Investigation of Leftover Hyperphosphatemia Drugs in Hemodialysis Outpatients

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Currently, various hyperphosphatemia drugs are administered orally to hemodialysis patients in order to lower serum phosphorus levels. However, it is known that medication adherence is poor, possibly due to greater pill burden taken each time and their complicated schedules. Therefore, large amounts of unused hyperphosphatemia drugs are likely to be leftover. The increase in leftover prescribed drugs leads to the unnecessary elevation of medical care costs. To date, however, the available information on leftover hyperphosphatemia drugs in hemodialysis outpatients is limited. In this study, we performed an interview survey of medication adherence to hyperphosphatemia drugs among 60 hemodialysis outpatients and evaluated the cost of the leftover drugs. Thirty-four patients showed good adherence. On the other hand, 19 patients self-adjusted to take hyperphosphatemia drugs according to their daily diet. When assessing the serum phosphorus levels for these patients over the past year, the values often exceeded the targeted range (3.5–6.0 mg/mL). Furthermore, 35 patients kept hyperphosphatemia drugs at their home. When estimating the cost derived from leftover drugs using the bootstrap method, main distribution of drug cost was shown to be in the range of 2000 to 2500 yen. This drug cost seemed to in part reflect preparation for an emergency. A serious problem was that 14 patients had previous experience in discarding hyperphosphatemia drugs. This study suggested that more appropriate pharmaceutical care according to each patient’s situation is essential in improving phosphorus control in hemodialysis outpatients and in reducing the waste of medical resources.

Key words—hyperphosphatemia drug; hemodialysis outpatient; leftover drug; medication adherence; interview survey

INTRODUCTION

Hemodialysis patients lose almost completely the ability to excrete serum phosphorus, which leads to hyperphosphatemia. Hyperphosphatemia is closely related to bone mineral disorder (MBD) and serious cardiovascular events (CVEs) such as atherosclerosis, heart failure, and myocardial infarction.1) According to “The Japanese Society for Dialysis Therapy (JSDT) clinical practice guidelines for the management of secondary hyperparathyroidism (SHPT) in chronic dialysis patients” published in 2012,2) the target range for the serum phosphorus level is 3.5 to 6.0 mg/dL. It is generally understood that a regular hemodialysis regimen of once every three days together with diet control is insufficient to maintain serum phosphorus levels in the target range. In order to lower it, therefore, various types of hyperphosphatemia drugs have been developed and administered orally to hemodialysis patients along with the consumption of a low protein diet.3,4) A previous report by the JSDT revealed that the ratio of hemodialysis patients who did not receive one or two hyperphosphatemia drugs was approximately 25% in 2009.5) Currently, precipitated calcium carbonate (PC), sevelamer hydrochloride (SH), lanthanum carbonate hydrate (LC), bixalomer, (BX), ferric citrate hydrate (FC), sucroferric oxyhydroxide (SO) are commercially available as hyperphosphatemia drugs in Japan.6) However, it is often pointed out that medication adherence to these drugs among hemodialysis outpatients is poor due to the large number of drugs taken each time and/or their complicated schedules (immediately before meals, etc.).7–9)

Previously, we investigated the serum phosphorus levels of 331 outpatients undergoing hemodialysis at five general hospitals in Sapporo and found that the serum phosphorus levels in approximately 40% hemodialysis outpatients exceeded the target range, implying that poor medication adherence to hyperphosphatemia drugs was critical.10)

Poor medication adherence also results in unused drugs being leftover in the patient’s home and the
unnecessary elevation of pharmaceutical costs. Therefore, efforts to reduce leftover drugs have been introduced.\textsuperscript{11,12} The number of hemodialysis patients in Japan was approximately 340000 in 2018\textsuperscript{13} and the medical expenses for hemodialysis patients is well over 1 trillion yen each year in total. However, while leftover drugs among hemodialysis outpatients is recognized as prevalent,\textsuperscript{14} information on the costs associated with leftover hyperphosphatemia drugs is limited. Moreover, we often hear that hemodialysis patients self-adjust their use of hyperphosphatemia drugs in accordance with the contents of their daily meals. However, there are few reports describing the current status of this group of hemodialysis patients.

In this study, in order to assess the current situation regarding the above-mentioned issues in hemodialysis outpatients, we performed an interview survey of 60 outpatients undergoing hemodialysis at Sapporo Minami Ichijo Hospital and estimated drug costs accrued by leftover hyperphosphatemia drugs using the bootstrap method.

**METHODS**

This study was approved by the Ethics Committee of Sapporo Minami Ichijo Hospital and carried out in conformity with the Declaration of Helsinki. First approval was obtained for the preliminary survey about leftover hyperphosphatemia drugs in August, 2019. The protocol which included additional survey items (residual dose, discarding, etc.) was approved on December 16, 2019.

The purpose of this study and the protection of personal information were explained orally and by written document to the outpatients who underwent hemodialysis in August 2019 and received hyperphosphatemia drugs. Finally, sixty patients (male 39, female 21) participated in this study. Their ages, dialysis vintage, complication of diabetes, and employment status were checked by review of their medical records. Patient backgrounds are shown in Table 1. Serum phosphorus levels were also checked, if necessary. The questions regarding medication status are shown in Table 2. Interview survey was carried out during dialysis at the outpatient dialysis room.

The costs derived from leftover drugs for each patient was calculated as follows:

\[
\text{[drug cost]} = \text{[drug price]} \times \text{[one-day dose]} \times \text{[number of days]}
\]

*means the number of dosing days equivalent to

| Table 1. Patient Backgrounds |
|-----------------------------|
| Number of patients          | 60 |
| Age (years)                 | 65.3 ± 12.3\textsuperscript{*}(38–93) ** |
| Gender (male/female)        | 39/21 |
| Dialysis vintage (months)   | 112.2 ± 105.1\textsuperscript{*}(4–515) ** |
| Complication of diabetes    | 19 |
| In employment               | 15 |
| Median medication possession ratio | 1(0.63–1.24) ** |

* expresses the mean ± S.D. ** expresses the range.

| Table 2. Questions to 60 Hemodialysis Outpatients about Medication Status |
| Q1. Do you take prescribed hyperphosphatemia drugs according to direction? (multiple answers allowed) |
| A. I take them regularly and precisely. |
| B. I self-adjust to take them according to daily diet. |
| C. I forget to take them. |
| D. I hardly take them. |
| Q2. How often did you self-adjust or forget to take hyperphosphatemia drugs in last 7 days? (This question was done to the patients who answered B & C in Q1.) |
| A. 1 to 3 times |
| B. 4 to 6 times |
| C. More than 7 times |
| Q3. Are you keeping hyperphosphatemia drugs at your home? |
| A. Yes |
| B. No |
| Q4. How many hyperphosphatemia drugs are you keeping at your home? |
| A. Equivalent to 1 week supply |
| B. Equivalent to 2 to 4 weeks |
| C. Equivalent to 1 to 3 months |
| D. Equivalent to 4 to 6 months |
| E. Equivalent to more than 7 months or unidentified |
| Q5. Did you discard hyperphosphatemia drugs before? |
| A. Yes |
| B. No |

the amount of unused drugs.

The cost described here did not include the cost of discarded hyperphosphatemia drugs. Interval estimation of the cost of unused drugs was approached using the bootstrap method.\textsuperscript{15}

Statistical analysis was done using the free software package EZR (ver. 1.40, Jichi Medical University Saitama Medical Center, Saitama),\textsuperscript{16} Microsoft Excel 2010, and Statcel (OMS Publications, Higashiku-
RESULTS

Responses of Hemodialysis Outpatients to Five Questions Regarding Q1, 34 patients responded that they took hyperphosphatemia drugs precisely and regularly (Table 3). On the other hand, including multiple responses, 19 patients self-adjusted one-day doses of hyperphosphatemia drugs in accordance with the contents of their daily meals. Moreover, 10 patients had experience with forgetting to take hyperphosphatemia drugs. When asked “How often did you self-adjust or forget to take hyperphosphatemia drugs in last 7 days?”, 17 patients (65.4%) responded “1 to 3 times”, 3 patients (11.5%) responded “4 to 6 times”, and 6 patients (23.1%) responded “more than 7 times” (Q2, Fig. 1). With regard to the leftover hyperphosphatemia drugs at home, 35 patients (58.3%) responded “Yes” (Q3, Fig. 1). When asked “How many hyperphosphatemia drugs are you keeping at your home?”, 19 patients (54.3%) responded that they had a supply to last “about 1 week”. Five patients (14.3%) had sufficient for “2 to 4 weeks”, and 9 patients (25.6%) had sufficient for “1 to 3 months” (Q4, Fig. 1). When the 35 patients keeping hyperphosphatemia drugs at home were asked “Did you discard hyperphosphatemia drugs before?”, 14 patients (40%) responded “Yes” (Q5, Fig. 1).

Transition of Serum Phosphorus Levels among 19 Hemodialysis Outpatients Who Self-adjusted Taking Hyperphosphatemia Drugs Table 4 shows transition of serum phosphorus levels among 19 hemodialysis outpatients with self-adjustment. The patients whose serum phosphorus levels were maintained within the target range in the last twelve months were only 2 (10.5%). Six out of 19 patients had experience in discarding hyperphosphatemia drugs before. For comparison, serum phosphorus levels in 32 hemodialysis outpatients with good adherence were assessed (2 patients were excluded due to the lack of enough data). The number of patients keeping target levels all year was 9 (28.1%).

Effect of Patient Age on Non-adherence to Hyperphosphatemia Drugs Table 5 shows a comparison of three non-adherence factors (leftover drugs, self-adjustment, discarding) by age groups. The proportions of leftover drugs and self-adjustment seemed more prevalent in the age group of 51 to 60 years.

Effect of Combined Use of Hyperphosphatemia Drugs on Medication Adherence of Hemodialysis Outpatients Among 6 hyperphosphatemia drugs currently available, the most prescribed was LC (n = 27), followed by PC (n = 25) > FC (n = 18), SO (n = 18) > SH (n = 14) > BX (n = 4). The situation of medication adherence in one or multiple kinds of hyperphosphatemia drugs is presented in Table 6. LC was most used in single prescription. On the other hand, there was no one prescription of BX. In the two or three prescriptions of hyperphosphatemia drugs, distinctive pattern of combination was not observed (data not shown). There was a tendency that the proportion of good adherence was greater in the patients taking two or three kinds of hyperphosphatemia drugs than those taking one kind of hyperphosphatemia drug.

Estimation of Costs Associated with Leftover Hyperphosphatemia Drugs At the time of this interview survey, the prices of the 6 brand-name hyperphosphatemia drugs were SO 176.1 yen (250 mg tablet), LC 162.9 yen (250 mg tablet), FC 81.2 yen (250 mg tablet), BX 29.1 yen (250 mg capsule), SH 22.1 yen (250 mg tablet), and PC 6.3 yen (500 mg tablet). According to these prices, the highest cost associated with leftover drugs was calculated to be 37620 yen. In this case, the patient (70 years old with 5 years of hemodialysis treatment) kept 120 tablets of LC and 360 capsules of BX at home. Based on non-restored extraction using the bootstrap method, the most frequent distribution of the cost associated with leftover hyperphosphatemia drugs was shown to be in the range of 2000 to 2500 yen, which occupied 21.5% of the whole (Fig. 2). This range was followed by 2500 to 3000 yen (17.4%) and 1500 to 2000 yen (12.3%). The 2.5 and 97.5 percentiles were 0 and 4808.2 yen, respectively.
According to the Ministry of Health, Labour and Welfare, national medical expenses reached 42.6 trillion yen in 2018. Pharmaceutical costs totaled 5.5 trillion yen in all, occupying approximately 18% of total medical expenditure. In 2015, the Central Social Insurance Medical Council (CSIMC) took up the waste of medical resources due to leftover prescription drugs as a critical issue in the care of outpatients. The CSIMC also emphasized that the contribution of pharmacists to reusing leftover drugs could reduce medical expenses and improve medication adherence. In this context, there are several papers that estimated the value of leftover drugs.\(^{17,18}\)

In the present interview survey, the number of patients with good adherence was 34. Therefore, the ratio of non-adherence was approximately 43% (26 out of 60). This value was similar to that reported previously.\(^{19}\) Surprisingly, this interview survey revealed that the number of patients who self-adjusted the one-day dose of hyperphosphatemia drugs in accordance with daily meals became greater than that of patients who had experience in forgetting to take hyperphosphatemia drugs (Table 3). While self-adjustment of the one-day dose is considered intentional non-adherence, a missed dose is regarded as unintentional non-adherence. Therefore, an important aspect regarding the non-adherence to hyperphosphatemia drugs found in this interview survey was that inten-
Table 4. Transition of Serum Phosphorus Levels among 19 Hemodialysis Outpatients Who Self-adjusted Taking Hyperphosphatemia Drugs

| Patient No. | 2018 Sep. | 2018 Oct. | 2018 Nov. | 2018 Dec. | 2019 Jan. | 2019 Feb. | 2019 Mar. | 2019 Apr. | 2019 May | 2019 June | 2019 Jul. | 2019 Aug. |
|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 1          | 6.6       | 6.8       | 6.9       | 3.7       | 3.5       | 5.0       | 4.3       | 5.5       | 4.9       | 5.9       | 5.0       | 5.3       |
| 2          | 5.1       | 4.9       | 4.5       | 4.0       | 5.4       | 4.3       | 3.9       | 3.9       | 4.6       | 4.2       |           |           |
| 3          | 6.5       | 5.9       | 5.5       | 5.2       | 5.4       | 6.7       | 6.7       | 4.7       | 6.4       | 6.5       | 5.2       | 4.8       |
| 4          | 4.5       | 3.9       | 2.9       | 4.0       | 4.6       | 4.4       | 4.0       | 4.6       | 3.7       | 3.5       | 4.6       | 4.0       |
| 5          | 4.9       | 6.3       | 5.9       | 7.3       | 9.1       | 8.9       | 8.2       | 8.2       | 8.9       | 8.0       | 8.3       | 7.5       |
| 6          | 7.9       | 5.4       | 6.2       | 8.0       | 7.1       | 6.0       | 7.0       | 6.7       | 6.6       | 5.9       | 6.3       | 6.5       |
| 7          | 4.4       | 4.2       | 5.9       | 5.0       | 5.2       | 6.9       | 7.2       | 8.3       | 8.6       | 5.7       | 4.7       | 5.3       |
| 8          | 5.9       | 4.6       |           | 2.1       | 3.6       | 4.1       | 6.6       | 6.1       | 5.2       | 4.4       | 4.2       | 3.6       |
| 9          | 5.4       | 5.1       | 7.6       | 6.1       | 5.7       | 5.4       | 5.7       | 5.9       | 7.7       | 6.6       | 6.5       | 3.9       |
| 10         | 7.1       | 7.1       | 5.5       | 6.8       | 5.5       | 5.0       | 5.1       | 6.0       | 5.8       | 7.0       | 5.0       | 6.4       |
| 11         | 6.0       | 5.5       | 6.1       | 5.0       | 5.6       | 6.4       | 5.7       | 6.3       | 5.7       | 5.0       | 4.6       | 4.7       |
| 12         | 5.1       | 4.9       | 5.3       | 4.4       | 4.8       | 5.2       | 6.6       | 6.3       | 4.2       | 3.9       | 4.0       | 3.7       |
| 13         | 7.1       | 7.0       | 6.1       | 7.6       | 5.5       | 4.1       | 4.1       | 8.3       | 9.5       | 5.6       | 8.1       | 5.1       |
| 14         | 4.6       | 5.3       | 5.7       | 6.3       | 6.2       | 5.8       | 5.1       | 6.0       | 5.5       | 7.1       | 5.8       | 5.3       |
| 15         | 5.5       | 5.3       | 6.5       | 5.1       | 4.6       | 4.6       | 4.9       | 6.0       | 5.6       | 5.8       | 6.2       | 6.1       |
| 16         | 7.6       | 6.5       | 6.9       | 7.4       | 7.0       | 5.2       | 6.5       | 6.4       | 7.1       | 7.1       | 6.9       | 6.1       |
| 17         | 5.8       | 5.8       | 5.2       | 5.3       | 5.5       | 5.4       | 5.1       | 4.9       | 5.7       | 5.3       | 5.0       | 6.5       |
| 18         | 7.0       | 7.1       | 7.9       | 8.3       | 7.3       | 6.8       | 5.7       | 5.4       | 6.5       | 6.8       | 5.6       | 7.5       |
| 19         | 3.4       | 3.6       | 3.8       | 2.9       | 3.0       | 3.6       | 4.9       | 4.5       | 6.9       | 4.6       | 3.2       | 3.0       |

The value underlined exceeds the target range (3.5–6.0 mg/dL) of serum phosphorus level.

Table 5. Comparison of Three Non-adherence Factors among Ages

| Age | Participants | Leftover | Self-adjustment | Discarding |
|-----|--------------|----------|----------------|------------|
| ≤ 50 | 7            | 2(28.6%) | 2(28.6%)       | 0          |
| 51–60 | 10          | 8(80.0%) | 5(50.0%)       | 3(30%)     |
| 61–70 | 23         | 14(60.9%) | 8(34.8%)       | 7(30.4%)   |
| 71–80 | 11         | 5(45.5%) | 1(9.1%)        | 1(9.1%)    |
| ≥ 81  | 9           | 6(66.7%) | 3(33.3%)       | 3(33.3%)   |
| Total | 60         | 35(58.3%) | 19(31.7%)      | 14(23.3%)  |

Table 6. Effect of Multiple of Kinds of Hyperphosphatemia Drugs Prescribed on Medication Adherence in Hemodialysis Outpatients

| Number of kind of hyperphosphatemia drugs prescribed | Number of patients |
|-----------------------------------------------------|--------------------|
| Total                                               |                    |
| Good adherence                                     | 12(48%)            |
| Non-adherence                                      | 13(52%)            |
| One                                                |                    |
| Good adherence                                     | 12(48%)            |
| Non-adherence                                      | 13(52%)            |
| Two                                                |                    |
| Good adherence                                     | 16(64%)            |
| Non-adherence                                      | 9(36%)             |
| Three                                               |                    |
| Good adherence                                     | 6(67%)             |
| Non-adherence                                      | 3(33%)             |
| Four                                                |                    |
| Good adherence                                     | 0                  |
| Non-adherence                                      | 1(100%)            |

Tional non-adherence was more frequent than unintentional non-adherence. It can be said that this is a characteristic of hemodialysis outpatients. In order to know whether serum phosphorus levels are well controlled in these patients, we checked their monthly clinical data over the previous year. As shown in Table 4, the number of patients whose serum phosphorus levels were maintained within the target range all year was only 2 out of 19 (10.5%). In many cases, self-adjustment of the one-day dose led to poor, often extremely poor, control of serum phosphorus levels. Therefore, pharmacists are required to positively admonish such patients to refrain from self-adjustment. When investigating serum phosphorus levels in the patients with good adherence, the portion of patients whose serum phosphorus levels were kept within the target range all year remained 28.1%,
indicating that the control of serum phosphorus levels is
not easy even if patients take hyperphosphatemia
drugs precisely and regularly.

As shown in Table 5, leftover drugs and self-ad-
justment seemed prevalent among patients aged 51 to
60 years. In a separate study, we found that the con-
trol of serum phosphorus levels was significantly
worse in the patients under 60 years old than in the
patients over 61 years old (unpublished data). Although the number of patients in this study was
small, it is likely that the present result reflects the
results obtained in the separate study. Non-adherence
among patients aged 51 to 60 years may attribute par-
tially to that they are working generation. It is known
that greater pill burden causes poor medication ad-
herence of patients in various disease including
hemodialysis.9,20,22 In this study, number of hyper-
phosphatemia drugs taken in a day widely ranged
from 2 to 21. However, the meaningful effect of
greater pill burden on the medication adherence to
hyperphosphatemia drugs was not evident (data not
shown), being consistent with a previous report.23 On the other hand, as shown in Table 6, medication
adherence was better in the patients taking two or
three kinds of hyperphosphatemia drugs than in those
taking one kind of it. It is possible that patient’s
awareness about progression of hyperphosphatemia
and about an enhanced risk of fatal CVEs improved
medication adherence to the therapeutic agents in
these groups. Further survey is required to assess this
possibility.

In this interview survey, leftover hyperphosphat-
emia drugs were reported by more than half of the
patients. It was difficult to ask all patients about the
reasons for the high proportion of leftover drugs. Ac-
cording to the responses from a few patients, we sus-
pected that a portion of the leftover hyperphospha-
temia drugs was kept in preparation for not being able
to visit hospital due to a natural calamity such as an
earthquake or typhoon. This type of leftover drug is
acceptable as it is inevitable that such situation will
arise. The analysis using the bootstrap method rev-
ealed that the cost associated with the leftover drugs
was the greatest in the range from 2000 to 2500 yen
(Fig. 2). When considering the prices of hyper-
phosphatemia drugs, this cost may reflect the fact that
the amounts of leftover dugs in more than half of the
patients was a store lasting about 1 week (Q4, Fig.
1). Accordingly, leftover drugs in the range of 2000
to 2500 yen might be in part considered as emergency
preparations. In this connection, it has been reported
that elderly patients accumulate surplus drugs as
emergency house-fold drugs.24 The maximum cost of
leftover hyperphosphatemia drugs calculated in this
study was 37620 yen in a patient receiving LC chewa-
table tablet and BX capsule. There was a possibility that
the hardness of LC chewable tablets and the size of
BX capsule (major axis: 19 mm) made them unsuita-
bly to this patient. There is a recent paper demonstra-
ing that appropriate replacement of a hyper-
phosphatemia drug to another one can lead to the reduction of total medical costs among hemodialysis patients. Although the reason for preferentially prescribing BX capsule to this patient is unclear, replacement of BX capsule should be considered.

One issue that cannot be overlooked is the discarding of hyperphosphatemia drugs reported by 14 patients (Q5, Fig. 1). Although we here could not calculate the actual costs due to discarding hyperphosphatemia drugs, the accumulated waste of medical resources is considered significant among hemodialysis outpatients. These patients should be provided with information on the reuse of hyperphosphatemia drugs repeatedly.

In conclusion, although the scale of this interview survey was small, it was found that medication adherence to hyperphosphatemia drugs among hemodialysis outpatients is relatively poor and that leftover hyperphosphatemia drugs due to intentional non-adherence is quite widespread. Therefore, pharmacists should provide more appropriate pharmaceutical care according to each patient’s situation in order to improve phosphorus control in hemodialysis outpatients and decrease the waste of medical resources.

Conflict of Interest The authors declare no conflict of interest.

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