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A comparative study between excess-dose users and regular-dose users of rhubarb contained in Kampo medicines

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Summary

With prolonged use of rhubarb-containing Kampo medicines, some patients come to ask for high-dose rhubarb because of deteriorated reactivity to rhubarb. We divided patients into two groups in terms of rhubarb-dose, and compared clinical backgrounds between regular-dose group and excess-dose group. Patients who were treated with rhubarb-containing Kampo extracts (manufactured prescriptions) or Kampo formulae (decoctions) for more than 12 months were enrolled. These two groups were compared for age, sex, shape of stool, abdominal symptoms, existence of hemorrhoids, Kampo diagnosis of abdomen, past stimulant laxative use, duration of stimulant laxative use before the first administration of rhubarb, duration of rhubarb use in our hospital, and initial existence of stimulant pain caused by taking stimulant laxatives for the first time. No significant difference was shown between the two groups in terms of age, duration of stimulant laxative-use before the first prescription of rhubarb, shape of stool, abdominal symptoms, existence of hemorrhoids, or duration of rhubarb-use. However, most patients in the regular-dose group had initial stimulant pain of the abdomen upon taking stimulant laxatives for the first time, but most patients in the excess-dose group did not ($p < 0.001$). All patients except one in the regular dose group had the sign of "umbilical region tenderness on pressure", but half of the excess-dose group did not have it ($p = 0.041$). Based on these findings, the absence of "initial stimulant pain" and the absence of "umbilical region tenderness on pressure" may predict increasing or excess use of rhubarb, and long-term use of rhubarb should be discouraged more strongly in the patients without these signs.

Key words: Kampo medicine, herb, rhubarb, (*Rheum palmatum*) Rhei Rhizoma, lazy bowel syndrome, laxative abuse

Introduction

Anthranoid-containing herbal medicines such as senna, aloe, cascara, frangula, and rhubarb are used as stimulant laxatives (Siegers, 1992). These drugs are currently recommended for short-term treatment (1–2 weeks), because melanosis coli and neuronal degeneration in the colon, "lazy bowel" syndrome, may occur in patients who use stimulant laxatives for a long time (Friedman and Isselbacher, 1994). In these patients, deteriorated reactivity to stimulant laxatives is sometimes an omen of neuronal degeneration in the colon (Ikeda, 1992).

Kampo medicines containing rhubarb (Rhei Rhizoma, *Rheum palmatum* L.) are sometimes used for long-term treatment of patients with chronic diseases including chronic functional constipation. In the field of Kampo medicine, rhubarb is not only a laxative but also an anti-inflammatory or a tranquilizer (Terasawa, 1993). Rhubarb is also used for improving "Oketsu" syndrome (syndrome caused by blood stagnation). However, even with the traditional manner of rhubarb-use, some patients with prolonged use come to ask for

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high-dose rhubarb because of deteriorated reactivity to rhubarb. We divided patients into a regular-dose group and an excess-dose group, and compared the clinical backgrounds between the two groups. The aim of this study were to analyze risk factors of increasing or excess use of rhubarb.

Patients and Methods

Among the outpatients of Johetsu General Hospital (Johetsu, Japan) affiliated with our department, we included in the study group all patients who were treated with rhubarb-containing Kampo extracts (manufactured prescriptions) or Kampo formulae (decoctions) for more than 12 months and visited the hospital between January and June 2001. In Japan, Kampo medicines are prescribed with either forms Kampo extracts or Kampo formulae. The existence of identifiable cause of constipation was studied by stool testing for occult blood and/or laboratory studies including a complete blood count and serum electrolyte analysis. Patient who did not undergo these examinations or patients with an identifiable cause of constipation, including constipating medicines, were excluded from this study.

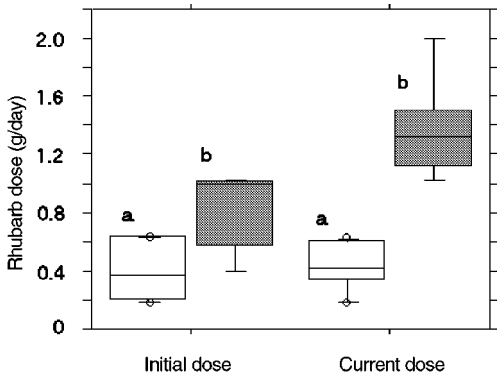

Fig. 1. Rhubarb dose contained in Kampo extracts (manufactured prescriptions) of the regular-dose group (▫) and the excess-dose group (▩). Initial rhubarb dose and current rhubarb dose are shown. (a: $p = 0.917$, b: $p = 0.043$)

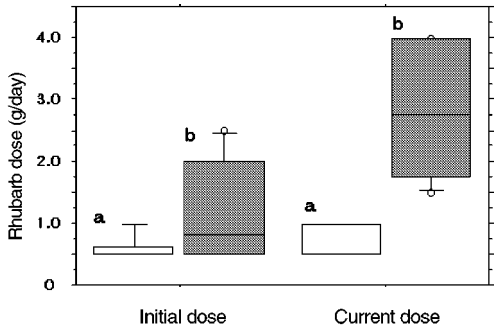

Fig. 2. Rhubarb dose contained in Kampo formulae (decoctions) of the regular-dose group (▫) and the excess-dose group (▩). Initial rhubarb dose and current rhubarb dose are shown. (a: $p = 0.179$, b: $p = 0.028$)

Patients were divided into an excess-dose and a regular-dose group. We defined patients as "regular dose" if a Kampo extract (manufactured prescription) were used within the stated dose recommended for each extract by the Ministry of Health and Welfare (Japan), or if 1g or less of rhubarb was added to Kampo formulae (decoctions). We defined as "excess-dose" when more than the recommended dose of manufactured Kampo extracts was used or any rhubarb-containing laxatives were used in addition to the maximum dose of a manufactured Kampo extract, or when more than 1 g of rhubarb was added to Kampo decoctions.

Firstly, we examined the transition in rhubarb dose using medical records from the first visit until the study period in regular-dose group and excess-dose group (analyzed by Wilcoxon signed-ranks test). Secondly, the two groups were compared for age, sex, shape of stool (small and hard stool or not), abdominal symptoms, existence of hemorrhoids, Kampo diagnosis of abdomen, past stimulant laxative use, duration of stimulant laxative use before the first administration of rhubarb, duration of rhubarb use in our hospital, and initial existence of stimulant pain caused by taking stimulant laxatives for the first time. Categorical variables were compared by Fisher's exact test or Mann-Whitney's U test, and continuous variables were compared by Student's *t*-test. *P*-value less than 0.05 was considered statistically significant.

Results

Among the outpatients, 28 patients diagnosed with chronic functional constipation were enrolled in this study. In 15 of these patients, a regular dose of laxatives was used, and in 13 patients an excess-dose of laxatives was used during the study period. In daily practice, the dose of rhubarb was decided by the subject's physicians according to subject's demand. No conscious intervention was performed in the prescription of rhubarb.

The initial rhubarb dose contained in manufactured Kampo extracts (Figure 1) and Kampo decoctions (Figure 2) was higher in the excess-dose group than that in the regular-dose group. Before the first administration of rhubarb in our hospital, half of the patients in the excess-dose group had continuously taken high-dose stimulant laxatives (data not shown). In these patients, the initial dose of rhubarb was inevitably high. Moreover, in the excess-dose group, the rhubarb-use increased significantly during the period from the first

Table 1. Background and clinical features in the regular-dose group and the excess-dose group.

Clinical feature		Regular dose (N = 15)	Excess dose (N = 13)	Total (N = 28)	*P* value
		number of users with events (%)			
Age		49.1	51.3	50.1	0.692
Sex	male	0	2 (15.4%)	2	
	female	15 (100%)	11 (84.6%)	26	
Past stimulant laxative-use		8 (53.3%)	8 (61.5%)	16	0.662
Duration of stimulant laxative-use (years)		7.9	10.6	9.2	0.563
Duration of rhubarb use (months)		30.5	39.9	34.9	0.227
Stimulant pain		12 (80.0%)	1 (7.7%)	13	<0.001
Small and hard stool		8 (53.3%)	5 (38.5%)	13	0.431
Abdominal fullness		10 (66.7%)	7 (53.8%)	17	0.489
Accelerated bowel movement		2 (13.3%)	4 (7.7%)	6	0.262
Increased abdominal gas		4 (26.7%)	5 (38.5%)	9	0.505
"Abdominal tension"	excess	4	5	9	0.945
	balanced	8	4	12	
	reduced	3	4	7	
"Umbilical region tenderness on pressure"		14 (93.3%)	8 (61.5%)	22	0.041
"Lower abdominal tenderness on pressure"		2 (13.3%)	3 (23.1%)	5	0.502
Hemorrhoids		4 (26.7%)	4 (30.8%)	8	0.811

prescription of rhubarb until the study period, in sharp contrast to the regular dose group (Figures 1, 2).

No significant difference was shown between the two groups in terms of age, duration of stimulant laxative-use before the first prescription of rhubarb, duration of rhubarb-use in our hospital, shape of stool (small and hard stool or not), abdominal symptoms, or existence of hemorrhoids (Table 1). Only two factors, “initial stimulant pain” and “umbilical region tenderness on pressure” were significantly different between the two groups. Most patients in the regular-dose group had initial stimulant pain of the abdomen upon taking stimulant laxatives for the first time, but most patients in the excess-dose group did not ($p < 0.001$). All patients except one in the regular dose group had the sign of “umbilical region tenderness on pressure”, but half of the excess-dose group did not have ($p = 0.041$).

Discussion

In the field of “Western“ medicine, the long-term use of stimulant laxatives is discouraged (Friedman and Isselbacher, 1994). In the field of Kampo medicine, rhubarb-containing medicines are sometimes used for a long time. This discrepancy between the two fields of medicine led us to this study.

Kampo medicines containing rhubarb were used within the recommended dose range in half of the enrolled patients even with prolonged use. Kampo medicines are composed of several herbs, and the combined herbs may cooperatively affect patients with constipation. Some herbs may act as wetting laxatives and some as osmotic laxatives, and rhubarb acts as a stimulant laxative. For example, Toukaku-johki-to (Tao he cheng qi tang) used to treat some patients in this study contains Tonin (Persicae semen), Keihi (Cinnamomi cortex), Bosho (Natrium sulfuricum), Kanzo (Glycyrrhizae radix) and rhubarb. Bosho, Na_2SO_4, is an osmotic agent. Tonin and Kanzo may affect like wetting agents (Terasawa, 1993). As a result of the cooperative effects, Kampo medicines containing rhubarb may not necessarily cause deteriorated reactivity to themselves, as shown in the regular-dose group. In this study, we should consider effects of other component herbs in Kampo medicines except rhubarb. Toukaku-johki-to was administered to about half patients both in the regular-dose group and in the excess-dose group, and other Kampo medicines administered to the regular-dose group were similar to those administered to the excess-dose group. Therefore, other component herbs except rhubarb may not have caused the difference in rhubarb dose between the two groups.

In contrast to the regular-dose group, the rhubarb-dose in the excess-dose group significantly increased during the period from the first prescription of rhubarb until the study period. The initial rhubarb-dose in Kampo extracts and Kampo formulae was higher in the excess-dose group than that in the regular-dose group. This difference in the initial dose may not have affected the subsequent course of the rhubarb-dose, because the subsequent rhubarb-dose in the excess-dose group in-

creased greatly even in patients started with low-dose rhubarb. Half of the patients in the excess-dose group had taken high-dose stimulant laxatives before the first prescription of rhubarb, therefore, some initial conditions of the patients in the excess-dose group may have caused the increasing use of rhubarb.

In this study, the absence of "initial stimulant pain" was predictive of the increasing use of rhubarb. Patients who experienced stimulant pain may have controlled laxative-use by themselves, and Kampo doctors may have been reluctant to increase the rhubarb-dose for these patients. However, the absence of "initial stimulant pain" may be related to some specific and intrinsic condition of the intestine, for example, potential neuronal dysfunction of the intestine. Excess-dose type patients seems to be insensitive to the stimulation of the intestine by rhubarb, whereas regular-dose type patients seems to be sensitive to it. We can adopt another hypothesis that the proportion of some intestinal bacteria have affected the increase of rhubarb dose. A previous study demonstrated that the laxative potential of sennoside A, B is influenced by the particular bacteria in the large intestine of each individual (Akao et al., 1994; Takada et al., 1998).

Patients' complaints are usually highly valued in Kampo diagnosis and treatment (Tarasawa, 1993; Guang, 2001); therefore, rhubarb-use is likely to be perceived as unsuitable for patients with stimulant pain caused by rhubarb. However, this study revealed that the use of rhubarb in the patients with stimulant pain did not increase even after long-term use, suggesting that rhubarb-use may be more suitable for patients with stimulant pain than for patients without it.

Another factor, the sign of "umbilical region tenderness on pressure" was absent in half of the patients of the excess-dose group. According to the Kampo theory, the sign of "umbilical region tenderness on pressure" is a sign of the "Oketsu" syndrome (syndrome caused by blood stagnation) (Terasawa, 1993). Long ago, rhubarb was originally used as an agent to treat "Oketsu" syndrome (Mikage, 1996). Thus, "umbilical region tenderness on pressure" is an indication for the use of rhubarb-containing Kampo medicines in the view of Kampo medicine. The significant difference we observed between the two groups in terms of "umbilical region tenderness on pressure" may be related to these Kampo theories.

Other hypotheses can be proposed : 1) in patients with stimulant pain, a low threshold of pain may affect the presence of "umbilical region tenderness on pressure", 2) if the phenomenon of "umbilical region tenderness on pressure" is caused by intra-lumenal stagnation, stimulant laxatives may cause such pain through increased intestinal motility. Therefore, the symptom "initial stimulant pain" may be related to the sign "umbilical region tenderness on pressure" to some degree.

In any case, based on the findings of this study, the absence of "initial stimulant pain" and the absence of "umbilical region tenderness on pressure" may predict increasing or excess use of rhubarb, and long-term use of rhubarb should be more strongly discouraged in patients without these signs. Although no physiological studies (e.g. colonic transit time, cinedefecography, anal manometry, anal electromyography, etc.) were performed in the present study, these findings may offer useful suggestion on long-term rhubarb use in daily practice. To optimize the use of rhubarb, further experimental studies of the mechanism of anthranoids' effects and a larger population study to confirm the findings made in this study are warranted.

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