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Phosphate binders. Is selection determined by price? No

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The controversy alluded to in the title has arisen due to substantial differences in price between two different types of phosphate binders: those that contain calcium (lower price) and those that are calcium free (higher price). In this article, we will refer to phosphate binders with calcium as "calcium-based binders" and those without calcium as "calcium-free binders."

I defend the opinion that price should not determine the choice made by doctors upon which drug to administer, in this case phosphate binders. The main points of my argument are:

1. The value of a medication must replace the focus on cost.

2. Calcium-free phosphate binders have an added health benefit.

3. The role of the doctor is to provide the maximum possible benefit to the patient.

THE VALUE OF A MEDICATION MUST REPLACE THE FOCUS ON COST

There is a complex network of official commissions and authorities, supported by well-defined legislation, that determine the price of medications.[1] Each of these authorities holds sway over different territories: the European Medicines Agency, centred in London, which has the power to authorise the commercialisation of a drug in any country in the European Union; at the National level, the Spanish inter-ministerial committee on medical prices (Ministry of the Economy and Ministry of Industry, Tourism, and Commerce), the Spanish drug and healthcare product agency (elaborates the report on therapeutic usefulness), and the Ministry of Health and Consumer Affairs (regulating the financing of the National Health System); at the regional level, each individual region has its own organisation controlling these regulations. Finally, in order to avoid inequalities, an oversight committee acts as arbiter between different regions. In parallel, there is also an Inter-regional council for the evaluation of new medicines where several regions are represented: Catalonia, Andalusia, Basque Country, and Aragón.

This organisational complexity reflects the need to reach a fair price based on a compromise between several different interests: a) industrial interests, which seek an economic benefit for the manufacturing company that allows for a sufficient profit margin for investment in research and development, b) public health interests, which have the urgent need to control pharmaceutical costs, and c) medical interests, which seek only to benefit patient health through new medicines.

However, the concept of "**price**" is obsolete, and a simplistic view of price can lead us to use ineffective low-cost drugs instead of effective high-cost drugs. As such, it is logical to establish whether a certain drug is worth what it costs, that is to say, whether society is willing to pay the price asked for the health benefits provided.

As such, the different agencies and authorities involved must settle upon a price that has been adjusted for the ***added*** *value* of the drug. This is a laborious process, requiring specific knowledge, and it must be carried out by professional experts. The concepts of *price* and *value* are established using certain tools and during various stages. The first stage is an evaluation of "therapeutic usefulness" (efficacy and safety) through trials that compare the drug to a placebo, which leads to an authorisation for commercialisation. The second stage is an analysis of the "added therapeutic value" (value of the drug as compared to similar drugs that are already on the market), which is derived from "head to head"

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trials that compare the new drug with already established alternatives; this leads to an authorisation for public financing. The last step is to establish "social value" (what society is willing to pay). This varies by country, but generally establishes a quantity per quality-adjusted life year (QALY), which is set as a threshold that should not be exceeded. In Spain, a treatment is considered efficient when its cost-effectiveness ratio falls below a threshold of 30 000€ per QALY.[2]

There is a great deal of variability between countries. In England, where the NICE (National Institute for Health and Clinical Excellence) has served as the standard for this model, inequalities arose that led the British government to propose, by 2014, the introduction of a new system for fixing the prices of medicines based on value (value-based system).[3]

These procedures, carried out by specialised professionals, should provide doctors the assurance necessary to prescribe any drug available on the market while acting for the exclusive health benefit of the patient. However, doctors are often asked to make a decision based on price with economic and occasionally demagogic arguments. Joint responsibility for drug costs does not mean placing the importance of costs above health benefits, but rather involves adopting an active role in searching for added value, regardless of industry interests.

CALCIUM-FREE BINDERS HAVE AN ADDED HEALTH BENEFIT

These drugs:

a) Do not contribute to damaging calcium overloads in chronic kidney disease (CKD).

b) Slow the progression towards vascular calcification.

c) May reduce hospitalisation and mortality rates in patients older than 65 years?

d) Play a greater role in prevention as can be used in earlier stages of CKD.

e) Sevelamer has beneficial pleiotropic effects.

Do not contribute to damaging calcium overload in CKD

Calcium-based binders that are available on the market have different calcium content levels and thus have different impacts on calcium overload. Daugirdas et al[4] calculated the quantity of calcium required per unit chelating capacity, resulting in calcium carbonate: 400mg, calcium acetate: 250mg, and OsvaRen® (435mg calcium acetate/235mg magnesium carbonate): 213mg.

We must also distinguish between two different contexts of CKD patients when evaluating the risk of calcium overload: before and after starting dialysis or losing renal function.

Calciuria decreases progressively as renal function deteriorates. The calcium overload caused by this situation is buffered by progressive decreases in calcitriol and thus a reduced intestinal absorption of calcium.[5] At this stage, administering calcium and/or vitamin D compounds in any form increases the risk of calcium overload in proportion to the severity of renal failure.

In the dialysis stage, renal losses disappear and we must evaluate kinetic analyses with a view on several variables, such as level of ultrafiltration and calcium content in the dialysate. In a comprehensive study, Gotch et al[6] introduced the concept of adapting the calcium concentration in the dialysate based on vitamin D treatment and the type of calcium content in phosphate binders. Ceasing treatment with vitamin D in order to treat a patient with calcium compounds is indefensible based on the available evidence, since vitamin D has beneficial effects for survival. Its administration should be prioritised, with later adjustments made to calcium intake as needed (dialysate and/or oral supplements).

When the calcium input outweighs losses, the excess should be deposited in the bones. However, the buffering capacity of the bones as a calcium reserve decreases with age, and practically disappears in adult ages. This capacity also depends on other variables, such as parathyroid hormone (PTH) levels. Low levels cause bone disorders and the inability of the bones to absorb calcium, and elevated levels increase bone reabsorption, with calcium passing from the bones to the plasma.

Doctors come up against the following question: to what extent can we administer calcium? Unfortunately, there is no useful plasma marker for calcium overload, and our decision must be based on our knowledge of physiology in order to use the following concepts correctly:

- **Plasma calcium is not an indicator of total organic calcium.** Extracellular calcium is only 0.1% of total calcium. However, the majority of studies that defend using calcium compounds claim an absence of adverse effects based on the number of episodes of hypercalcaemia or plasma calcium levels. To quote the review by Moe[7] arguing a position against the use of calcium-based phosphate binders: "*Advocates of calcium-based binders stop here and argue that calcium-based binders therefore are toxic only in the setting of hypercalcaemia, but the nephrologist (and endocrinologist and the physiologist)*

who understands the difference between homeostasis and balance knows that there is more to calcium than meets the eye on the laboratory reports."

- **The concept of calcium homoeostasis must not be confused with calcium balance.** The balance of any system is the difference between gains and losses. Nature has created a system that allows for maintaining a positive balance while bones grow, with peak bone calcium content between 20 and 30 years of age. In women, a negative balance starts following menopause. Homeostasis attempts to maintain normal plasma calcium levels through a complex mechanism of inter-related regulating processes.[7]

Calcium overload has been shown to be detrimental in the general population. A recent meta-analysis performed by Bolland et al[8] demonstrated an increased risk of myocardial infarction in women receiving calcium supplements and several studies have been carried out in patients with CKD. The results of the study by Miller et al[9] involving 107 200 haemodialysis patients showed the negative effects of calcium overload, in which mean serum calcium levels over 5 years increased mortality when over 10mg/dl, within a range of serum phosphorous levels between 3.5mg/dl and 5.5mg/dl.

Slow the progression towards vascular calcification

The first randomised study comparing quantified coronary and aortic calcification through axial computed tomography between patients treated with sevelamer and calcium compounds was the Treat to Goal Study,[10] sponsored by Genzyme, in which coronary arteries had a significantly lower progression after 26 and 52 weeks in patients treated with sevelamer (14% vs 0% and 25% vs 6%, respectively). The results were similar in the aorta. The RIND study,[11] carried out in incident patients on haemodialysis, randomised patients to receive sevelamer or calcium-based binders. When measured after 6, 12, and 18 months, the absolute increase in calcification was greater in patients receiving calcium compounds.

These studies were unable to establish whether or not the reduced progression of vascular calcification with sevelamer was due to the beneficial effects on the patient's lipid profile. Under the sponsorship of Fresenius, the CARE-2 "non-inferiority" trial stated in the conflicts of interest section that one co-author was an employee of Fresenius and another an employee of Nabi Biopharmaceutical (which commercialised Phoslo®).[12] This study involved administering atorvastatin to two groups in order to reach an LDL cholesterol level <70mg/dl. There were no differences observed in the progression of coronary calcification, which led to the conclusion that the beneficial effects of sevelamer are probably due to its lipid-lowering capacity. A careful analysis of these data reveals important limitations: 1) the percentage of patients treated with statins (with a different lipid-lowering mechanism from the one found in sevelamer) was greater in patients treated with calcium-based binders (97% vs 79%, respectively), 2) there was a notable loss in follow-up (42.7% and 30%, respectively), and 3) the study population had higher PTH levels, more smokers, and more diabetic patients than in the Treat to Goal Study.

May reduce hospitalisation and mortality rates?

It is logical to think that, if increased cardiovascular mortality/morbidity in CKD patients is at least in part due to the severity and early onset of vascular calcification, a drug that could affect this process would in turn reduce these rates. With this objective, and with financing from Genzyme, the DCOR study was carried out with a randomised design to study sevelamer and calcium compounds.[13] Despite reaching a sample size (1068 patients) and number of events (580) that would allow for statistical power, the authors were unable to demonstrate a superior two-year survival in patients treated with sevelamer. However, the statistical analysis demonstrated a significant relation between treatment and age (P=.02), which led to a sub-analysis of patients older than 65 years old. This sub-analysis revealed a 23% lower mortality rate in patients treated with sevelamer.

St Peter et al[14] performed a sub-analysis of the DCOR results, with a follow-up based on the data from clinical histories compiled at Medicare and Medicaid Services centres (not in follow-up visits). Although patients were grouped by intention to treat, and some patients changed between groups, the longest follow-up time yielded 857 deaths vs the 442 from the DCOR study. Despite this, there were no differences between groups in terms of survival. There was also a correlation between treatment and age (P=.01), but after adjusting for other variables, the P-value did not reach statistical significance (P=.06), and so a sub-analysis by age did not follow. It is interesting to note that minimal differences in the P-values obtained from analyses of the same dataset could lead to different conclusions with significant implications in clinical practice. One interesting result of this study is the lower frequency of hospitalisations (10%) and shorter hospital stays (12%) in patients treated with sevelamer, which should be taken into account in cost-effectiveness analyses.[15]

However, a *post-hoc* analysis of the RIND study[16] was able to demonstrate a higher survival rate for sevelamer (11 deaths vs 23 deaths) in incident patients on haemodialysis that were monitored for 44 months, with only two patients lost to follow-up.

Similar beneficial results for survival were observed in a study involving 1354 patients older than 65 years, with a prospective and randomised design similar to the DCOR study,[17] in which lanthanum carbonate was used as the calcium-free binder.

Play a greater role in prevention as can be used in earlier stages of CKD

When there is a decrease in calciuria, administering calcium increases the risk of calcium overload, especially in patients that receive vitamin D in any form.

Few studies have analysed this issue in early stages of CKD. The only study of stages 3-5 in CKD[18] compared the progression of coronary calcification after 2 years in patients with a diet low in phosphorous, calcium compounds, and sevelamer, showing that this condition did not increase only in patients treated with sevelamer. Surprisingly, serum phosphorous was within normal ranges for all three groups.

Sevelamer has beneficial pleiotropic effects

It is well known that sevelamer improves lipid profiles. Perhaps less well known are its anti-inflammatory effects, as demonstrated using C-reactive protein or fetuin-A as biological markers, both of which are involved in atheromatosis, malnutrition, vascular calcification, and mortality.[19]

In a short (3 months) but well-designed study (prospective and randomised), Navarro et al[20] observed that inflammatory interleukin levels dropped in patients treated with sevelamer and that these values increased significantly in patients treated with calcium acetate. Simultaneously, endotoxin and CD4 levels dropped in patients treated with sevelamer, with no changes in patients treated with phosphate binders. Although more specific studies are needed to understand the anti-inflammatory mechanism of sevelamer, we must remember these enlightening results.

THE ROLE OF THE DOCTOR IS TO PROVIDE THE MAXIMUM POSSIBLE BENEFIT TO THE PATIENT

In choosing which drug to administer, doctors are subjected to a series of "pressures." Once the commercialisation of a drug has been authorised (drug leaflet), the drug has gone through the regulation system for prices of new drugs, and it has been incorporated into guidelines for clinical practice, the doctor could come to the conclusion that he/she is free to prescribe based solely on the benefit provided to the patient.

However, doctors tend to expand their knowledge base using the available information sources: medical literature and scientific conferences. The Internet has facilitated access to a large number of scientific texts that are normally selected based on the prestige afforded to the authors or the journal in which the articles are published. However, certain information is provided at the end of the article that is of the utmost importance for interpreting the data: the conflicts of interest, which must be closely monitored in order to discern between funding without intervening in the study design, indicating that the sponsor has no information regarding the study until the article is published, and other forms of funding in which employees of the pharmaceutical industry are listed among the authors.

Pharmaceutical conferences provide another major source of information, although this venue may not always objectively state opinions that go against the interests of the organisers.

Additionally, the difficulty in publishing negative results provokes a state of biased information.

Finally, the policies to control pharmaceutical expenditure are imposed more and more heavily in the context of the current unprecedented financial crisis. As such, doctors must form an opinion, based on the available objective information and his/her own clinical experience.

What criteria should prevail when deciding upon a prescription? In my opinion, the benefit to a patient's health, which has been the essence of the medical profession from the time of Hippocrates to the Declaration of Geneva, should be the basis of our ethical framework.[21]

I would like to repeat the words of the English minister of health in defence of a value-based pricing system: "*It is vital that doctors are able to prescribe medicines that they think will benefit their patients. They must be able to focus on what matters most – achieving the best health outcomes for their patient, not debating the price of a drug. Value-based pricing will ensure this happens.*"[22]

This does not imply that doctors should maintain a passive attitude in the complex field of fixing the price/value of medications. Their responsibility to the public health system, and as citizens, demands an active role in order to reach a fair price that is adjusted to what our society is willing to (or can) pay.

Finally, I would like to make a number of recommendations that should be promoted by scientific societies:

1. Promote scientific debates that are independent of the pharmaceutical industry.

2. Establish transparency mechanisms and codes of ethics that allow for collaboration with the pharmaceutical industry in order to promote the innovation and

development of new drugs that provide benefits to the health of our patients. The fact that a study is funded by a pharmaceutical laboratory does not invalidate it. The exaggerated costs of trials that require large sample sizes in order to reach the necessary statistical power makes it very difficult to carry out such studies using public funds.

3. Make the responsibility of controlling pharmaceutical costs fall on the shoulders of the agencies and authorities designed for this task, so that medications arrive on the market with a "price" that is adjusted to their "value."

Without a doubt, demanding mechanisms that guarantee transparency in the relationships between research, clinical practice, and industry does not imply that sources of funding cannot be trusted. We must recognise and thank the pharmaceutical industry for providing the means to facilitate continuing education and its enormous contribution in pharmacological development and innovation.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

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