MEDwave

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
*Medwave*2017;17(Suppl2):e6942 doi: 10.5867/medwave.2017.6942

Sevelamer versus calcium-based phosphate binders for chronic kidney disease?

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Citation: Bravo-Soto GA, Madrid T. Sevelamer versus calcium-based phosphate binders for chronic kidney disease. *Medwave*2017;17(Suppl2):e6942 doi: 10.5867/medwave.2017.6942
Submission date: 1/3/2017
Acceptance date: 1/3/2017
Publication date: 12/5/2017

Abstract

Chronic kidney disease-mineral and bone disorder is prevalent. There is controversy regarding whether calcium-based phosphate binders or sevelamer - a non-calcium phosphate binder – constitute a better therapeutic alternative. Searching in Epistemonikos database, which is maintained by screening multiple information sources, we identified 12 systematic reviews comprising 61 studies of which 41 correspond to randomized trials addressing the question of this article. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded sevelamer may decrease hypercalcemia, but with a higher incidence of gastrointestinal effects than calcium based phosphate binders. It is unclear if there are differences in mortality because the certainty of the evidence is very low.

Problem

Chronic kidney disease – mineral and bone disorder is manifested by one or a combination of the following [1]:

- Abnormalities of calcium, phosphorus, parathyroid hormone or vitamin D metabolism.
- Abnormalities in bone turnover, mineralization, volume, linear growth or strength.
- Vascular or other soft tissue calcification.

Hyperphosphatemia is linked to multiple aspects of CKD-MBD. Guidelines recommend to lower serum phosphorus in patients with hyperphosphatemia with phosphate binders. There are two main therapeutic alternatives; calcium-based phosphate binders (calcium acetate and calcium carbonate) and non-calcium phosphate binders, in particular sevelamer, a polymer of allylamine hydrochloride. However, there is still controversy regarding which alternative constitute a better option.

Methods

We used Epistemonikos database, which is maintained by screening multiple information sources, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Sevelamer compared to calcium-based phosphate binders may decrease hypercalcemia events, but with a higher incidence of gastrointestinal effects.
- It is unclear if there are differences between sevelamer and calcium-based phosphate binders in mortality because the certainty of this evidence is very low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 12 systematic reviews reported in 13 references [2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14] that included 61 primary studies reported in 75 references [15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[71],[71],[72],[73],[74],[75],[76],[77],[78],[79],[80],[81],[82],[83],[84],[85],[86],[87],[88],[89]. Of these, 41 studies (54 references) were randomized trials.This table and the summary in general are based on the latter because observational studies did not increase the certainty of the evidence, or provide additional relevant information.
What types of patients were included*	Regarding the stage of nephropathy, 27 trials [15],[18],[18],[20],[22],[26],[33],[34],[35],[36],[37],[41],[43],[44],[47],[50],[52],[53],[54],[56],[57],[64],[68],[69],[74],[75],[81],[84] included patients in hemodialysis, three [31],[39],[61] in peritoneal dialysis, nine [23],[27],[29],[38],[46],[63],[73],[85],[88] included patients on stage III or IV without dialysis, one trial [77] did not specify the type of dialysis, only that patients had more than six months in this therapy and one trial [89] only required that they were in stage V**.
What types of interventions were included*	All of the trials used sevelamer as intervention in dose adjusted to phosphorus levels. It was not possible to extract more detailed dosing data from systematic reviews. Six trials [33],[34],[36],[47],[53],[75] used vitamin D as cointervention by any route of administration, one [20] used oral vitamin D, three [18],[39],[69] used intravenous vitamin D, one trial [68] used atorvastatin and one [77] calcium carbonate in low-dose. Regarding comparison, 14 trials [18],[20],[27],[46],[47], [56],[57],[61],[63],[64],[68],[69],[88],[89] used calcium acetate, 20 trials [15],[26],[29],[31],[36],[37],[38],[39],[41],[43],[50],[52],[53],[54],[73],[74],[75],[77],[84],[85] used calcium carbonate, and five [22],[33],[35],[44],[81] used calcium carbonate and calcium acetate.
What types of outcomes were measured	The outcomes were pooled by the different systematic reviews as follows: • Mortality • Cardiovascular mortality • Hospitalizations • Composite outcome of cardiovascular events • Coronary calcification • Vascular calcification • Gastrointestinal events (nausea, vomiting, diarrea, constipation and abdominal distention) • Hypercalcemia • Serum phosphorus • Serum calcium • Calcium-phosphorus product • Vitamin D • Serum bicarbonate • iPTH • Bone density The average follow-up was 36.5 weeks ranging from 3-144 weeks.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.
** Stage of chronic renal failure according to MDRD-4.

Summary of findings

The information on the effects of sevelamer compared to calcium-based phosphate binders is based on all trials included in this summary, which include 5928 patients.
Thirty-one randomized trials [18],[20],[22],[23],[26],[27],[29],[33],[36],[37],[38],[39],[41],[47],[50],[53],[54],[56],[57],[61],[63],[68],[69],[73],[74],[75],[81],[84],[85],[88],[89] reported mortality including 5011 patients. Twenty trials [20],[23],[27],[29],[33],[35],[39],[41],[43],[50],[53],[54],[56],[57],[63],[68],[74],[75],[81],[88] reported gastrointestinal adverse events including 2863 patients. Nineteen trials [20],[22],[23],[26],[27],[33],[36],[38],[39],[43],[47],[56],[57],[68],[69],[74],[75],[81],[88] reported hypercalcemia including 2867 patients.

The summary of findings is the following:

- Sevelamer compared to calcium-based phosphate binders might decrease hypercalcemia events. The certainty of the evidence is low.
- Sevelamer compared to calcium-based phosphate binders might increase the incidence of gastrointestinal effects. The certainty of the evidence is low.
- It is unclear if there are differences in mortality between sevelamer and calcium-based phosphate binders because the certainty of the evidence is very low.

Sevelamer compared to calcium-based phosphate binders for chronic kidney disease				
Patients	Chronic kidney disease			
Intervention	Sevelamer			
Comparison	Calcium-based phosphate binders			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	Calcium-based phosphate binders	**Sevelamer**		
	Difference: patients per 1000			
Mortality	183 per 1000	110 per 1000	RR 0.60 (0.37 to 0.99)	⨁◯◯◯[1,2] Very low
	Difference: 73 patients less per 1000 (Margin of error: 2 to 115 less)			
Gastrointestinal adverse effects	128 per 1000	178 per 1000	RR 1.39 (1.02 to 1.86)	⨁⨁◯◯[1,2] Low
	Difference: 50 patients more per 1000 (Margin of error: 4 to 110 more)			
Hypercalcemia	189 per 1000	64 per 1000	RR 0.34 (0.24 to 0.49)	⨁⨁◯◯[1] Low
	Difference: 125 patients less per 1000 (Margin of error: 96 to 144 less)			

Margin of error = 95% confidence interval (CI).
RR = Risk ratio.
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* The risk **WITH calcium-based phosphate binders** is based on the risk in the control Group of the trials. The risk **WITH sevelamer** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] The certainty of the evidence was downgraded in two levels for serious risk of bias in primary studies. Only one level was downgraded for gastrointestinal adverse effects since bias would probably be in favor of sevelamer.
[2] The certainty of the evidence was downgraded in one level for inconsistency because some primary studies have results that favor the intervention and others favor control.

Follow the link to access the interactive version of the Summary of Findings (iSoF) table

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary applies to patients with chronic kidney disease at risk for bone and mineral disorder independent of etiology.
- Trials included mostly or exclusively dialysis patients. However, it seems reasonable to extrapolate these conclusions to other patients at risk of developing mineral and bone disease in the absence of direct evidence.

About the outcomes included in this summary

- The outcomes included in this summary are those considered critical for decision-making by the authors of this summary. They coincide with the outcomes mentioned by most systematic reviews and guidelines.
- We selected hypercalcemia for the summary of findings table althought it is a surrogate outcome, because it is one of the most feared adverse effects of calcium-based phosphate binders, so it might be relevant for decision making.

Balance between benefits and risks, and certainty of the evidence

- Considering the uncertainty regarding the effect on mortality, and the low certainty about gastrointestinal side effects and hypercalcemia, it is not possible to make an appropiate balance between benefits and risks of sevelamer compared to calcium-based phosphate binders.

Resource considerations

- Sevelamer is more expensive than calcium-based phosphate binders and the clinical benefits are not clear.
- Cost differences between the two alternatives probably would be key in the choice, depending on the context and the availability of resources.

What would patients and their doctors think about this intervention

- The evidence presented in this summary should lead to significant variability in decision making; those who privilege an uncertain benefit may prefer sevelamer, and those who put more value on preventing adverse effects, costs, or in the certainty of the evidence, may prefer calcium-based phosphate binders.
- There may be also variability among doctors, which would be exacerbated by the existence of discordant recommendations in major guidelines.

Differences between this summary and other sources

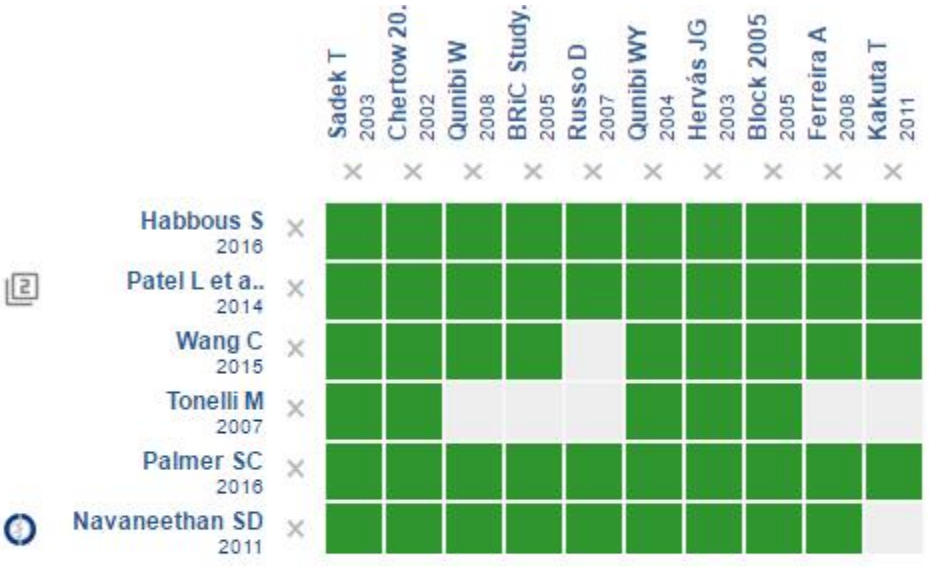
- The conclusions of this summary are consistent with most systematic reviews identified.
- There are differences between the main guidelines; KDIGO guideline [90] and the National Kidney Foundation (KDOQI) guideline [91] report no differences between calcium-based phosphate binders and sevelamer, and recommend the choice should be individualized. The Canadian Society of Nephrology guideline [92] reports there is insufficient evidence to recommend non-calcium phosphate binders.

Could this evidence change in the future?

- The probability that future evidence changes the conclusions of this summary is high due to the uncertainty of the evidence.
- We did not identify ongoing trials in the International Clinical Trials Registry Platform of the World Health Organization or published trials not included in the systematic reviews identified.
- The identified systematic reviews address a low proportion of the trials included in this summary, so new reviews could provide relevant information.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Sevelamer versus calcium salts for chronic kidney disease

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrices and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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