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Oral phosphate binders: History and prospects

Junichiro James Kazama *

Division of Nephrology and Intensive Care Medicine, Niigata University Medical and Dental Hospital, Niigata, 951-8510, Japan

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ABSTRACT

The use of an oral phosphate binder is a promising and most practical strategy for the prevention of vascular calcification in patients with chronic kidney disease (CKD). To secure the safety: 1) the oral phosphate binder must not cause adverse effects in the gastrointestinal tract; 2) the oral phosphate binder should be non-absorbable or barely absorbable through the gastrointestinal tract, or 3) if partially absorbed through the gastrointestinal tract, it must be eliminated from circulation through a pathway other than urinary excretion, and 4) even if it accumulates in the body, it should not cause organ dysfunctions. Metal salt type oral phosphate binder is the most classical type of oral phosphate binders that includes aluminum hydroxide gel and lanthanum carbonate. These oral phosphate binders effectively adsorb phosphate ions, however, have a potential risk for accumulation and intoxication. Calcium salt type oral phosphate binder was the most widely prescribed oral phosphate binder in the last decade but is now believed to exert potential harm, favoring progression of vascular calcification through excessive intestinal calcium load. However, recent studies failed to detect an inferiority of calcium salt type oral phosphate binders as compared to non-calcium salt type oral phosphate binders in terms of mortality and/or morbidity of hemodialysis patients. Polymerized resin type is a safe and relatively effective oral phosphate binder, which is supported by many clinical evidences. However, it sometimes causes severe constipation, especially in Japanese patients. Among metal compound type oral phosphate binder, other promising compounds include boehmite-type aluminum and hydrotalcite-like compounds but they are not yet available in the clinical setting.

Preface

Reduction of the serum phosphate level is the most promising strategy for the prevention and treatment of ectopic calcification[1]. It also has the potential to prevent the development of ectopic ossification around vascular smooth muscle cells [2]. It is quite difficult to satisfactorily remove circulating phosphate by blood purification therapy in most of patients with end-stage chronic kidney disease (CKD) [3]. Therefore, the restriction of intestinal phosphate absorption is necessary to prevent the development of hyperphosphatemia. However, it is difficult to restrict oral phosphate intake without avoiding malnutrition, because the amount of phosphate in food is almost parallel to the amount of protein, and thus the use of an agent that effectively captures free phosphate anion in the gastrointestinal tract, namely an oral phosphate binder, becomes necessary.

Oral phosphate binder must have a high binding affinity to phosphate anions. In addition, attention must be paid to the safety of oral phosphate binders. To secure the safety of oral phosphate binders, the following 4 conditions must be satisfied: 1) the oral phosphate binder must not cause clinical symptoms in the gastrointestinal tract; 2) the oral phosphate binder should be non-absorbable or barely absorbable through the gastrointestinal tract, or 3) if oral is thus absorbed through the gastrointestinal tract, it must be eliminated from circulation through a pathway other than urinary excretion, and 4) even if it accumulates in the body, it should not cause organ dysfunctions. Although many oral phosphate binders are presently available in clinical practice, none of them have satisfied all 4 of these conditions simultaneously.

Metal salt type oral phosphate binders (Fig. 1-1)

Metal salt type oral phosphate binders dissolve into anions and free metal cations in the gastrointestinal tract. Thereafter, the free metal cations capture phosphate anions to form new insoluble metal phosphate salt. By this pharmacological mechanism, metal salt type oral phosphate binders inhibit intestinal phosphate absorption. Aluminum hydroxide gel, the first oral phosphate binder widely applied to CKD patients [4], is a typical example of this type of oral phosphate binder. From the perspective of the intestinal phosphate binding efficacy, we have not yet obtained obviously better agents than aluminum hydroxide gel (Fig. 1-1).

Before capturing phosphate anions to form insoluble aluminum phosphate salt, some of the free aluminum cations are absorbed through the intestine. Once absorbed, aluminum cation has a strong binding affinity to the calcified front in bone, thus causing severe osteomalacia [5–7]. It is also accumulated in the central nervous

* Fax: +81 25 227 0775.
E-mail address: jjkaz@med.niigata-u.ac.jp.

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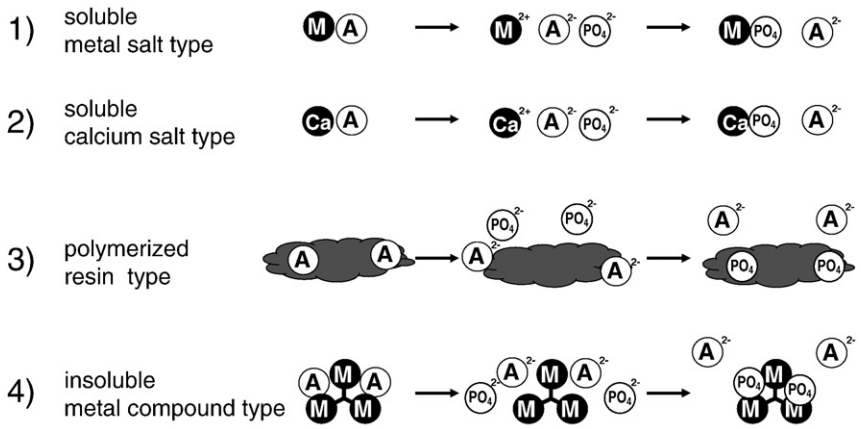

Fig. 1. Classification of OPBs.

system and causes dementia [8]. Ever since these severe side effects were observed, the use of aluminum hydroxide gel has been extremely limited. Intestinal cation absorption and subsequent cation accumulation are more or less unavoidable for any of the metal salt type oral phosphate binders. The specificity of accumulated aluminum may be responsible for the remarkable toxicity of aluminum hydroxide gel. Therefore, a metal salt type oral phosphate binder using iron as a cation instead of aluminum is being developed [9,10]. The toxicity of accumulated iron seems to be less severe than that of aluminum, and in fact iron agent targeted for iron deficient anemia is absorbed through the gastrointestinal tract without obvious major side effects. Oral iron absorption in patients with advanced stages of CKD is generally reduced and that the administration of iron-containing oral phosphate binder could be beneficial in those with iron deficiency. Nevertheless, excess iron overload is known to cause skeletal abnormality in CKD5 patients [11,12].

Lanthanum carbonate is a recently developed metal salt type oral phosphate binder that is drawing attention [13]. Lanthanum cation has a strong binding affinity to phosphate anion. The phosphate binding effect of lanthanum carbonate was reported to be no worse than that of aluminum hydroxide gel *in vitro* and *in vivo* [14]. From the perspective of phosphate binding efficacy, lanthanum carbonate would be the most promising oral phosphate binder among those available today.

Like other oral phosphate binders in the metal salt type group, ionization is necessary for lanthanum carbonate to perform its phosphate binding effect. Therefore, it is unavoidable for some lanthanum cations to be absorbed through the gastrointestinal tract. Although most of the circulating lanthanum is eliminated through the hepato-billary tract into feces, its circulating level is slightly elevated during the therapy. However, the level then reaches a plateau, indicating that intestinal absorption and hepato-billary excretion achieve an equilibrium condition. On the other hand, the risk of lanthanum accumulation in particular organs, including the liver or bone, was indicated by animal experiments [15,16]. However, experiments that detect trace elements like lanthanum are technically quite delicate. Therefore, these results might have been caused by contamination from the feces of the animals [17]. Moreover, even if lanthanum is really accumulated in certain organs, it is still unknown whether or not the accumulated lanthanum demonstrates pathogenicity, like accumulated aluminum does. Lanthanum carbonate has already been applied in clinical practice, but no specific adverse effects have been reported. Nevertheless, no one noticed the side effects of aluminum hydroxide gel for a decade after it was applied as an oral phosphate binder in CKD patients [4,5]. We must not forget this fact to use lanthanum carbonate for clinical application.

Calcium salt type oral phosphate binder (Fig. 1-2)

Ever since the use of aluminum hydroxide gel as an oral phosphate binder was restricted due to its severe side effects, calcium carbonate became widely used as its substitute [18]. In a broad sense, calcium carbonate also belongs to metal salt type oral phosphate binders which become ionizers to capture phosphate anions and release free cations. However, unlike other metals used for oral phosphate binder, calcium is a natural major component of the human body. From this point of view, magnesium salt stands at a similar position to calcium salts. Patients with end-stage CKD used to be generally hypocalcemic. Therefore, the harm caused by calcium accumulation and/or over intake was not considered when calcium salt type oral phosphate binder was supplied for clinical use. The phosphate binding effect of calcium carbonate is inferior to that of aluminum hydroxide gel, but not to that of sevelamer hydrochloride (described later). Its drug efficacy is largely dependent on the pH condition. Since the pH level of gastric juice is extraordinarily elevated in the majority of CKD5 patients [19], its phosphate binding effect in clinical practice may be less than that expected from *in vitro*/*in vivo* experiments. In contrast, the phosphate binding effect of calcium acetate is relatively stable to the pH condition. Another attractive point of these calcium salt type oral phosphate binders is that they are inexpensive.

Calcium salt type oral phosphate binder, calcium carbonate and calcium acetate, cause the elevation of free calcium cation levels in the gastrointestinal tract and the subsequent increase of intestinal calcium absorption. As described before, this phenomenon was not previously regarded as a harmful one, since calcium balance in CKD5 patients used to be considered generally negative.

However, the calcium balance in CKD5 patients dramatically improved after the use of active vitamin D agents became widespread. Today, a negative calcium balance is no longer a common phenomenon in CKD5 patients, and it is presumed to be a major cause of the increased prevalence of adynamic bone [20]. The amount of intestinal calcium absorption was further increased by the use of calcium salt type oral phosphate binders. Moreover, the increase of intestinal calcium absorption was reported to be associated with the development of vascular calcification[21–28]. Ever since the benefits of using active vitamin D agents have become known, the use of calcium salt type oral phosphate binder has been restricted. The K/DOQI clinical practice guidelines have set an upper limit on the amount of calcium type oral phosphate binder that can be used [29].

Nevertheless, it seems unlikely that this upper limit amount set by the K/DOQI guidelines will be internationally acceptable. It is still in controversy how much amount of calcium salt type oral phosphate binder is tolerable for CKD5 patients, since some of recent studies

failed to detect its inferiority than non-calcium salt type oral phosphate binders in mortality and/or morbidity of hemodialysis patients[30–33]. In fact, the Japanese Society of Dialysis Therapy (JSDT) clinical practice guideline applied a higher level of calcium salt type oral phosphate binder amount as the upper limit for clinical use [34]. Finally, the toxicity of calcium salt type oral phosphate binder should be enhanced by the use of active vitamin D agents. Therefore, it is still inconclusive whether or not the harm caused by calcium salt type oral phosphate binder is mitigated by the use of calcimimetic agents, whose use for managing secondary hyperparathyroidism has become widespread [35].

Polymerized resin type OPB (Fig. 1-3)

After it became recognized that the phosphate binding effect of calcium salt type OPB was not quite satisfactory, and that its overuse might induce vascular calcification, polymer type oral phosphate binder drew the attention of many clinicians. Generally, this type of oral phosphate binder is considered to be safer because it is not absorbed through the gastrointestinal tract.

Sevelamer hydrochloride is a widely applied oral phosphate binder today [36]. Chloride anions are released from the basal polymer structure and phosphate anions are captured thereafter. Although it was feared that released chloride would accelerate metabolic acidosis, little specific adverse effects associated with this phenomenon have ever been reported. The binding effect is non-specific to phosphate, and therefore it also captures many other substances, including cholesterol. This property has an additional beneficial effect on lipid metabolism [37]. Sevelamer carbonate does not induce metabolic acidosis, which may develop in those using sevelamer hydrochloride.

The phosphate binding efficacy of sevelamer hydrochloride is comparable or no better than that of calcium carbonate [38]. It is nearly impossible to overcome hyperphophatemia in end-stage CKD patients with sevelamer hydrochloride alone. Nevertheless, the use of sevelamer hydrochloride decreased serum inorganic phosphate levels, ameliorated secondary hyperparathyroidism [39,40], and inhibited the development of vascular calcification [41] in CKD5 patients. Even life prognosis may be improved by the therapy [27]. The beneficial effects of sevelamer hydrochloride on vascular metabolism may in part be caused by its effect on lipid/cholesterol metabolisms.

While sevelamer hydrochloride is rarely associated with extra-gastrointestinal side effects, it sometimes causes severe constipation, especially in Japanese patients [42], and even a case with mortality was reported. Although the eating habits and anatomical properties of the Japanese seem to be a factor in this, the precise reason why severe constipation is mainly observed in Japanese patients remains obscure. Polymer type oral phosphate binders with a molecular size smaller than that of sevelamer hydrochloride may reduce the frequency of this side effect.

Metal compound type OPB (Fig. 1-4)

Generally, oral phosphate binder has to release anions when it absorbs phosphates. However, as in the polymer type oral phosphate binder, cationic substances do not have to become free cations after releasing anions. Therefore, even if cationic metal is applied for capturing phosphate anion, the risk of cation absorption through the gastrointestinal tract can be avoided if the metal is entrapped into a larger compound (Fig. 1). Moreover, it may not induce constipation as frequently as polymer type oral phosphate binders because the molecular size of such metal compounds is much smaller. No agent of this type of oral phosphate binder has ever been applied to clinical practice, but several drugs are now being developed for future use.

The concept of metal compound type oral phosphate binder is most typically demonstrated by boehmite-type aluminum (B-alm). Aluminum has a satisfactory drug efficacy as an oral phosphate binder. The reason why the use of aluminum hydroxide gel has been strictly restricted is that absorbed aluminum cation from the intestine accumulated in the body and demonstrated severe toxicity. Therefore, if aluminum cation were not absorbed through the gastrointestinal tract, all problems would be solved. B-alm is a crystal formed aluminum hydroxide compound which is expressed as $A_lO(OH)_nH_2O$. It is insoluble in ethanol and hardly soluble in water. Moreover, because of its crystal structural property, more aluminum molecules directly face the outside environment in B-alm than in aluminum hydroxide gel. Thus, the phosphate absorbing efficacy of B-alm surpasses that of aluminum hydroxide gel *in vitro* and *in vivo* (Fig. 2).

Unfortunately, the trial for the clinical use of B-alm as an oral phosphate binder has already been abandoned. Although its crystal structure is quite stable, some crystal structures were broken down in the alkaline condition and, therefore, a very small amount of aluminum cations were absorbed through the intestine. However, B-alm had the potential to become a safer and more effective oral phosphate binder than conventional aluminum hydroxide gel, despite sharing the same phosphate absorbing metal as a main component.

The titanium oxide-like compound (TiOLC) is a water containing non-crystal formed compound that is expressed as $TiO_2(SO_4)_2(OH)_2 \cdot {}_nH_2O$. This structure is so stable that it is almost insoluble in water from acidic to alkaline conditions. In the gastrointestinal tract, TiOLC releases SO_4 anions and captures phosphate anions instead, while the basal cationic structure containing titanium is stable and not absorbed through the intestine. The phosphate binding affinity of TiOLC is

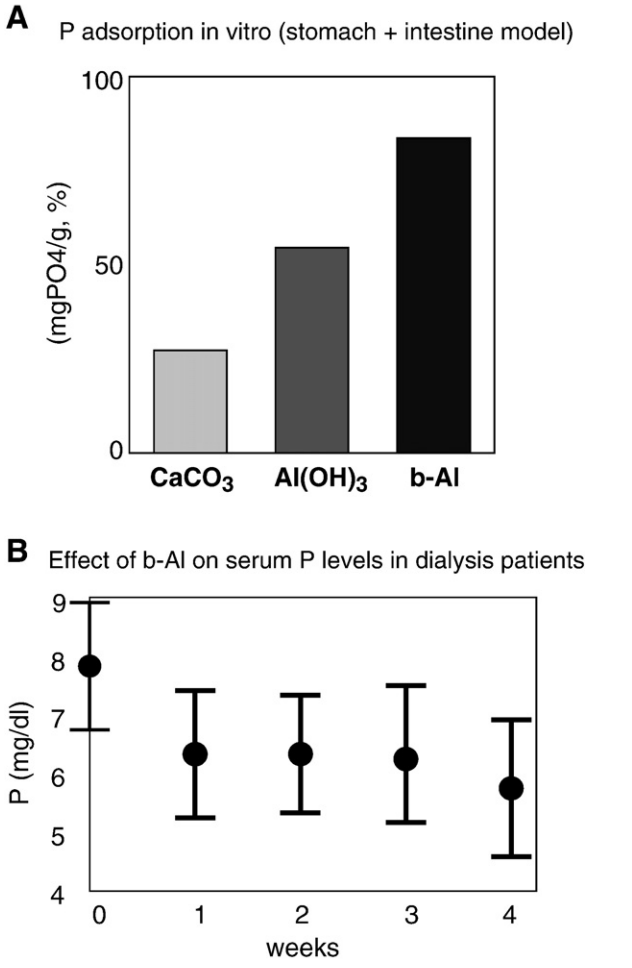

Fig. 2. (A) The amount of phosphate adsorbed was markedly higher with B-alm than with same amount of $Al(OH)_3$ *ex vivo* experimental intestine + stomach model. (B) The administration of B-alm successfully decreased serum inorganic phosphate levels in maintenance hemodialysis patients.

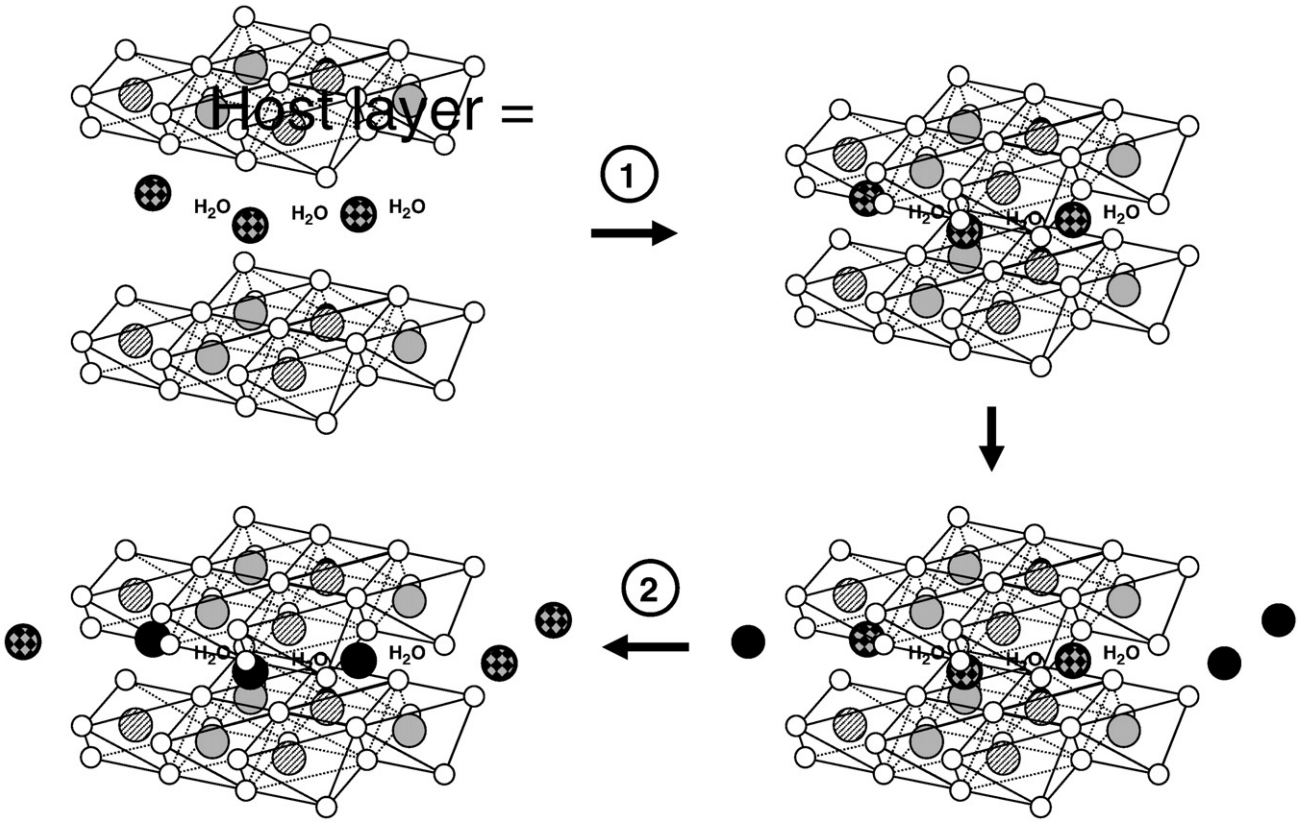

Fig. 3. The mechanism of phosphate adsorption by hydrotalcite-like compounds. (1) Cationic host layers $[M^{2+}{}_{1-x}M^{3+}{}_{x}(OH)_2]$ entrap guest anions (A) and water. (2) Entrapped anions are replaced by phosphate anions.

estimated to be comparable to that of sevelamer hydrochloride *in vitro* and *in vivo*, and is only slightly affected by the pH condition.

Of note for titanium, this metal has been applied for food/drug additives, and artificial joints. Unlike TiOLC, titanium compounds used for food/drug additives are relatively soluble in water and therefore possibly absorbed through the gastrointestinal tract. Nevertheless, no specific organ dysfunction has yet been reported in association with its use, even in chronic dialysis patients. Although titanium containing artificial joints have been in direct contact with extracellular fluid for a long time, no specific side effects have been reported. No specific organ dysfunction has yet been reported in association with its use, even in chronic dialysis patients. Thus, TiOLC has potential to become a promising oral phosphate binder, especially from the perspective of its safety.

Finally, hydrotalcite-like compounds are sandwich-like layered compounds expressed as $[M^{2+}{}_{1-x}M^{3+}{}_{x}(OH)_2][A^{n-}{}_{x/n}\cdot zH_2O]$. $[M^{2+}{}_{1-x}M^{3+}{}_{x}(OH)_2]$ indicates the host layer and $A^{n-}{}_{x/n}\cdot nH_2O$ indicates the guest layer. When a bivalent metal cation (M^{2+}) is replaced by a tervalent metal cation (M^{3+}) in the host layers, guest anion (A^{n-}) is inserted between the host layers for the electrical compensation (Fig. 3). The most remarkable property of hydrotalcite-like compounds is that while the guest anions are exchangeable, the structure of the host layers is stable as $[M^{2+}{}_{1-x}M^{3+}{}_{x}(OH)_2]$.

Using this unique property, a hydrotalcite-like compound has already been applied for clinical use as a gastric antacid. When the structure of the host layer is properly designed, hydrotalcite-like compounds can insert phosphate anions as a guest between the host layers. Of note, a hydrotalcite-like compound is used to remove phosphate from the sea to prevent a hypernutritional condition [43]. The stability of the host layer composition suggests less probability of cation release during anion intake, and this property suggests that hydrotalcite-like compounds have the potential to become safe oral phosphate binders. A hydrotalcite-like compound in which M^{2+} was designed as Mg^{2+} and M^{3+} as Fe^{3+} was applied for this purpose [44,45]. However, hydrotalcite-like compounds are generally relatively unstable in an acidic condition, and this might become a problem when considering their use as oral phosphate binder.

Closing remarks

Oral phosphate binder is, and presumably will continue to be in the future, the most promising medical strategy to prevent/treat vascular calcification in patients with CKD, since no other effective therapy has yet been developed. Oral phosphate binder is often classified into calcium containing oral phosphate binder and non-calcium containing oral phosphate binder. However, this classification may induce misunderstandings because variable oral phosphate binders are classified into non-calcium containing ones regardless of their molecular structure. Therefore, a new classification is advocated in this present review, and the oral phosphate binders described according to the history of their application to clinical practice. Other types of intestinal phosphate absorption inhibitor, like phosphate transporter antagonist, may become available in the future.

Aluminum hydroxide gel failed as an oral phosphate binder, and clinicians need to take the lessons from this failure into account when developing safe and effective next-generation oral phosphate binders.

Conflict of interest

Authors have not conflict of interest.

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