A review of intravenous versus oral vitamin D hormone therapy in hemodialysis patients

Mazess R B, Elangovan L

CRD summary
This review compared intravenous and oral vitamin D regimens for the treatment of secondary hyperparathyroidism in haemodialysis patients. The authors concluded that there was insufficient evidence to reach a conclusion about the comparative safety and efficacy of oral and intravenous regimens. These conclusions are likely to be reliable.

Authors' objectives
To compare intravenous (i.v.) and oral vitamin D administration for the treatment of secondary hyperparathyroidism in haemodialysis patients.

Searching
PubMed was searched using the keywords stated. The reference lists in identified studies were also screened. Studies published either as abstracts or full publications were included.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not explicitly stated in terms of study design, although it was clear that controlled trials were included. The review included crossover and parallel-group randomised controlled trials (RCTs), and non-randomised controlled clinical trials (CCTs).

Specific interventions included in the review
Studies that compared i.v. and oral vitamin D regimens were eligible for inclusion. The included studies were of calcitriol (weekly dose: 1.8 to 34.3 microg oral; 2 to 7.4 microg i.v.), alpha-calcidol (weekly dose: 3.2 to 7 microg oral; 3.2 to 7 microg i.v.) or doxercalciferol (weekly dose: 23 microg oral; 11 microg i.v.). All of the included studies used a pulsed regimen for i.v. drugs, but used either daily dosing or a pulsed regimen for oral treatments.

Participants included in the review
Studies of haemodialysis patients were eligible for inclusion. The review stated that there were differences between patients in the included studies, but did not describe the characteristics of the patients other than stating that most patients had mild to moderate secondary hyperparathyroidism.

Outcomes assessed in the review
The inclusion criteria were not specified in terms of the outcomes. The review assessed efficacy using the speed or extent of suppression of elevated parathyroid hormone (PTH), and side-effects. The definition of hypercalcaemia varied across the studies, with threshold values ranging from 10.5 to 12.0 mg/dL, while hyperphosphataemia was defined as greater than 7 or 8 mg/dL.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The validity of the included studies was not formally assessed, but quality was discussed with respect to sample size, study duration and therapeutic equivalence of oral and i.v. regimens. The authors did not state how the papers were assessed for validity, or how many of the reviewers performed the assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The reviewers tried, where possible, to transform reported episodes of hypercalcaemia into events per patient-year, but this transformation was not attempted for studies that reported the event rate as a percentage of either observations or patients.

Methods of synthesis

How were the studies combined?
A narrative synthesis of the studies was undertaken.

How were differences between studies investigated?
The results for studies published in abstract form were presented separately from those for studies reported in full publications. Differences between the studies were discussed with respect to the treatment regimen, the criteria used to define hypercalcaemia, and the equivalence of oral and i.v. dosing regimens.

Results of the review

Sixteen studies that were reported in full publications and five reported as abstracts were included. The full publications comprised 10 RCTs (190 patients) and 6 non-randomised CCTs (257 patients). The abstracts related to 1 RCT (27 patients) and 4 CCTs (60 patients).

The studies were generally small and only two had more than 25 patients per treatment arm. Only one study, published in abstract format, lasted 52 weeks; the majority of the studies lasted for 16 weeks or less. Some studies used non-equivalent oral and i.v. dosing regimens: 19 studies used oral doses that were less than half as active, therapeutically, than the i.v. treatment for comparison. The included studies differed markedly in the criterion used to define hypercalcaemia.

Twelve studies published in full used calcitriol, three full publications were of alpha-calcidol and one full publication was of doxercalciferol. All the abstracts were of calcitriol.

Five studies (and two abstracts) showed that i.v. administration significantly reduced the time to PTH suppression and/or suppressed PTH to a greater extent than oral administration. Two of the five full publication studies (and one abstract) used a much greater i.v. than oral dose.

Side-effects were only reported in detail in 9 studies.

Hypercalcaemia (9 studies): the results for hypercalcaemia differed among the studies. The event rate for hypercalcaemia varied from 0.15 to 13 events per patient-year. Six studies found no significant difference between oral and i.v. dosing. Two studies found that oral treatment significantly increased hypercalcaemia, while one study found that i.v. treatment significantly increased hypercalcaemia. One larger crossover study (70 patients) that used therapeutically equivalent (defined as the dose required to produce equal reductions in PTH) found that oral doxercalciferol significantly increased hypercalcaemia (greater than 11.2 mg/dL) compared with i.v. dosing (1.6 compared with 0.5 events per patient-year, P<0.001); two other studies found similar results. The largest parallel-group study (151 patients) found that i.v. dosing increased hypercalcaemia, but the i.v. dose used was higher than the oral dose.

Hyperphosphataemia (3 studies): none of the studies found any significant difference between oral and i.v. dosing.

Authors’ conclusions

There was insufficient evidence to reach a conclusion about the comparative safety and efficacy of oral and i.v. regimens.
CRD commentary
The review question was clear in terms of the intervention and participants, although none of the inclusion criteria were explicitly defined. Only one database was searched and this might have resulted in the omission of other relevant studies. No details of the dates searched, or any language restrictions applied, were reported. The methods used to select the studies, assess validity and extract the data were not described; hence, any efforts made to reduce errors and bias cannot be judged. The validity of the included studies was not formally assessed, but some aspects of validity were discussed.

The tabulated information on the included studies was limited and there were no details of the characteristics of the patients; hence, the generalisability of the results cannot be judged. A narrative synthesis was appropriate given the small number of studies. However, although the results were reported separately for studies published in full or abstract form, the studies were not discussed separately with respect to study design and better quality evidence from RCTs was not highlighted. Some of the limitations of the review were discussed in the text. The evidence presented did appear to support the conclusion that there is insufficient evidence.

One of the authors is employed by, holds shares in, and is the Chairman of the Board of Bone Care International. Another author is a medical consultant for Bone Care International.

Implications of the review for practice and research
Practice: The authors stated that oral doses of vitamin D should be used with caution in patients with elevated PTH.

Research: The authors stated that large studies are required to compare long-term safety and efficacy outcomes for therapeutically equivalent doses of oral and i.v. vitamin D.

Bibliographic details

PubMedID
12779092

Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Oral; Drug Administration Routes; Ergocalciferols /administration & dosage; Humans; Hyperparathyroidism, Secondary /drug therapy /etiology; Injections, Intravenous; Renal Dialysis /adverse effects

AccessionNumber
12003001259

Date bibliographic record published
31/03/2005

Date abstract record published
31/03/2005

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.