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Hypokalemia and Related Symptoms by Yokukansan in Patients with Behavioral and Psychological Symptoms of Dementia (BPSD): A Retrospective Study of Elderly Inpatients

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Abstract

Yokukansan is a Japanese traditional medicine that has been used for behavioral and psychological symptoms of dementia. Although the efficacy of Yokukansan have been reported, few studies have focused on its adverse effects. In this study, the adverse effects in hospitalized patients treated with Yokukansan were evaluated retrospectively and compared with those listed in the Japanese Adverse Drug Event Report database from the Pharmaceutical and Medical Device Agency. A total of 21 patients who were prescribed Yokukansan at Rakuwakai Otowa Hospital from April 2013 to September 2013 were registered as subjects for this study. Patient profiles, such as age, gender, serum potassium levels, AST and ALT, were evaluated. Serum potassium levels decreased significantly from 4.3 ± 0.6 mEq/L to 3.6 ± 0.4 mEq/L after treatment with Yokukansan, and 61.9% of the patients demonstrated hypokalemia. In addition, the pre-treatment serum potassium levels were associated with the induction of hypokalemia by Yokukansan. The onset date of hypokalemia was varied from 2 to 1,154 days in Otowa data and from 2 to 1,533 days in JADER data. In terms of the number of days to the onset of hypokalemia, there was no significant difference between the Rakuwakai Otowa Hospital and results of Japanese Adverse Drug Event Report database. It is necessary to pay attention to patients during the treatment with Yokukansan, even if treatment period was long term.

Keywords: Yokukansan; Behavioral and Psychological Symptoms of Dementia (BPSD); Hypokalemia; Pseudohyperaldosteronism; Japanese Adverse Drug Event Report (JADER)

Introduction

Dementia is a syndrome that hinders daily and social life due to the chronic decline of mental function. It is difficult that patients live without any care during the last stage of dementia due to dysmnesia and disorientation. Therefore, caregiver burden is also serious problem. In particular, behavioral and psychological symptoms of dementia (BPSD), such as delusion, hallucination, irritability and aggression, are the major factors that increase caregiver burden.

Yokukansan is a Japanese traditional medicine formula derived from Yi-Gan San in traditional Chinese medicine. Yokukansan consists of 7 herbal medicines: Bupleuri radix, Glycyrrhizae radix, Cnidii rhizoma, Angelicae radix, Atractylodis lancea rhizome, and Poria, Uncariae ramulus cum uncis. It is prescribed to treat neurosis, insomnia, nighttime crying, emotional distress and agitation in children. In recent years, Yokukansan has been used for BPSD or other mental symptoms [1-5]. Iwasaki et al. have conducted a 4-week randomized controlled trial to evaluate the effect of Yokukansan in dementia patients, and they reported that BPSD was significantly improved [4]. In a 4-week randomized cross-over study, with and without Yokukansan, Mizukami et al. have also reported that BPSD improve significantly without rebound due to withdrawal [1]. Monji et al. have compared the effect of Yokukansan with patients treated with sulpiride alone and patients treated with sulpiride and Yokukansan, and BPSD significantly improved in the patients treated with sulpiride and Yokukansan [6]. In a study targeting patients who took donepezil, Okahara et al. have reported that Yokukansan decreases BPSD, in addition to decreases by donepezil [7]. Matsuda et al. have conducted a systematic review and meta-analysis using these randomized controlled trials [8]. The Ministry of Health, Labour and Welfare forecasted that the number of dementia patients would continue increasing to over 7 million people in 2025. Therefore, the effects and adverse events of Yokukansan on BPSD will become more important. In contrast, adverse effects of Yokukansan have been reported to the Pharmaceuticals and Medical Devices Agency (PMDA). In a serious case report of PMDA in 2009, a pneumonitis patient died. Based on this report, Japanese drug labeling of Yokukansan was revised in 2010, and pneumonitis was described as a serious side effect of Yokukansan. However, 3 additional fatal cases were reported from 2011 to 2012. In addition to pneumonitis, 13 cases of hypokalemia and 26 cases of pseudoaldosteronism have been reported as adverse effects of Yokukansan from 2006 to 2012.

Although the adverse effects of Yokukansan were often seen as a problem, few investigations focusing on these adverse effects have been performed [9]. Yokukansan consists of 7 herbal medicines. Component of Yokukansan, which induce hypokalemia and pseudoaldosteronism, was considered to be Glycyrrhizae radix. Glycyrrhizae radix contained glycyrrhizin (GL) as main component and it was metabolized to be 3-monoglucuronyl-glycyrrhetinic acid (3MGA) and glycyrrhetinic acid (GA) by intestinal bacteria. Both 3MGA and GA inhibit 11 β-hydroxysteroid dehydrogenase in renal tubules and induce pseudoaldosteronism and hypokalemia [10].

For effective and safety treatment with Yokukansan, information about its adverse events is important. In this study, we retrospectively surveyed the adverse events experienced by hospitalized patients treated with Yokukansan, and the results were compared with data from the Japanese Adverse Drug Event Report database (JADER) to clarify the safety of Yokukansan. The results of our investigation should help to develop safety protocols and determine the proper use of Yokukansan.

Methods and Patients

Patients

A total of 21 patients who were prescribed Yokukansan for BPSD at Rakuwakai Otowa Hospital (Kyoto, Japan) from April 2013 to September 2013 were registered as subjects for this study. Some patients were excluded for this investigation, according to the following criteria:

1. Patients who were administered drugs that directly affect serum potassium levels, such as potassium chloride, potassium L-aspartate and calcium polystyrene sulfonate jelly during treatment with Yokukansan.
2. The start date of the Yokukansan treatment was unknown.
3. Serum potassium levels before or after the Yokukansan treatment were not available.

All clinical data were obtained from the patients' medical records and retrospectively analyzed.

Ethical statement

This study was performed in accordance with the Declaration of Helsinki, as well as the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The study was approved by the ethics committees of Rakuwakai Otowa Hospital and of Kyoto Pharmaceutical University.

Measured outcomes

We collected data for gender, age, height, weight, types of dementia, Yokukansan dose and the reasons for administration as the basic patient profiles. In addition, hematologic parameters, such as serum potassium levels, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine (Cr), blood urea nitrogen (BUN) and uric acid (UA), were also collected before and after the start of Yokukansan treatments. The latest parameters before the Yokukansan treatment were defined as "pretreatment data", and the highest (in AST, ALT, Cr, BUN and UA) or lowest data measurements (in serum potassium) after the Yokukansan treatment were defined as "posttreatment data." When the serum potassium levels reached a level below 3.5 mg/dL (based on the normal value), hypokalemia was diagnosed.

Statistical Analysis

The serum potassium levels were assessed with a paired t-test, and the Wilcoxon signed-rank test was performed to assess the AST, ALT, Cr, BUN and UA values. The difference of serum potassium levels between pretreatment and post treatment were determined using Student's t-test (Figure 1). The differences of pretreatment serum potassium between the patients with or without hypokalemia were determined using Student's t-test (Figure 2). In addition, some statistical analyses were performed to examine the correlations between the changes in the serum potassium levels and patient profiles. Student's t-test was conducted to determine the correlations between the changes in serum potassium levels and patient gender (Figure 3A). One-way analysis of variance (ANOVA) was performed for the prescribed dosage (Figure 3C). For age, body surface area (BSA) and pretreatment values of AST, ALT, Cr, BUN and UA, least-squares linear regression analyses were conducted (Figures 3 and 4). The significance level for each statistical analysis was determined $p < 0.05$.

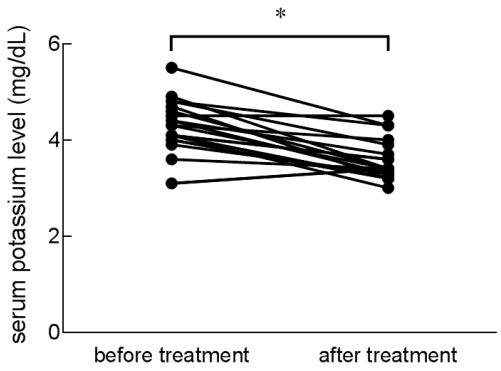

Figure 1: Serum potassium levels pre- and posttreatment of Yokukansan at Rakuwakai Otowa Hospital.

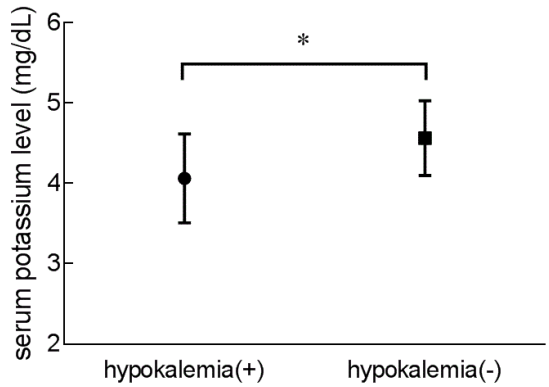

Figure 2: Serum potassium levels at pretreatment of Yokukansan. Hypokalemia (+) indicates the patients group in which the serum potassium levels decreased to the level of hypokalemia. Hypokalemia (-) indicates the patient group in which hypokalemia was not induced.

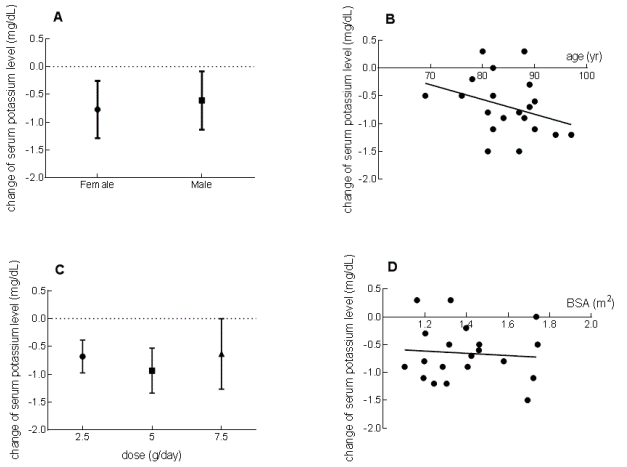

Figure 3: Relationship between the change in the serum potassium level and the patient characteristics: (A) sex, (B) age, (C) dose of Yokukansan, and (D) body surface area.

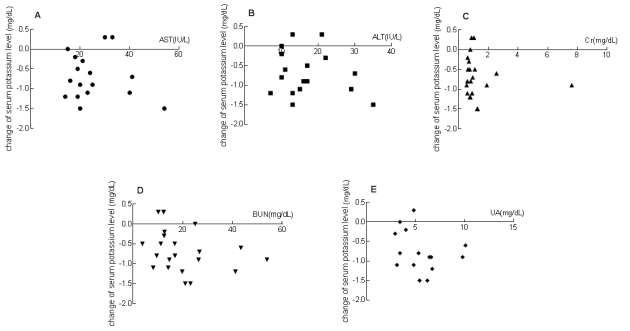

Figure 4: Relationship between the change of serum potassium level and the hematologic test values: (A) aspartate aminotransferase, (B) alanine aminotransferase, (C) serum creatinine, (D) blood urea nitrogen, (E) uric acid.

Analyses of the profiles of patients suffering from adverse events related to Yokukansan in JADAR

In this study, adverse events related to Yokukansan were extracted from the JADAR database using methods similar to those used in our previous studies [11,12]. The database was queried using the keyword "Yokukansan" as a primary suspected drug (http://info.pmda.go.jp). The cases reported from 2004 to 2014 were obtained from the JADAR database. Each case report was manually downloaded from the web site. The data regarding adverse events and patient background were collected. Finally data from the 86 patients were found, and 28 reports were excluded because the patient diseases were not dementia or were not described. Finally, 58 reports were included in this analysis. Patient profiles, such as the date of the report, gender, age, dosage, start date of Yokukansan treatment and occurrence dates of the events, were also manually collected from the web site and added to our original datasheets for the subsequent analyses. Male-female ratio was compared between Otowa data and JADER data by chi-square test (Figure 5). In addition, occurrence day of hypokalemia was compared between Otowa data and JADER data using Student's t-test.

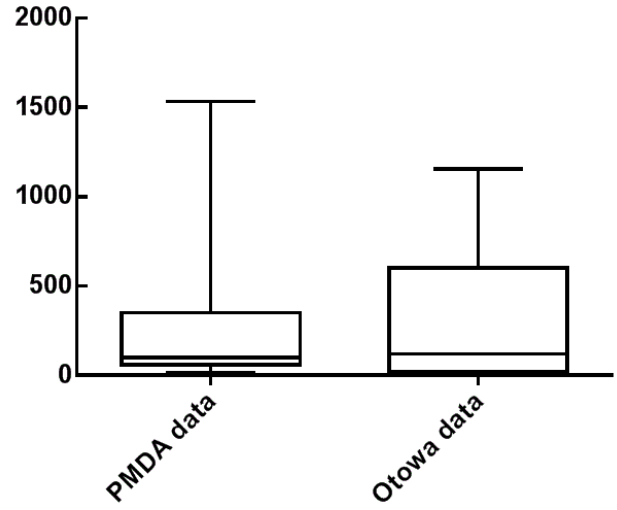

Figure 5: Comparison of the number of days until hypokalemia appeared between the JADER and Rakuwakai Otowa Hospital.

Results

Adverse events of the hospitalized patients treated with Yokukansan

We identified a total 21 patients (11 women and 10 men) who were administered Yokukansan for BPSD in Rakuwakai Otowa Hospital. All patient demographics and clinical characteristics are summarized in Table 1. The patient age was 84.5 ± 6.2 years (mean ± SD), and 66.7% of the patients were in the 80s. More than half of patients (n=11) had been taking the usual dose (7.5 g/day). The most common type of dementia was Alzheimer's disease (n=10), and the type of dementia was not described in the medical records of 4 patients. Although there were 5 patients who were not diagnosed with dementia, their reasons for taking Yokukansan were symptoms similar to BPSD, such as agitation and night wandering. The reasons for Yokukansan administration were agitation (n=6) and night syndromes, such as night wandering (n=5). Other reasons included delirium (n=4), anxiety (n=3), aggressive remarks (n=1) and hallucination (n=1), which are known as symptoms of BPSD. In many cases, the patients had more than 2 symptoms of BPSD.

Figure 1 shows the changes in the serum potassium levels during the Yokukansan treatments. The serum potassium level significantly decreased from 4.3 ± 0.6 mEq/L (mean ± SD) to 3.6 ± 0.4 mEq/L ($p < 0.05$), and hypokalemia emerged in 13 patients (61.9%) after treatment with Yokukansan. The change in the serum potassium level was -0.7 ± 0.5 mEq/L (mean ± SD), and the maximum decrease was 1.5 mEq/L. As described previous reports [10], it was considered that the decrease of serum potassium level was caused by 3MGA and GA of Glycyrrhizae radix, a main component herb of Yokukansan.

	Number of patients	(%)
Gender		
Male	10	47.6
Female	11	52.4
Age (years old)		
60-69	1	4.8
70-79	3	14.3
80-89	14	66.7
90-99	3	14.3
Diagnosis		
Alzheimer's disease	10	47.6
Lewy body	2	9.5
Dementia	4	19.0
Other	5	23.8
Dose of Yokukansan		
2.5 g/day	5	23.8
5.0 g/day	5	23.8
7.5 g/day	11	52.4
Reason for Yokukansan administration		
Agitation	6	28.6
Night syndrome	5	23.8
Delirium	4	19.0
Other	13	47.6

Table 1: Characteristics of patients in Rakuwakai Otowa Hospital.

Figure 2 shows the serum potassium levels before the Yokukansan treatments. The pre-treatment mean serum potassium levels were compared between the patients who developed hypokalemia and the patients who did not develop hypokalemia after the treatment. In patients who developed hypokalemia during the treatment, the mean serum potassium levels before Yokukansan treatment was 4.1 ± 0.6 mEq/L. In contrast, in patients who did not develop hypokalemia, the mean serum potassium levels before the Yokukansan treatment was 4.6 ± 0.5 mEq/L. The between-group difference was statistically significant ($p < 0.05$).

In terms of the clinical parameters for hepatic function, AST changed from 25.4 ± 10.9 IU/L to 36.7 ± 36.6 IU/L (Figure 6A) and ALT changed from 17.0 ± 8.0 IU/L to 23.2 ± 15.7 IU/L (Figure 6B) during the treatment. These changes were statistically significant. In terms of the clinical parameters for renal function, the serum Cr level changed from 1.3 ± 1.5 mg/dL to 1.5 ± 1.7 mg/dL (Figure 6C), BUN changed from 20.2 ± 12.5 mg/dL to 28.6 ± 20.1 mg/dL (Figure 6D), and UA changed from 5.6 ± 2.1 mg/dL to 5.6 ± 1.9 mg/dL (Figure 6E). The changes in serum Cr and BUN were significant ($p < 0.05$), while the change in UA was not significant (p=0.75).

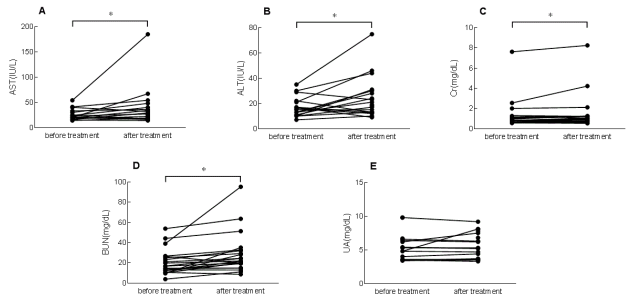

Figure 6: The values of hematologic testing pre- and posttreatment of Yokukansan (A) AST, (B) ALT, (C) serum creatinine, (D) BUN, and (E) UA.

Next, the relationship between demographics and changes of clinical parameters were evaluated (Figures 4 and 5). There was no significant difference between males and females in changes of the serum potassium level. The mean serum potassium level changes were -0.6 ± 0.5 mEq/L in males and -0.8 ± 0.5 mEq/L in females (Figure 3A). There was no correlation between the change in serum potassium levels and age (Figure 3B).

In addition, the dose of Yokukansan did not affect the change in the serum potassium levels (Figure 3C). There was no correlation between the change in the serum potassium levels and BSA (Figure 3D). Figure 5 shows the individual plots of the change in the serum potassium levels and the hematologic parameters.

Linear regression analysis suggested that there were no significant correlations between the change in the serum potassium levels and the AST, ALT, Cr, BUN and UA values.

Adverse events of Yokukansan reported in the JADER database

A total of 58 cases related to Yokukansan-related adverse events were reported in the JADER database. The patient profiles of these cases are summarized in Table 2.

Nineteen patients were male (32.8%), and 39 patients were female (67.2%). The mode of the age range was 80s years old (56.9%). These characteristics were similar to those of patients in Rakuwakai Otowa Hospital. Among the 58 patients, 17 patients had Alzheimer's disease and 6 had dementia with Lewy bodies. The most frequently reported adverse event was hypokalemia, and pseudohyperaldosteronism was second.

As shown in Table 3, there was no significant difference of male-female ratio between JADER and Otowa hospital. The onset date of hypokalemia was varied from 2 to 1,154 days in Otowa data and from 2 to 1,533 days in JADER data (Figure 5).

Table 4 summarized onset data of adverse events of Yokukansan in JADER data. In addition, Figure 6 shows comparison of the onset days of hypokalemia following Yokukansan administration between the Rakuwakai Otowa Hospital and JADAR database results.

There was no significant difference between the Rakuwakai Otowa Hospital and JADAR database results.

	Number of patients	(%)
Gender		
Male	19	32.8
Female	39	67.2
Age (years old)		
60-69	4	6.7
70-79	16	27.6
80-89	33	56.9
90-99	5	8.6
Diagnosis[a]		
Alzheimer's disease	17	47.6
Dementia with Lewy bodies	6	9.5
Vascular dementia	1	19.0
Frontotemporal dementia	1	23.8
Unknown	33	56.9
Type of side effects		
Hypokalemia	23	39.7
Pseudohyperaldosteronism	10	17.2
Interstitial pneumonia	8	13.8
Heart disease	7	12.1
Hepatopathy	5	8.6
Other	20	34.5
Unknown or not described	8	

Table 2: Characteristics of patients reported in the JADER database.

	Male	Female
JADER	4	19
Otowa Hospital	5	8

Table 3: Comparison of the number of male and female hypokalemia cases between the JADER database and Otowa Hospital (chi-squared test) χ^2=0.16.

	Number of patients
< 1 month	15
1-3 months	12
3-6 months	13
6-1 year	5
< 1 year	5

Table 4: Occurrence dates of adverse events due to Yokukansan reported in the JADER database.

Discussion

Many groups have reported the effects of Yokukansan, and they have revealed a key component of the contained herbal medicines. It has been previously reported that effects of Yokukansan are mainly derived from action on the 5-HT1A receptor by Uncariae uncis cum ramulus [13,14], in addition to GABAA receptor activities [15]. However, Yokukansan contains Glycyrrhizae radix, which includes GA as a main component. GA increases cortisol by inhibiting 11 β-hydroxysteroid dehydrogenase. Cortisol acts on the glucocorticoid receptor at the renal tubule and increases the excretion of potassium and the reabsorption of sodium. Therefore, some adverse effects events, such as hypokalemia and pseudohypoaldosteronism were induced [16,17].

Although the adverse effects of Yokukansan were often viewed as a problem, few studies have focused on these adverse effects. In this study, we evaluated serum potassium levels after Yokukansan treatments. The average decrease in serum potassium levels was -0.7 mEq/L in this study (Figure 1), and our result is not conflict with those of previous reports [18]. This adverse effect might be induced by 3MGA and GA of Glycyrrhizae radix, main component of Yokukansan. It was shown that a low serum potassium level before treatment was a risk factor for hypokalemia (Figure 2). A statistically significant difference in the serum potassium level before treatment was found between the patients who developed hypokalemia and the patients who did not develop hypokalemia. These results indicated that careful attention is needed when administering Yokukansan to patients whose serum potassium levels are close to the lower limit of the normal range.

As shown in Figure 1, 61.9% of the patients demonstrated hypokalemia after treatment with Yokukansan. This ratio was considerably higher than that estimated in previous research [2,3,7,8,18]. Several reasons for these differences were postulated. In one case, the follow-up period was postulated as a potential factor. The follow-up period of the patients in this study was longer than that of other studies. The longest follow-up period in this study was 1,659 days, whereas 78 weeks (546 days) was the longest follow-up in other studies. Indeed, in 4 cases, hypokalemia occurred more than 78 weeks after the start of Yokukansan treatment. In one case, hypokalemia occurred 1,154 days after the start of Yokukansan treatment. Therefore, it was suggested that medical staffs must be careful of the potential of hypokalemia during Yokukansan treatment, regardless of the administration period.

As shown in Figure 6, AST, ALT serum creatinine and BUN were significantly changed after the Yokukansan administration. However, the result was considered to be equivocal. In one case, all clinical parameters were severely worsened during the Yokukansan treatments. It was considered that multiple organ failure had developed in this patient and that the changes were not induced by the Yokukansan treatment. In other cases, prominent changes of AST, ALT serum creatinine and BUN were not detected. Although the adverse effects of Yokukansan in special populations should be evaluated in future studies, the hepatic and renal adverse effects of Yokukansan are likely rare.

Recently, adverse effects of Yokukansan were reported in diabetic patients and patients with chronic renal failure [5,19]. However, the risk factors for decreased serum potassium levels could not be detected in this study (Figure 3). In addition, the dose of Yokukansan was not related to the decreased serum potassium level (Figure 3C). There are large dispersions in these clinical parameters among patients in this study. The pathophysiological futures of the patients were complicated, which may be one of the reasons that risk factors were not detected in this study. In particular, A low dose of Yokukansan (2.5g/day) was able to decrease serum potassium levels (Figure 3C). Rate of serum potassium change were not significantly different between dosage groups. It is possible that Yokukansan can decrease serum potassium levels even if low dose. Recently, urinary and/or plasma 3MGA is thought as marker for pseudoaldosteronism by Glycyrrhizae radix [10]. 3MGA is one of main components of Yokukansan. In future, it is expected to find appropriate markers to detect the adverse effects of Yokukansan.

Pseudohypoaldosteronism, which is induced by 3MGA and GA and a severe adverse effect of Yokukansan, was observed in one patient of the Rakuwakai Otowa Hospital. This patient demonstrated hypokalemia 5 years after the first administration of Yokukansan, and the Yokukansan treatment was discontinued one week after the detection of pseudohypoaldosteronism. After the discontinuation of Yokukansan and the administration of potassium chloride, the symptoms of pseudohypoaldosteronism improved immediately. It is possible that pseudohypoaldosteronism was developing for 5 years, which is an extremely long period. These results indicate that it is important to pay close attention to a patient's clinical data, even if the Yokukansan treatment is long-term.

In comparing the data of Rakuwakai Otowa Hospital with the JADAR database (Tables 2 and 4; Figure 5), the patient age distribution and onset days were similar. However, the reported number of pseudohyperaldosteronism and hypokalemia was 10 and 23, respectively, in the JADAR database. In the data of Rakuwakai Otowa Hospital, the reported number of pseudohyperaldosteronism and hypokalemia was 1 and 13, respectively. Compared to the data of Rakuwakai Otowa Hospital, the reported number of hypokalemia in the JADAR database seems small. Based on the ratio in the study of Rakuwakai Otowa Hospital, more than 100 cases should be reported in the JADAR database. It is possible that there is reporting bias in the JADAR database.

This study has some limitations. First, concomitant drugs that affect serum potassium were not excluded completely. Although the patients who received potassium chloride, potassium L-aspartate and calcium polystyrene sulfonate jelly were excluded in this study, other drugs, such as the angiotensin II receptor antagonists or angiotensin-converting-enzyme inhibitor, were not considered. Elderly patients often use multiple drugs, and the effects of concomitant drugs should be considered in large studies. Second, the patient profiles were not followed repeatedly because of the retrospective nature of the study. Prospective studies should be designed to clarify more important information about the adverse events associated with Yokukansan.

Conclusion

The present study showed that serum potassium levels decreased regardless of the dose and treatment period of Yokukansan and that pseudohypoaldosteronism developed in severe cases. It is necessary to pay attention to patients during the treatment with Yokukansan, even if treatment period was long term. However, we could not clarify the risk factors associated with adverse events following Yokukansan treatment. A prospective study with enough number of patients is needed to determine the appropriate use of Yokukansan for BPSD.

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