous variables, the mean difference (MD), and its 95% CI will be calculated using the end of treatment values of the variable in the experimental and control groups. Data will be summarised using standard and cumulative random-effects meta-analysis (based on year or publication).

Assessment of heterogeneity
Heterogeneity of treatment effects between studies will be tested formally using the Q (heterogeneity chi-square) and the I² statistic (Higgins 2003). We will consider a P value below 0.10 to indicate significant heterogeneity.

Assessment of reporting biases
To assess potential bias from small study effects, funnel plots for the log risk ratio in individual studies against the SE of the risk ratio will be generated and formally assessed for asymmetry by using the Egger regression test (Egger 1998).

Data synthesis
Data will be pooled using a random effects model. For each analysis, the fixed effects model will also be evaluated to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity
Additional pre-specified subgroup analyses and univariate random-effects meta-regression will be performed to explore potential sources of heterogeneity in treatment effects on all-cause mortality, parathyroidectomy, hypocalcaemia and nausea. We will evaluate the effects of age, proportion of male participants, baseline serum PTH concentration, baseline serum calcium concentration, trial duration, allocation concealment (adequate versus unclear) and year of publication. In addition, for the outcome of hypocalcaemia we will evaluate the serum calcium concentration used to define one or more hypocalcaemia events as a source of
heterogeneity in treatment effects for this outcome.

**Sensitivity analysis**
We will analyse data excluding trials in which randomised co-interventions (vitamin D compounds) are not equal between study groups. We will also restrict analyses to studies in which follow up duration was 6 months or longer.

**Results**
**Description of studies**

**Risk of bias in included studies**

**Effects of interventions**

**Discussion**

**Authors' conclusions**

**Implications for practice**

**Implications for research**

**Acknowledgements**

**Contributions of authors**

**Declarations of interest**

**Differences between protocol and review**
The protocol has been updated since first publication in 2006. The updated protocol now includes additional risk of bias items (sequence generation, selective outcome reporting and other sources of bias) according to The Cochrane Collaboration’s standardised methods. The protocol now also includes pre-specified subgroup and univariate meta-regression analyses to explore for sources of heterogeneity between treatment estimates and additional sensitivity analyses. The electronic search strategies now exclude searches in Ovid MEDLINE, as these citations are included in searches of the Cochrane Renal Group’s specialised register.
Published notes

Characteristics of studies

Characteristics of included studies

Characteristics of excluded studies

Characteristics of studies awaiting classification

Characteristics of ongoing studies

Summary of findings tables

Additional tables

1 Electronic search strategies

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EMBASE

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8. predialysis.tw.
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18. Calcimimetic Agent/
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22. calcimimetic$.tw.
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24. or/18-23
25. and/17,24

References to studies

Included studies

Excluded studies

Studies awaiting classification

Ongoing studies

Other references
Additional references

Albaaj 2003

ANZDATA 2004

Avram 1996

Besarab 1998

Block 2004b

Borrows 2004

Bucher 1999

CARI 2005

Churchill 1997

Courant 1993
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**Cunningham 2004**

**Dickersin 1994**

**Egger 1997**
Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. BMJ 1997;315(7109):629-34. [MEDLINE: 9310563]

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**FDA 2004**
US Food and Drug Administration. Sensipar (cinacalcet HCl) tablets.

**Ganesh 2001**

**Higgins 2003**

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**Juni 2003**

**Kestenbaum 2005**

**Lefebvre 1996**
Leyland-Jones 2004

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Marco 2003

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Moher 2001

NKF 2003

Ott 1998
Ott SM. Calcimimetics–new drugs with the potential to control hyperparathyroidism. Journal of Clinical Endocrinology & Metabolism 1998;83(4):1080-2. [MEDLINE: 9543121]

Psaty 1999

Qi 1995
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Simes 1986

Stehman-Breen 2004

Stevens 2004

Temple 1999

Urena 2003

Wang 1995

Young 2004

Ziolkowska 2000

Other published versions of this review
Strippoli 2006
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Data and analyses

Figures

**Figure 1**

Study flow diagram.
Sources of support

Internal sources
- No sources of support provided

External sources
- No sources of support provided

Feedback

Appendices