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HTA-Report | Summary

Effectiveness and cost-efficiency of phosphate binders in hemodialysis

Brunner-Ziegler S, Fröschl B, Hiebinger C, Wimmer A, Zsifkovits J

German Agency for HTA
at DIMDI (DAHTA)
Waisenhausgasse 36-38a
50676 Köln
Germany

Tel.: +49 221 4724-525
Fax: +49 221 4724-444
dahta@dimdi.de
www.dimdi.de

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Health political background

Chronic renal insufficiency is the reduced ability of both kidneys to excrete metabolic end products (e. g. urea, creatinine, uric acid). This results in an increase of these substances in the organism. Diabetes mellitus (particularly type 2) is one of the most frequent causes for renal insufficiency.
In 2006, the prevalence of chronic renal insufficiency in Germany was 91,718, the tendency is clearly growing. Chronic renal insufficiency particularly occurs in older patients: in 2006, 55 % of prevalent patients were 65 years of age or older. Among therapies for chronic renal insufficiency, renal transplantation and various forms of dialysis (hemodialysis, peritoneal-dialysis) are available. Dialysis is a blood purification measure to eliminate urophanic substances, other metabolic (end) products and water from the organism. In 2006, 66,508 patients were on dialysis in Germany. This is a rise of 4.9 % compared to 2005. Despite the fact that the number of renal transplantations has increased compared to the previous year, the number of new registrations on the waiting list still exceeds the number of transplantations conducted. Therefore, renal chronic insufficiency is not only an individual, but also a significant financial problem for the health system. The costs incurred by the German health insurance fund for the about 65,000 dialysis patients are more than 2 % of the health budget. The expenditures for a renal transplantation redeem within two to three years.
The most frequent cause of death for chronic renal insufficient patients is cardiovascular disease. Due to the disturbed mineral balance, phosphate is deposited at vascular walls, soft tissue and cardiac valves. If the control of phosphate levels is not achieved by restricting phosphate intake through diet, or if phosphate intake restriction lead to malnutrition, phosphate binders (p-binders) need to be administered in dialysis patients. The present Health Technology Assessment (HTA-) report discusses the effectiveness and cost-efficiency of these measures.

Scientific background

Chronic renal insufficiency can have many causes, e. g. hypertension, obesity, and diabetes. A healthy kidney not only detoxifies the organism, but also regulates the mineral metabolism. Is kidney function reduced, the calcium-phosphate-metabolism becomes disbalanced and this leads to hyperphospataemia and/or secondary hyperparathyroidismus.
The calcium- and phosphate levels in the blood are held constant within little scope by vitamin D and parathyroid hormone (PTH). Vitamin D is taken up from food or can be produced in the skin through UV-radiation. The kidneys thereafter produce the active form 1.25 Dihydroxycholecalciferol, also called calcitriol. In patients with pronounced renal insufficiency, the formation of the active form of endogenous calcitriol is reduced or totally lacking. This leads to reduced calcium absorption in the intestines and increased calcium excretion through the kidneys.
To counteract this, the parathyroid produces more PTH. PTH mobilizes calcium from bones and reduces the renal calcium loss; however, in advanced stages of renal insufficiency (4 to 5) the resultant hypocalcaemia

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becomes apparent. In addition, the kidney cannot excrete phosphate sufficiently which leads to hyperphosphataemia. Hyperphosphataemia is the strongest independent risk factor for mortality in renal patients. With each milligram serum phosphate, the risk of a coronary arterial death increases by nine percent and that of sudden cardiac death by six percent.
The complete clinical picture of secondary hyperparathyroidismus is associated with a softening and/or brittleness of bones. Different bone diseases can exist in renally insufficient patients, all of which are subsumed as renal osteodystrophy. Nowadays, secondary hyperparathyroidismus is linked with an increased calcification of soft tissue, particularly arteries, which leads to an increased cardiovascular mortality. The basis of any therapy for hyperphosphataemia is the reduction of phosphate intake through nutrition, however, this alone is not effective.
Usually, the amount of phosphate filtered out during dialysis (typically 75 % of absorbed phosphate) is also insufficient to lower the serum phosphate levels to the recommended target value. Therefore, p-binders are normally administered during predialysis already. P-binders are chelating agents and are taken orally during meals. In the digestive tract, they bind alimentary ingested phosphate and thus indirectly contribute to the reduction of serum phosphate concentrations as phosphate cannot reach the blood stream. Further therapy options for the treatment of secondary hyperparathyroidismus are vitamine D-therapy (gold standard) and the prolongation of dialysis (six to seven times a week for eight to ten hours). A couple of years ago, Cinacalcet, a calcimimeticum, has been licensed to treat secondary hyperparathyroidismus. Calcimimetica are administered orally and suppress PTH-secretion without increasing the levels of calcium and phosphate in the serum. The most effective therapy is renal transplantation.
Four different groups of p-binders are distinguished: calcium and aluminum salts are the traditional treatment, sevelamer and lanthan carbonate are recent developments on the market. In day-to-day practice, p-binders often are prescribed in a combination therapy of two or three in order to keep the number of side effects low. Primarily, binders within one drug class are combined. In dialysis patients with resistant hyperphosphataemia, a combination therapy of calcium containing p-binders with calcium- and aluminiumfree binders is sometimes prescribed. In addition, vitamine D derivatives and calcimimetica are used and the concentration of calcium in the dialysate is adopted to the individual patient. At various doses, all p-binders are able to effectively lower phosphate concentrations. However, drug therapies have achieved recommended phosphate levels in only 50 % of patients during the last years.
Aluminum containing p-binders are very effective. However, due to the danger of chronic intoxication their use is not recommended any more. Calcium acetate and calcium carbonate are used most frequently. They provide an effective therapy to reduce serum phosphate levels, however, the cumulative calcium administration plays a significant role in the formation of vascular calcifications. Sevelamer-Hydrochlorid (Renagel®) is a p-binder free of calcium and aluminum which is licensed for the German market since 2000. Lanthan carbonate (Fosrenol®) is a p-binder containing metal and was licensed in the European Union in 2006.

Research questions

How effective and efficient are the different p-binders in chronic renal insufficient patients? Are there differences in the benefit for patients? What are the ethical, social and legal implications?

Methods

This HTA-report was prepared by applying the methods for a systematic literature review. The systematic literature search (DIMDI-HTA-superbase databases, February 2008) yielded 1,251 abstracts. Following a two-part selection process according to standard, predefined criteria 13 medical and four economic publications were included in the assessment. One publication was used to cover ethical, social, and legal aspects. Assessment of the studies was performed according to predefined criteria. 50 publications were added by hand search.

Results

This report refers to p-binder therapy in adults with renal insufficiency and the evaluation of the effectiveness of p-binders regarding mortality, calcification and bone metabolism. In the studies included, only modern p-binders are evaluated, calcium containing p-binders are only used as control.
One systematic review on the clinical effectiveness of sevelamer compared to calcium containing p-binders is available. The study design of the majority of primary studies included is inadequate, a publication bias can be demonstrated.
The levels of serum phosphate and iPTH are lower when using calcium containing p-binders compared to Sevelmer, the serum calcium levels are higher. The heterogeneity of studies for all three parameters is substantive. The absolute risk of hypercalcaemia is lower by 21 % when using sevelamer. The median duration of hypercalcaemia or of its clinical consequences are not specified in any of the studies. The difference in the mortality risk is not significant. The cardiovascular degree of calcification was analysed in two studies included in the present report; it is significantly lower in the patient groups treated with sevelamer in both studies. Length of stay is shorter in patients treated with sevelamer, however, the differences are not significant. None of the studies evaluate parameters such as quality of life, bone fractures or pain. The incidence of adverse drug events (ADE) among patients is not different from that of dialysis patients in general. The clinical significance of these ADE and how they influence quality of life cannot be deducted of the available data.
The authors of the systematic review conclude that the use of sevelamer can be useful in specific clinical subpopulations (e. g in patients with high base levels of serum calcium), however, that the routine administration of sevelamer is not supported through available data. The authors state that the external validity of available studies is given due to the great number of different countries, dialysis centres and patients included in the studies. However, they demand studies of high quality with robust study designs and transparent documentation for the future.
Ten of the eleven primary studies included refer to a total of only 539 patients from five patient collectives. These data are analysed from different perspectives and published in various journals. It must be criticized that this limitation is not always clearly described. Therefore the significance of final conclusions may be overestimated. All studies are multicenter studies, most of them are conducted in several countries which increase the external validity of the results. However, almost all studies are supported by the industry and are relatively short-term (usual treatment period only one year).
Like the systematic review, all primary studies included arrive at the conclusion that serum phosphate, -calcium and iPTH can be controlled effectively with all p-binders. Only the number of episodes of hypercalcaemia is higher

when using calcium containing p-binders compared to sevelamer or lanthan carbonate. Additionally, sevelamer significantly lowers total cholesterol and low-density-lipoprotein cholesterol.
Regarding safety, the ADE-rate for all p-binders is comparable and is equal to that of dialysis patients. In one study, a significantly higher rate of gastro-intestinal symptoms with sevelamer is reported.
Two studies evaluate the effect of sevelamer and calcium containing p-binders on mortality. Based on the available results, no final conclusions can be drawn. It seems that particularly older patients (over 65 years of age) can profit from a therapy with sevelamer. In a study of 2008 in which 1,065 patients complete the study after an average observation period of 20 months, no difference between the two treatment groups can be shown regarding total or cause-specific mortality rate (death due to cardiovascular causes, infection, other causes). However, age significantly influences treatment effect. In patients aged more than 65 years (44 % of the study population), total mortality rate is significantly reduced in the sevelamer group compared to the group receiving calcium therapy ($p = 0.02$), however, no difference is shown in cardiovascular mortality ($p = 0.10$).
In a smaller study ($n = 127$ patients starting dialysis) of 2007 with an average observation period of 44 months the mortality rate in the calcium-group is higher than that in the sevelamer-group ($p = 0.05$). After adjusting for the parameters age, ethnicity, sex, diabetes, albumin, atherosclerotic disorders in the medical history, C-reactive protein and calcification score at study start, statistical significance is achieved for the higher mortality rate in the calcium-group ($p = 0.02$).
Three studies in two patient populations evaluate the effect of p-binders on bone metabolism. After one year, no significant differences in bone metabolism parameters can be shown in 98 patients newly on dialysis receiving either lanthan or calcium carbonate. In the lanthanum-group, a normalization of the bone turnover is achieved in a higher percentage of patients after one year (71 % and 89 %) compared to the calcium-carbonate group (42 % and 50 %). The total bone cell activity (osteoclast- and osteoblast activity) expressed as activation frequency improved in a higher percentage of patients in the lanthanum-group compared to the calcium-group. The risk to develop osteopenia is also reduced in patients receiving lanthan carbonate.
In another study of 2008, 91 patients are evaluated who had been on dialysis an average of 3.5 years. Mineralisation delay, activation frequency and number of osteoblasts and osteoclasts/bone circumference did not show significant changes within or between treatment groups (sevelamer and calcium carbonate). Osteoid thickness significantly increases in both groups, bone formation rate/bone surface significantly increases in the sevelamer-group during the study period, but not in the calcium carbonate group. The differences in changes of spongiosa volume, trabecular thickness and trabecular separation between the treatment groups are not significant for any of these three parameters.
There are six publications on cardiovascular calcifications in three patient collectives. In all studies, the effect of sevelamer-therapy was evaluated using electron beam tomography (EBT) compared to calcium-containing p-binder therapy. In the first three studies (2002, 2003 and 2004) the effect of sevelamer-therapy on calcification of the aorta, coronary blood vessels and cardiac valves (aortic valve and mitral valve) are reported compared to therapy with calcium-containing p-binders (calcium azetat and carbonate). The calcification score (calcium-score) of Agatston is used as a measure of the course of calcification. After 26 weeks as well as 52 weeks observation period, a significant progression of the calcification of cardiac blood vessels and the aorta is shown in the calcium-group, but not in the sevelamer group.

All differences between the groups are significant. A separate analysis of the data of calcium acetat and carbonate also show a significant increase in the calcification of cardiac blood vessels and the aorta in the calcium acetate-group. Using the calcification score of aortic and mitral valves as primary endpoint, a significant increase of the calcification in the area of the aortic valve and a corresponding non-significant increase of the calcification in the area of the mitral valve is reported after 52 weeks in patients receiving calcium-containing p-binders compared to those receiving sevelamer. In a multivariate model, sevelamer remains to be superior to calcium after adjusting for the parameter calcification score at study start, average calcium-phosphate-product, geographical origin of the patient, calcium-preparation (calcium carbonate versus calcium acetate), cholesterol values and lipid-lowering therapy with statins.
The first long-term comparison (52 months) of sevelamer with calcium containing p-binders is a study published in 2004 in 108 patients. Compared to therapy with sevelamer, therapy with calcium containing p-binders lead to a significant increase of the calcification score of the cardiac blood vessels and the aorta. The multivariate analysis shows that the calcification score at study start and, on the other hand, the use of calcium containing p-binders are the strongest predictors for a progression of calcification. In a follow-up study of 2005, the further course of artery calcification is evaluated. Analogous to the results of the first year of treatment, the patient group (n = 52) receiving calcium containing p-binders show a stronger increase of the calcification score of the cardiac blood vessels ($p = 0.0178$) and the aorta ($p = 0.0039$).
In a further study in a patient collective of 129 patients new to hemodialysis, the calcification score (calcium-score according to Agatston) of the coronary artery is evaluated. After 18 months, patients on calcium-therapy show an increase of the calcification score of 127 points and thus show an increase eleven times higher than patients on sevelamer-therapy ($p = 0.01$). In patients who show relevant levels of calcification already at study start, the progression of calcification tends to be faster and stronger in the calcium-group at all time points of measurement compared to the sevelamer-group ($p = 0.0564$ after twelve months; $p = 0.0572$ after 18 months). A stabilization or reduction of the calcification score is reported more frequently in the sevelamer- compared to the calcium-group ($p = 0.003$ after twelve months, $p = 0.01$ after 18 months).
Analyzing Sevelamer, the economic studies show costs of 1,107 USD per life year gained up to costs per quality-adjusted life year (QALY) of 278,000 CAD and a budgetary strain of about 781 million USD in the USA and 26 million USD or 74 million CAD in Canada. The cost-effectiveness analysis of lanthan carbonate results in 25,033 GPD per QALY gained. Further prospective long-term studies with adequate sample sizes and comparable study designs need to be conducted on the effect of p-binder choice.

Discussion

Patients on chronic hemodialyis exhibit increased mortality risk in comparison to patients with normal renal function due to several reasons: on one hand, many underlying diseases for chronic renal failure, i. e. diabetes, hyperlipidemia and hypertonia, are per se associated with an increased risk for the occurrence of cardiovascular events and mortality, on the other hand the common use of calcium-containing P-binders may alter mortality risk by causing calcification of the arterial system.
The emergence of calcium-free p-binders, especially of the recently developed Renagel® (Sevelamer), creates high expectations in the pharmacolog-

ical treatment of patients on hemodialysis with respect to lowering arterial calcification and reducing mortality rates. The treat to goal (TTG) study proves the reduction of arterial calcification in patients on therapy with sevelamer in comparison to those on calcium-containing therapy, whereby first positive effects can be shown after only six months of therapy. Treatment with sevelamer for two years is associated with a 25 to 28 % reduction of calcification status of the aorto-coronary arterial system.

The marked advantage of sevelamer with respect to survival of patients aged more than 65 years, which is show in one of the studies on mortality, is explained by the fact that arterial calcification worsens with age and that older patients therefore benefit more from protective therapy than younger patients. With respect to cardiovascular mortality, sevelamer shows superiority over calcium-containing p-binders as well. However, patient numbers are too small to draw statistically significant conclusions. On the basis of the present results, the authors cannot explain whether the reduction of mortality risk under sevelamer treatment in the elderly is due to reduced deposition of calcium in the arterial wall, or whether it is a secondary effect of the lipid-lowering effect of sevelamer-therapy.

A further study which has been included in the medical section of the present HTA-report shows reduced mortality rates in patients under sevelamer treatment in comparison to patients under therapy with calcium-containing p-binders. However, differences reach significance only after multivariate control for parameters such as the extent of initial calcification of the coronary arteries at the beginning of the study. Again, it is not possible to completely exclude a contribution of the lipid-lowering properties of sevelamer treatment to the favorable effect on calcification. The inconsistent relationship between higher age and sevelamer-associated reduction of mortality rate among different studies is explained by the fact that different study designs have been used. Further long-term analyses are needed to clarify if measures, which prevent calcification early at the beginning of dialysis may help to improve mortality rates of patient on hemodialysis.

Patients with chronic renal failure and patients on chronic hemodialysis display a markedly increased risk to develop arterial calcification in comparison to age-matched people with normal renal function. As occurrence of cardiovascular events is common among patients on hemodialysis, a relationship between cardiovascular calcification and cardiovascular morbidity may be assumed. Furthermore, it is unlikely that the extremely high rate of severe cardiovascular calcification among renal patients is only related to the presence of traditional risk factors, such as diabetes, hypertonia and hyperlipidemia. Instead, a multifactorial origin of cardiovascular calcification is assumed, comprising i. e. a disbalance of mineral metabolism, resulting from treatment with vitamin-D and p-binders.

The extent of increase of cardiovascular calcification is neither correlated to hypercalcemic episodes, nor to serum lipid concentrations. A potential beneficial effect of treatment with vitamin D or statin therapy cannot completely be excluded, even if the authors discuss such effects to be extremely unlikely. However, the rise of the calcification score is related to the level of suppression of PTH in patients with calcium-containing therapy. A possible explanation is that reduced concentrations of PTH below recommended levels may decrease skeletal uptake of calcium and thereby cause deposition of calcium in the tissue. Besides the severity of calcification at the beginning of the study, treatment with calcium-containing P-binders is the strongest predictor for progression of calcification of the aorto-coronary arterial system.

Three publications evaluate the effect of p-binders on bone metabolism. The nominal classification in different disease stages used in the earliest studies

leads to a loss of information, as particularly the mixed renal osteodystrophy covers a wide range of bone metabolism parameter values. Possible limitations of the significance of the studies are that EBT is not the gold standard for assessing the bone architecture and – strength. Also, the importance of measuring bone density at different locations and the use of a bone phantom for calibration are pointed out. Regarding safety, the rate of ADE is comparable for all p-binders and is consistent with that of dialysis patients. The significantly higher rate of gastrointestinal symptoms with sevelamer is explained by the loss of the protective effect of calcium on the intestinal tract when changing from calcium-containing p-binders to sevelamer. Toxic effects on the bone such as were reported for aluminum-containing p-binders cannot be shown for lanthan carbonate. After approximately twelve weeks, the lanthan carbonate plasma concentration reaches a plateau and is independent of the dose administered. This is ascribed to patient specific differences in the gastrointestinal absorption.
The economic studies show different results on the cost-effectiveness of sevelamer compared to calcium-containing p-binders. Different assumptions on the effectiveness of sevelamer and different costs explain the differences in results. For lanthan carbonate, only direct drug costs are incorporated in the evaluation. According to a patient survey conducted by the European Association for renal patients, patients are content with dialysis care in Germany. Quality assurance in dialysis patient care is provided through the confederation of accredited physicians, the social security code V, and guidelines of the federal joint committee. However, the provision of transplants to renal insufficient patients could be improved in Germany. This could be achieved by improvements in hospital organisation, better education of the population, as well as the introduction of a federal live-donor register and harmonization of the processes and policies of the live-donor commissions.

Conclusions/recommendations

From an economic point of view, sevelamer and lanthan carbonate do not show a clear superiority over calcium-containing p-binders based on the present data. Regarding the effectiveness with regards to mortality, differences can be shown in certain patient-subgroups. For example, elderly patients benefit from sevelamer therapy regarding a lowering of the mortality rate. Regarding cardiovascular calcifications, sevelamer shows superiority over calcium-containing preparations. However, it needs to be taken into consideration that the studies significantly differ in their use of endpoints and statistical methods and often overestimate secondary endpoints or marginally significant results or trends in their conclusions. Of course, the extent of calcification at the beginning of treatment is of additional important impact on mortality risk. If measures to prevent calcifications can ultimately improve the survival rates of dialysis patients has to be clarified in long-term studies.
The validity of the present HTA-report is significantly limited due to the limited number of available publications, the low sample size of treated patients, as well as the fact that the majority of studies are based on the same patient collectives.
Prospective long-term studies not funded by the industry with adequate sample sizes and comparable study designs are called for to make authoritative statements regarding the medical effectiveness and safety of sevelamer and lanthan carbonate, as well as regarding their economic efficiency.