A Comparison of the Phosphorus Content in Prescription Medications for Hemodialysis Patients in Japan

Kazuki Shimoishi,a Makoto Anraku,b Ayako Uto,c Daisuke Iohara,b Fumitoshi Hirayama,d Daisuke Kadowaki,c Sachiko Zingami,e Toru Maruyama,c and Masaki Otagirib

aDepartment of Pharmacy, Japanese Red Cross Kumamoto Hospital; 2–1–1 Nagamine Minami, Higashi-ku, Kumamoto 861–8520, Japan; bFaculty of Pharmaceutical Sciences, Sojo University; 4–22–1 Ikeda, Nishi-ku, Kumamoto 860–0082, Japan; cDepartment of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto University; 5–1 Oe-honmachi, Chuo-ku, Kumamoto 862–0973, Japan; and dMinori Dispensing Pharmacy; 602–4 Toyoda, Ueki-machi, Kita-ku, Kumamoto 861–0106, Japan.

(Received January 13, 2017; Accepted March 1, 2017)

A high dietary intake of phosphorus is considered to be a significant health threat for hemodialysis (HD) patients. Prescription medications, which might be a major source of phosphorus, is largely unrecognized in Japan. However, the amount of phosphorus indicated on the package label, is not quantified. In this study, the phosphorus content of 22 of the most widely prescribed medications that are used in conjunction with HD therapy were examined and differences between branded and generic prescription medications were compared. All samples were selected from medications that are typically prescribed for HD patients. The samples were ground prior to analysis. Phosphorus was measured using the Wako L-Type Phosphate method. All instruments used in the study were calibrated according to the manufacturers’ specifications. Amlodipine (15 mg/tablet) and paroxetine (30.0 mg/tablet) were found to contain higher contents of phosphorus than the medications tested. Differences in phosphorus content between branded and generic drugs was also determined. The phosphorus content of all generic paroxetine preparations was significantly lower than the values for identical branded medications. On the other hand, the phosphorus content of several generic amlodipine preparations were significantly different from those of similar, branded preparations. Specific information regarding the phosphorus content of prescribed medications used by HD patient needs to be made available to the dialysis community.

Key words—hemodialysis; phosphorus; prescribed medication; generic; branded

INTRODUCTION

Individuals with moderate to severe renal disease, including hemodialysis (HD) patients, have an impaired ability to excrete phosphorus. As a result, they tend to develop hyperphosphatemia, especially under conditions of a high phosphorus intake. Elevated serum phosphorus levels are independently associated with increased mortality and morbidity. For example, serum phosphorus levels greater than the 5.5 mg/dL recommended by practice guidelines are independently associated with a 20% to 40% increase in the risk of mortality risk patients with end-stage renal disease (ESRD).1–4 In addition, hyperphosphatemia appears to be involved in the development of atherosclerotic heart disease, secondary hyperparathyroidism, and bone disease in renal patients.5,6 Therefore, limiting the amount of dietary phosphorus is very important in terms of managing HD patients.7 In fact, phosphorus intake is frequently restricted via the use of a phosphate binder in conjunction with a strict diet is often prescribed for HD patients.8,9 In addition to dietary phosphorus, however, the phosphorus content of prescription medications can be significant, but this source is largely unrecognized and unquantified. Sherman et al. recently estimated the phosphorus contents of some prescription medications. Their study found that 11.5% of the drugs that are most commonly prescribed to HD patients contained phosphorus. However, these data were limited to medications that are used in the United States.10

Prescription medications frequently contain additives that are designed to the pharmaceutical quality of a drug, such as solubility, pH adjustment, stabilizers and absorption in Japan. However, the contents of these additives in prescription medications are frequently not available. The high absorptivity of inorganic phosphorus from the intestinal tract, which contained medical additives such as anhydrous dibasic calcium phosphate can lead to hyperphosphatemia.
In this study, we explored the many unknown sources of phosphorus in the prescription medications to identify possible contributors to the total phosphorus intake of HD patients in Japan.

**METHODS**

**Materials**  We chose various oral 22 medicines such as antihypertensive agent (Norvase®, Diovan®, Tanotril®, Azilva®, Olmetec®, Accol®, and Atelec®), anti-peptic ulcers agents (Pariet®, Takepron®, Nexium®), a Hyperphosphatemia therapeutic drug (Caltan®, Riona®, Fosrenol®, Phosblock®), Hyperlipidemia medicine (Crestor®), Hyperuricaemia therapeutic drug (Feburic®), Anti-ademonia medicine (Paxil®), Anti-thrombosis medicine (Warfarin®), bone mineral metabolism drugs (Phosribbon®, Regpara®, Alfarol®), and vitamin (Pydoxal®) which a hemodialysis patient might use. All chemicals were of analytical grade.

**Measurement of Total Phosphorus in Prescription Medications**  We measured phosphorus content per one tablet of the drug using the Wako L-Type Phosphate method. In a typical run, we completely dissolved the drug in 1N HCl to take into account the presence of insoluble Ca salts. In addition, as a positive control, phosphoribon® combination granules containing 100 mg of phosphorus per tablet was examined. We also measured phosphorus content by the p-methyl aminophenol reduction (phosphaC-test Wako) method.

**Statistics**  Statistical significance was evaluated using two-tailed, unpaired Student’s *t* tests for comparisons between two means or ANOVA analysis followed by the Tukey-Kramer method for multiple comparisons. These results are expressed as the mean ± S.D.

**RESULTS**

**Measurements of Total Phosphorus in Branded Prescription Medications**  We first determined the phosphorus contents of 22 different branded prescription medications by using a phosphaC-test kit. As shown in Fig. 1, the phosphorus content greatly varied among the prescription medications, with paroxetine and amloclidine showing the highest content. The phosphorus content of phosphoribon®, a positive control in the total phosphorus measurements, gave the same contents as the actual content determined using the phosphaC-test kit. Thus, the adequacy of this assay system was established from these results (Fig. 1).

**Comparison of Phosphorus Contents among Branded and Generic Prescription Medications**  To compare the phosphorus contents among
branded and generic prescription medications, we selected two branded generic prescription medications (paroxetine and amlodipine), which showed high phosphorus contents in the above studies (Fig. 1). As shown in Fig. 2, the phosphorus contents among branded and generic paroxetine, decreased in the order: branded ≈ E > A ≈ D > B ≈ C. Interestingly, the phosphorus contents in almost all generic paroxetine preparations were significantly lower than that of the branded variety. We also estimated the phosphorus contents for branded and generic amlodipine. As shown in Fig. 3, the phosphorus contents in some generic amlodipine preparations (a, d, g, h) were significantly higher than that of branded preparations, otherwise the values for other generics were significantly lower than that of branded samples (b, f, m).

**DISCUSSION**

We compared phosphorus contents among 22 different prescription medications and among branded and generic prescription medications that are frequently prescribed to HD patients in Japan, and found that: (1) the phosphorus contents varied among the prescription medications; (2) amlodipine (15 mg/tablet) and paroxetine (30 mg/tablet) was observed to have higher contents of phosphorus than other prescribed medications; and (3) the phosphorus contents in several generic medications were significantly different from the branded variety. These findings suggest specific information on the phosphorus content of prescribed medications used by HD patient should be made available to the dialysis community.

The amount of protein in the diet can be used to predict overall phosphorus intake, since organic phosphorus is usually bound to protein. The intestinal absorption of organic phosphorus is lower when it comes from animal sources (absorbed by about 50%) than from vegetable sources (absorbed by about 20%). However, inorganic phosphorus that is added to processed foods is almost entirely absorbed in the intestine. Because the amounts of inorganic phosphorus are often not reported in processed food labels, estimating the actual phosphorus intake for chronic kidney disease (CKD) patients is challenging and likely exceeds recommended values. Since there are physiological adaptations to counteract excessive phosphorus retention, hyperphosphatemia typically occurs only when patients reach CKD stages 4–5.\(^{11}\) In CKD stages 4–5, elevated phosphate levels were reported to be direct predictors of mortality.\(^{12}\) Current recommendations for phosphorus intake in CKD stages 3–5 are to reduce phosphorus intake to 800–1000 mg/d, in conjunction with use of phosphate binders if this is considered necessary.\(^{13}\) Although non-controlled evidence is not unanimous in this regard, the results of a recent large randomized controlled trial (RCT) indicated that a low-phosphorus diet can be used to decrease serum phosphorus and fibroblast
growth factor-23 levels.\textsuperscript{14} Another recent RCT showed that the use of this diet combined with the use of phosphate binders proved to be more effective than each of these approaches alone.\textsuperscript{15} Therefore, a reduction in the intestinal load of phosphorus is important for the prevention and treatment of CKD-mineral. However, this strategy is limited by patients' poor adherence to dietary restrictions and by the existence of hidden sources of phosphorus, as mention above. In addition to food containing phosphate-based additives, it was recently claimed that medications may contribute to the increase in the load of phosphorus, mainly present as an excipient. To identify medications that contain phosphorus as an excipient, we systematically screened medications that might potentially be prescribed for chronic oral therapies in HD patients.

In this study, phosphorus content ranged from 0.1 mg/tablet [Crestor\textsuperscript{®} (Rosuvastatin) 2.5 mg, Shionogi & Co., Ltd.] to 30.0 mg (Paroxetine\textsuperscript{®} 10 mg, GlaxoSmithKline) among the 22 different prescription medications examined (Fig. 1). We found that different manufacturers of the same drug might use different amounts of phosphorus in their drug formulations. In fact, Paroxetine 10 mg by “B” or “C” Pharmaceuticals had 21.4 mg or 21.5 of phosphorus compared with 30.0 mg in the branded formulation sold by Shionogi (Fig. 2). Furthermore, a 5 mg tablet of amlodipine made by Pfizer Inc. contained 15.1 mg of phosphorus, whereas “a” Pharmaceuticals product contained 19.1 mg and “b” Pharmaceuticals product contained 7.94 mg (Fig. 3). From these results, the phosphorus burden imposed by phosphorus-containing medications is probably minor in most patients, but a close examination of the issue suggests that the burden may be notable in some cases. For example, consider a HD patient with an otherwise restricted daily dietary phosphorus intake of 1000 mg in whom dialysis removes 1000 mg at each of the three weekly treatments (an average of about 400 mg/d). Of the remaining 600 mg, about 60% (360 mg) is, on average, potentially absorbable. If this hypothetical patient is receiving “A” Pharmaceutical’s 5 mg of amlodipine, and brand’s 10 mg of Paroxetine, the estimated absorbable phosphorus will be 10% higher (50 mg). Further, Sherman \textit{et al.} suggested that vitamin products as a supplement marketed for dialysis patients contained 37.7 mg of phosphorus. If this above patient is also receiving a vitamin such as Renavite, the estimated absorbable phosphorus will be 25% higher (90 mg).\textsuperscript{10}

Another way to consider the impact of this largely unrecognized source of dietary phosphorus is to consider it in terms of the number of phosphorus binding tablets required to block the absorption of an amount of dietary phosphorus equivalent to that in the phosphorus-containing drug. One tablet of sevelamer (800 mg) binds \(~25.5\) mg of phosphorus, whereas a cap-
sule of calcium acetate (667 mg) binds ~28.5 mg.10,16 Thus, simply to bind the phosphorus in the two tablets of paroxetine and amlodipine noted above, this unlucky patient would require additional doses of sevelamer or calcium acetate. Further, a significant fall off in adherence to binder therapy might occur as the pill burden increases.17,18 From these results, prescribing these medications to dialysis patients might be harmful in that they add substantially to an already problematic phosphorus burden. It is possible to determine whether phosphorus is present in a medication by examining its package label that is usually available online from the manufacturer, both branded and generic. In fact, amlodipine and paroxetine were found to contain additives such as calcium hydrogen phosphate, neither of the drugs contained phosphate. Therefore, differences in additives containing phosphorus might lead to the differences in the concentration of phosphorus between branded and generic medicines. However, phosphorus-containing medications might contain clinically inconsequential or substantial amounts of phosphorus, a difference that is not apparent from the information provided on the label. The Japanese Society for Dialysis Therapy (JSDT) recently proposed that when the mineral metabolism of the CKD patients is managed, the phosphorus, calcium and PTH should be controlled. In the future, companies should determine the phosphorus content of all of their phosphorus-containing drugs and provide that information in the label. An even better strategy would be to make prescribers aware that their prescribed medications may be high in phosphorus and the consequences of this fact. How the details of this might be carried out can best be worked out by drug companies and pharmacies with encouragement from the dialysis community and other interested parties.

Acknowledgements Kazuki Shimoishi and Makoto Anraku contributed equally to the work as co-first authors. Correspondence should be addressed to Toru Maruyama and Masaki Otagiri. These two authors contributed equally to this work.

Conflict of Interest All of the authors declare that there are no competing interests.

REFERENCES


