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Risk Factors for Pseudoaldosteronism with Yokukansan Use: Analysis Using the Japanese Adverse Drug Report (JADER) Database

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Yokukansan is a Kampo formula that is commonly used by the elderly because it is expected to improve peripheral symptoms of dementia and delirium. However, side effects from its use are frequently reported in the elderly. In particular, pseudoaldosteronism caused by the licorice contained in yokukansan leads to hypertension, hypokalemia, and muscle weakness, which may result in death. This study aimed to identify the risk factors of pseudoaldosteronism with yokukansan use. Using cases reported in the Japanese Adverse Drug Report (JADER) database, the reporting odds ratio (ROR) was calculated and compared to assess the risk of pseudoaldosteronism for each licorice-containing Kampo formula. We also analyzed the risk factors for pseudoaldosteronism in patients taking yokukansan. Yokukansan (ROR 2.4, 95% confidence interval (CI) 1.9–2.8; p < 0.001) had a higher risk of pseudoaldosteronism than that of other licorice-containing Kampo formulas. Furthermore, the results of a logistic regression analysis in patients taking yokukansan showed that the licorice dose (OR 1.5, 95% CI 1.2–2.0; p < 0.01), dementia (OR 1.9, 95% CI 1.6–4.9; p < 0.001), low body weight (<50 kg, OR 2.2, 95% CI 1.1–3.5; p = 0.034) were risk factors for pseudoaldosteronism. Although not significant, treatment with loop diuretics (OR 1.8, 95% CI 0.98–3.5; p = 0.059) tended to increase the risk of pseudoaldosteronism. In summary, patients must understand the risk factors when considering taking yokukansan and reduce the licorice dose they consume.

Key words yokukansan; Japanese Adverse Drug Report; pseudoaldosteronism; kampo formula

INTRODUCTION

Yokukansan was originally used for irritability and crying at night in children. In recent years, it has been reported to be effective in improving the peripheral symptoms of dementia and delirium1–2) and has been frequently used in the elderly. However, side effects are commonly reported in the elderly, including many reports of pseudoaldosteronism.3) Pseudoaldosteronism causes hypertension, hypokalemia, muscle weakness, and death in some cases. Therefore, effective side effect management of pseudoaldosteronism is important for patients taking licorice-containing drugs.3,5)

The licorice dose and hypoalbuminemia are thought to be risk factors for pseudoaldosteronism when taking yokukansan.3) However, there are few previous studies on the development of pseudoaldosteronism when taking yokukansan, and only single-center cohort studies and case reports have been published.3,6) Therefore, there is a lack of sufficient evidence on this topic.

The Japan Adverse Drug Report (JADER) is a database that collects information on adverse drug reaction cases reported voluntarily to the Pharmaceuticals and Medical Devices Agency (PMDA). Some previous studies have used the JADER to investigate rare side effects.7,8) To perform an analysis using a larger number of cases, the JADER was used in this study.

Therefore, we conducted an analysis using the JADER database to identify undetected risk factors for pseudoaldosteronism when taking yokukansan. Based on the results, we provide recommendations on how to avoid pseudoaldosteronism when taking yokukansan.

MATERIALS AND METHODS

Large-Scale Database Analysis and Patient Selection

Data recorded from April 2004 to June 2019 in the JADER database were downloaded from the PMDA website (http://www.pmda.go.jp/). The JADER dataset consists of four tables containing the following information: 1) patient information such as gender, age, and body weight; 2) patient drug information; 3) patient adverse events and outcomes, etc.; and 4) medical history, primary illness, etc. These four tables were integrated using the FUND E-Z Backup Archive (FUND E-Z Development Corporation, NY, U.S.A.).

The cases were classified into groups (a) to (d) as follows: (a) individuals who received the drugs and exhibited pseudoaldosteronism; (b) individuals who received the drugs but did not exhibit pseudoaldosteronism; (c) individuals who did not receive the drugs and exhibited pseudoaldosteronism; and (d) individuals who did not receive the drugs and did not exhibit pseudoaldosteronism. The reporting odds ratio (ROR) was calculated using the following calculation method. A signal was considered detected when the lower limit of the 95% confidence interval (CI) of the ROR exceeded one.

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ROR = \frac{(a/b)}{(c/d)}
\]

95% CI = \exp \left[ \log(\text{ROR}) \pm 1.96 \sqrt{ \frac{1/a}{a} + \frac{1/b}{b} + \frac{1/c}{c} + \frac{1/d}{d} } \right]

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We selected 23 Kampo licorice-containing formulas for which more than 100 cases had been reported in the JADER dataset from April 2004 to June 2019. Based on all cases (586805 cases) in the JADER dataset from April 2004 to June 2019, the RORs and 95% CIs of pseudoaldosteronism were calculated for the 23 drugs (relative odds ratio vs. total cases in the JADER database). The analysis of this study was performed with reference to previous reports.9,10 In addition, the RORs and 95% CIs of pseudoaldosteronism associated with the 23 drugs were calculated using 12493 cases that used licorice-containing Kampo formulas (relative odds ratio vs. other licorice-containing Kampo formulas). When the lower limit of the 95% CI of the ROR exceeded one, the patients taking those drugs had a significantly higher risk of developing pseudoaldosteronism than patients taking the other Kampo formulas.

We also stratified by age for each licorice containing-drug reported in the JADER database (shakuyakukanzoto, 2137 cases; yokukansan, 1424 cases; and other licorice-containing Kampo formulas, 10715 cases).

For univariable analysis and the logistic regression analysis of pseudoaldosteronism in patients taking yokukansan, we selected cases yokukansan taking as suspected drug or concomitant drug (1424 cases) and excluded cases in which data on sex, weight, age, and yokukansan dose were missing (782 cases, 55% of total yokukansan cases). Thus, 642 cases (45% of total yokukansan cases) were selected. The case selection flowchart for this study is shown in Fig. 1. In univariable analysis, we analyzed possible factors associated with pseudoaldosteronism in yokukansan taker. In addition, body weight was analyzed by each sex for pseudoaldosteronism.

**Definitions of Side Effects and Medications** Based on previous studies using the JADER to assess pseudoaldosteronism11,12 and the Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver. 22.0, pseudoaldosteronism is considered a side effect when “Blood potassium decreased (PT code: 10005724),” “Hypokalemia (PT code: 10021015),” or “pseudoaldosteronism (PT code: 10037113)” were reported as adverse events. In addition, the following definitions of cases of dementia as an underlying disease were reported as: “Dementia in Alzheimer’s type (PT code: 10012271),” “Senile dementia (PT code: 10039966),” “Dementia with Lewy bodies (PT code: 10067889).” Licorice-containing Kampo formulas are defined as Kampo formulas that contain licorice and are listed in the PMDA’s prescription drug information in August 2019 as “herbal medicine” (Japanese standard product classification number: 875200) (anchusan, bakumondoto, bofutsushoan, biogoto, bushirituyo, byakkokanini, chikujontanto, chojokito, chitosan, daibofuto, daiokanzoto, eppikajutoto, gokoto, gorinsan, goshakusan, hainsankyuto, hangeshashito, heisan, hochuiketto, ireito, jidabokuippu, jiinkokin, jiinshito, jinsin, jizusoppu, jumihaidokuto, junchoto, juzentaihoto, kakkonjuktubuto, kakkonto, kakkontokakihanto, kamikihito, kamishoyosan, kanbukutaisoto, kanzoto, keigai-ryugyo, keihito, keikakukanto, shakuyakukanzobushito, shakuyakukanzoto, shiga, shikunshito, shimpito, Shishihakuhito, Shofusan, shokenchuto, shomakakkonto, shosaikoto, shosai-kokkakikyosekko, shoseiryuto, sokakakketsuto, tokakujikito, tokai, tokishigayakugoshibunokyo, tokito, tsudosan, unkeito, yakuinumito, yokuininto, yokukansan, and yokukansankachimpihan). In this study, some patients were taking licorice-containing kampo formula in combination with yokukansan. The licorice dose used in univariate analysis and logistic regression analysis of cases treated with yokukansan was calculated by adding the daily doses of licorice contained in yokukansan and other licorice-containing Kampo formulas. The licorice dose was shown as the dose per day (g/d).

**Statistical Analysis** All statistical analyses were performed using the R software version 3.4.0. The significance level was set at 0.05. We used the logistic regression model to calculate the RORs and 95% CIs of pseudoaldosteronism associated with the 23 drugs. The RORs of pseudoaldosteronism associated with each drug were adjusted for age and sex using the logistic regression model.
Table 1. Number of Cases and ROR of Each Licorice-Containing Kampo Formula

| Drugs        | Licorice content (g/d) | Total (n) | Case (n) | Non-case (n) | Relative odds ratio in total case in JADER database (ROR, 95% CI) | Relative odds ratio in licorice containing kampo formula (ROR, 95% CI) |
|--------------|------------------------|-----------|----------|--------------|------------------------------------------------------------------|---------------------------------------------------------------------|
| Total        |                        | 586805    | 3316     | 583489       |                                                                  |                                                                     |
| Licorice containing kampo formula |            | 12493     | 663      | 11830        |                                                                  |                                                                     |
| Shakuyakukanzoto | 5.0–6.0            | 2137      | 303      | 1834         | 32 (28–36)*                                                      | 5.4 (4.1–5.6)*                                                     |
| Shosetsu       | 3.0                  | 359       | 4        | 355          | 2.0 (0.74–5.3)                                                   | 0.19 (0.10–0.54)                                                   |
| Hangeshashinto | 2.5–3.0             | 604       | 14       | 590          | 4.2 (2.5–7.1)*                                                   | 0.41 (0.25–0.72)                                                   |
| Otsuji         | 2.0–3.0              | 150       | 1        | 149          | 1.2 (0.16–8.4)                                                   | 0.11 (0.02–0.85)                                                   |
| Shosaikoto     | 2.0                  | 201       | 6        | 195          | 5.4 (2.4–12)*                                                    | 0.52 (0.24–1.2)                                                   |
| Keishikajutsu  | 2.0                  | 104       | 7        | 97           | 13 (5.9–27)*                                                     | 1.2 (0.56–2.6)                                                    |
| Bukumondoto    | 2.0                  | 502       | 15       | 487          | 5.4 (3.2–9.1)*                                                   | 0.53 (0.32–0.92)                                                   |
| Bofutsusho     | 2.0                  | 568       | 14       | 554          | 4.4 (2.6–7.6)*                                                   | 0.44 (0.26–0.77)                                                   |
| Kakkonto       | 2.0                  | 715       | 12       | 703          | 3.0 (1.7–5.3)*                                                   | 0.29 (0.17–0.54)                                                   |
| Saihokuto      | 2.0                  | 156       | 2        | 154          | 2.3 (0.56–9.2)                                                   | 0.22 (0.10–0.93)                                                   |
| Saireito       | 2.0                  | 593       | 9        | 584          | 2.7 (1.4–5.2)*                                                   | 0.26 (0.11–0.53)                                                   |
| Boiogito       | 1.5–2.0              | 175       | 12       | 163          | 13 (7.2–23)*                                                     | 1.3 (0.69–2.3)                                                     |
| Kamishoyosan   | 1.5–2.0              | 307       | 7        | 300          | 4.1 (1.9–8.7)*                                                   | 0.40 (0.19–0.87)                                                   |
| Seishinrenshi  | 1.5–2.0              | 119       | 2        | 117          | 3.0 (0.74–12)                                                    | 0.29 (0.10–0.12)                                                   |
| Saikokeshitto  | 1.5–2.0              | 163       | 5        | 158          | 5.6 (2.3–14)*                                                    | 0.54 (0.23–1.4)                                                   |
| Daiokanzoto    | 1.0–2.0              | 342       | 19       | 323          | 10 (6.5–16)                                                      | 1.0 (0.63–1.6)                                                     |
| Maoto          | 1.5                  | 214       | 1        | 213          | 0.82 (0.12–5.9)                                                   | 0.08 (0.010–0.60)                                                  |
| Hochuekkito    | 1.5                  | 832       | 38       | 794          | 8.5 (6.1–12)*                                                    | 0.86 (0.62–1.2)                                                   |
| Yokukansan     | 1.5                  | 1424      | 141      | 1283         | 20 (17–24)                                                       | 2.4 (1.9–2.8)                                                     |
| Yokukansankachinpihange | 1.5 | 112 | 7 | 105 | 12 (5.4–25)* | 1.1 (0.52–2.4) |
| Rikkunshito    | 1.0–1.5              | 1037      | 27       | 1010         | 4.7 (3.2–6.9)                                                    | 0.47 (0.33–0.72)                                                   |
| Juzentaihoto   | 1.0–1.5              | 749       | 17       | 732          | 4.1 (2.5–6.6)                                                    | 0.40 (0.26–0.68)                                                   |
| Ninjinyoeito   | 1.0                  | 112       | 1        | 111          | 1.6 (0.22–11)                                                    | 0.15 (0.021–1.1)                                                   |

Using all cases (586805 cases) from the JADER dataset from April 2004 to June 2019, the reporting odds ratios (RORs) and 95% confidence intervals (CIs) of pseudolaldosteronism were calculated for 23 drugs (relative odds ratio vs. total cases in the JADER database). Using 12493 cases that reported taking licorice-containing Kampo formulas (relative odds ratio vs. other licorice-containing Kampo formulas).

Fig. 2. Each Licorice-Containing Kampo Formula Reported in the JADER Database Stratified by Age

For each licorice-containing Kampo formula (yokukansan, shakuyakukanzoto, other licorice-containing Kampo formulas), the cases reported in the JADER database were tabulated by age group, and the percentages are shown. Other licorice-containing drugs: Kampo formulas containing licorice other than yokukansan and shakuyakukanzoto. Not reported: cases with missing age reports were tabulated.
formed using EZR version 1.29 (Saitama Medical Center, Jichi Medical University, Saitame, Japan). Categorical variables were analyzed using Fisher’s exact test, and ordinary variables were analyzed using the Student’s t-test. The explanatory variables used in the logistic regression analysis were those that had a probability of at least 10%. The RORs and 95% CIs were calculated for each explanatory variable included in the multivariate model. Continuous variables were presented as the mean ± standard deviation. Statistical significance was defined as a p-value <0.05. All data analyzed in this study were assessed in two or more independent analyses.

RESULTS

Among the 586,805 cases reported from April 2004 to June 2019, 12,493 were treated with a licorice-containing Kampo formula, of which 663 developed pseudoaldosteronism. Based on the analysis of the ROR for each licorice-containing Kampo formula, significant ROR signals were detected in 17 drugs. Among them, RORs exceeding 10 were detected for shakuyakukanzoto, keishikaryojutsubuto, boiogito, daiokan-zoto, yokukansan, and yokukansankachimpihange. Using the 12,493 cases treated with licorice-containing Kampo formulas, we calculated the ROR of pseudoaldosteronism for each Kampo formula. The RORs were significantly higher for shakuyakukanzoto (ROR 5.4, 95% CI 4.1–5.6; p < 0.001) and yokukansan (ROR 2.4, 95% CI 1.9–2.8; p < 0.001) than for the other licorice-containing Kampo formulas (Table 1).

We stratified the patients treated with yokukansan, shakuyakukanzoto, and other licorice-containing Kampo formulas by age. There was a higher proportion of pseudoaldosteronism cases in patients over 70 years old who used yokukansan compared with patients who used shakuyakukanzoto and other licorice-containing Kampo formulas (Fig. 2).

The univariate analysis of each factor in the 642 cases treated with yokukansan showed that the female sex (68%, 52 of 76 vs. 51%, 289 of 566, p = 0.005), low body weight (<50 kg, 70%, 53 of 76 vs. 49%, 280 of 566, p = 0.001), old age (<70 years, 96%, 73 of 76 vs. 69%, 391 of 566, p < 0.001), high daily dose of licorice (p = 0.014), and dementia (72%, 55 of 76 vs. 41%, 233 of 566, p < 0.001) were risk factors for pseudoaldosteronism. Although not significant, treatment with loop diuretics also tended to increase the risk of pseudoaldosteronism (22%, 17 of 76 vs. 14%, 78 of 566, p = 0.058) (Table 2A). In univariate analysis of body weight in each sex showed that low body weight in female sex (<50 kg, 85%, 44 of 52 vs. 69%, 199 of 289, p = 0.020) was risk factor for pseudoaldosteronism (Table 2B).

A logistic regression analysis was conducted regarding the relationship between the onset of pseudoaldosteronism and risk factors such as dementia, daily licorice dose, low body weight (<50 kg), old age (<70 years), treatment with loop diuretics, and female sex. The results showed that dementia (OR 2.8, 95% CI 1.6–4.9; p < 0.001), daily licorice dose (OR 1.5,
DISCUSSION

This study determined that yokukansan use resulted in a higher risk of pseudoaldosteronism than other licorice-containing Kampo formulas. Furthermore, according to the logistic regression analysis, in addition to the licorice dose, which was reported as a risk factor in previous studies, age (<70 years), dementia, and low body weight (<50 kg) were newly identified risk factors for pseudoaldosteronism in patients taking yokukansan. Although not significant, treatment with loop diuretics (OR 1.8, 95% CI 0.98–3.5; p = 0.059) tended to increase the risk of pseudoaldosteronism (Table 3).

The causative compound of pseudoaldosteronism has not been identified. However, glycyrrhetic acid, 3-monoglucuronyl-glycyrrhetic acid, 18β-glycyrrhetinyl-3-O-sulfate and other compounds metabolized and produced from glycyrrhizic acid are considered candidates for causative compounds. Glycyrrhizic acid metabolites inhibit 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and suppress the metabolism of cortisol to cortisone. As a result, excess cortisol acts on the mineralocorticoid receptor to cause pseudoaldosteronism symptoms such as hypokalemia and hypertension. Pseudoaldosteronism symptoms are more likely to occur as the intake of glycyrrhizic acid increases. Yokukansan has a daily dose of 1.5 g of licorice, which is lower than that of other licorice-containing Kampo formulas. However, the risk of pseudoaldosteronism was suggested to be high in this study (Table 1). Most of the patients taking yokukansan were elderly people over 70 years old (Table 2), and according to the logistic regression analysis, elderly people over 70 years old have an increased risk of pseudoaldosteronism (Table 3). Therefore, it is thought that the incidence of pseudoaldosteronism from yokukansan is higher than that of other Kampo medicines because of the large number of elderly people who are treated. In elderly patients, 11β-HSD2 activity is reduced due to age-dependent declines in renal function, which leads to a decrease in the metabolism of cortisol to cortisone, which likely causes pseudoaldosteronism. Old age was not detected as a risk factor in a previously reported cohort study of yokukansan, but in an investigation on JADER data and case reports about other licorice containing-Kampo formulas, pseudoaldosteronism has been reported to occur frequently in the elderly. Yokukansan was originally used for irritability and crying at night in children rather than for the elderly. However, in recent years, improved peripheral symptoms of dementia and delirium have been reported with yokukansan use, and thus yokukansan use in the elderly has increased. However, side effects have been increasing in the elderly, who were not originally intended to use yokukansan.

In addition to old age, the results of the logistic regression analysis revealed that the licorice dose, dementia, and low body weight were independent factors that increased the risk of pseudoaldosteronism in patients treated with yokukansan. And, treatment with loop diuretics was identified as a possible risk of pseudoaldosteronism (Table 3). Dementia were previously unreported risk factors that were first detected in this study. There have been case reports in patients with dementia in which the detection of pseudoaldosteronism has been delayed and the symptoms have become severe. It may be difficult to notice the early symptoms of pseudoaldosteronism, such as weakness in the extremities and thirst, in dementia patients. Therefore, pseudoaldosteronism can progress and become severe in many dementia patients. Consequently, the number of pseudoaldosteronism cases reported in the JADER may have been high in dementia patients.

Loop diuretics act on the thin ascending limb of the loop of Henle and have lower blood potassium levels by inhibiting the reabsorption of sodium and potassium. Therefore, hypokalemia is exacerbated in pseudoaldosteronism. It has also been suggested that thiazide diuretics, like loop diuretics, reduce potassium and may be a risk factor for pseudoaldosteronism. However, only a few thiazide diuretics cases were included in this study, and it was not detected as a risk factor for pseudoaldosteronism.

In low body weight, often causes a decrease in blood albumin concentrations due to factors such as nutritional status. In previous cohort studies, hypoalbuminemia has been reported as a risk factor for pseudoaldosteronism. This may occur because 99% of glycyrrhetic acid exists in the state of being bound to albumin in the body. As the albumin concentration decreases, the free form of glycyrrhetic acid metabolites increase and act on 11β-HSD2.

According to the above results, when giving yokukansan to patients, it was suggested that be important to assess patient information such as age, body weight, and whether they are taking diuretics and consider whether yokukansan should be taken and whether the licorice dose can be reduced. However, in Japan, kampo formulas are mostly used as extract granule, and it is difficult to reduce the amount of licorice only. Therefore, in this case, it may be necessary to reduce the extract granule of yokukansan itself. As a reference for this, it has been reported that for behavioral and psychological symptoms of dementia (BPSD), yokukansan was administrated at two-

| Table 3. Independent Factors Affecting Incidence According to a Multivariable Logistic Regression Model |
|-------------------------------------------------|-----------|-----------------|--------|
| OR     | 95% CI | p     |
| Age > 70 (year) | 5.87 | 1.8–20 | 0.004 |
| Dementia | 2.76 | 1.6–4.9 | <0.001 |
| Body weight < 50 (kg) | 2.21 | 1.1–3.5 | 0.034 |
| Loop diuretic | 1.84 | 0.98–3.5 | 0.059 |
| Dose of licorice (g/d) | 1.54 | 1.2–2.0 | 0.002 |
| Female sex | 1.48 | 0.82–2.7 | 0.20 |

95% CI 1.2–2.0; p = 0.002), low body weight (<50 kg, OR 2.2, 95% CI 1.1–3.5; p = 0.034), and age (<70 years, OR 5.9, 95% CI 1.8–2.0; p = 0.004) were significant and independent factors that increased the risk of pseudoaldosteronism. Although not significant, treatment with loop diuretics (OR 1.8, 95% CI 0.98–3.5; p = 0.059) tended to increase the risk of pseudoaldosteronism (Table 3).
thirds of the normal dose, and it was effective for BPSD.\(^{23}\)

This may prevent the onset of pseudoadosteronism. In addi-
tion, patients with dementia are assumed to be unable to com-
plain of the subjective symptoms of pseudoadosteronism, and
therefore more frequent side effect monitoring is necessary.

The JADER database does not provide quantitative data on
weight and height, therefore, evaluations such as body mass
index (BMI) cannot be used. Therefore, in this study, we ana-
lyzed only weight as a risk factor. In addition, no information
such as food intake or body composition that might be asso-
ciated with a low body weight and albumin state in JADER
database, therefore, it was not possible to analyze whether low
body weight (<50kg) reflects low albumin status. In addition,
in the JADER database, it was not possible to obtain informa-
tion on quantitative values of age, blood potassium, etc. Fur-
thermore, the dose of licorice in this study is a standard dose
estimated from the description in the database, in addition,
temporary interruption or dose changes of yokukansan may
not be reflected in the database, thus, it may differ from the
actual dose. In addition, the administration period of yoku-
kansan is not taken into consideration in this study. Therefore,
the above-mentioned problems should be investigated in fu-
future cohort studies and RCT.

Furthermore, because cases in the JADER database are
spontaneously reported, there may be reporting bias. Only
data on patients who develop side effects are available. There-
fore, there is a concern that the research data may be targeting
a patient group distinct from those generally present in actual
clinical practice.\(^{24}\) Therefore, the results of this study must
be further evaluated through cohort studies and randomized
controlled trials. However, by using the JADER database,
we were able to examine a larger number of cases than in
previous cohort studies. As a result, we were able to detect
new risk factors for pseudoadosteronism and clarify the pa-
ient background that should be noted for the clinical use of
yokukansan.

According to the results of this study, dementia, old age,
and low body weight were detected as risk factors for the de-
velopment of pseudoadosteronism when taking yokukansan.
And, treatment with loop diuretics might be detected as a
possible risk of pseudoadosteronism. Therefore, when taking
yokukansan, it was suggested that it be important to assess
these risk factors and consider whether they should take yoku-
kansan and the dose of licorice. These findings will be very use-
ful for avoiding the onset of pseudoadosteronism.

Conflict of Interest  The authors declare no conflict of
interest.

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