The examination of endoscopic findings in 221 cases of rheumatoid arthritis treated with Japanese Oriental (Kampo) medicine

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Abstract

OBJECTIVES: To evaluate the efficacy of Japanese Oriental (Kampo) medicine on treatment of rheumatic arthritis (RA) patients from the point of view of preventing the complication of gastroduodenal ulcer. ***METHODS***: We examined endoscopic findings and contents of treatment in 221 rheumatoid arthritis (RA) cases treated with Japanese Oriental (Kampo) medicine retrospectively. ***RESULTS***: A gastroduodenal ulcer was found in 10 patients (4.5%), an ulcer scar was found in 21 patients (9.5%) and a cancer was found in 6 cases (2.7%). Next, we compared the incidence of gastroduodenal ulcers in the group of patients who were receiving nonsteroidal antiinflammtory drugs (NSAIDs) therapy with the group of patients treated with Kampo medicine alone. The incidence of gastroduodenal ulcers was 9.3 % in NSAIDs group and 2.1 % in the group of patients treated with Kampo medicine alone. ***CONCLUSIONS***: The incidence of gastroduodenal ulcers in RA patients treated with Kampo medicine was lower than that in other studies carried out in patients with RA. These findings suggested that treatment with Kampo medicine for RA is beneficial from the point of view of preventing gastroduodenal complication.

Key words RA, gastroduodenal ulcer, Kampo medicine, herbal medicine, NSAIDs.

Abbreviations Alb, albumin; ampir, ampiroxicam; ARA, The American Rheumatism Association; aspi, aspirin; DMARDs, disease modifying antirheumatic drugs; DU, duodenal ulcer; dicl, diclofenac; ESR, erythrocyte sedimentation rate; glb, globulin; GU, gastric ulcer; Hb, hemoglobin; Hct, hematocrit; indo, indomethacin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; napr, naproxen; po, peros; PSL, prednisolone; Plt, platelet; RA, rheumatoid arthritis; RBC, red blood cell; sup, suppository; tiap, tiaprofenac acid; NSAIDs, nonsteroidal antiinflammtory drugs; WBC, white blood cell.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the relief of the symptoms of rheumatoid arthritis (RA). In patients with RA, symptom relief through use of NSAIDs is firmly established, although it remains whether they influence the course and outcome of the diseases.[1)] However, NSAIDs are associated with serious side effects, particularly, ulceration, bleeding and perforation of the gastrointestinal tract.[2,3)] On the other hand, we are using Japanese Oriental (Kampo) medicine for treatment of RA patients. Keishi-ka-ryo-jutsu-bu-to, Keishi-ni-eppi-itto, Keshi-shakuyaku-chimo-to, Yokuininn-to and Dai-bouhu-to are often used for treatment of RA. Some of the patients are treated by Kampo medicine alone and remain in good condition. As a result, we can observe endoscopic findings of RA patients treated without NSAIDs. In this study, we examined endoscopic findings and contents of treatment in 221 rheumatoid

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arthritis (RA) cases treated with Kampo medicine retrospectively.

Patients and Methods

A total of 221 patients visiting our department, were treated with Kampo medicine from January 1980 to October 2000. Those who received upper gastroduodenal endoscopic examination and fulfilled the criteria given below were involved in this study.

1. The patients who fulfilled the criteria of ARA[4] and were evaluated for the stage and class of RA.
2. The patients whose contents treatment of 2 months before endoscopy could be confirmed.
3. The patients who were evaluated for Lansbary Index,[5] blood cell counts, ESR and blood chemistry within 4 weeks before endoscopy.

Endoscopic examination was carried out randomly. Table I shows a summary of the 221 patients. Endoscopic findings were examined retrospectively by the report and photographs focusing on ulceration, erosion, superficial gastritis, atrophic gastritis and cancer.

Results

Contents of treatment (Table II)

Although all patients were treated with Kampo medicine, 96 patients (43.4%) did not receive any other treatment and 107 patients (48.4%) were treated with NSAIDs. Forty-three patients were administered NSAIDs orally, 53 patients were administered suppository and 11 patients were administered both orally and suppository. Steroids were used for 55 patients (24.9%) and DMARDs for 14 (6.3 %) patients.

The endoscopic findings of upper gastrointestinal tract (Table III)

Gastroduodenal ulcers were found in 12 patients (5.4%). of the 12 patients, 9 patients had gastric ulcer and 3 patients had duodenal ulcers. Ulcer scars were found in 21 patients (9.5%), 16 were gastric ulcer scar and 5 were duodenal ulcer scars. Superficial gastritis, erosive gastritis, verrucous gastritis and atrophic gastritis were found in 23 patients (10.4%), 12 patients (5.4%), 4 patients (1.8%) and 62 patients (28.0%), respectively. Early gastric cancer, advanced gastric cancer and duodenal cancer were found in 4 patients, 1 patient and 1 patient, respectively.

Table I Profile of 221 patients with rheumatoid arthritis (RA)

		Male	Female	Total
		46	175	221
Age (years)	-40	1	10	11
	-50	13	35	48
	-60	8	61	69
	-70	15	52	67
	71-	9	17	26
Duration (years)	- 5	20	48	68
	-10	14	59	73
	-20	11	49	60
	-30	1	13	14
	-40	0	4	4
	40-	0	2	2
RA stage	I	9	17	26
	II	16	39	55
	III	9	32	41
	IV	12	87	99
RA class	I	7	21	28
	II	26	104	130
	III	11	45	56
	IV	2	5	7

Table II Treatment in the 2 months preceding endoscopy

Kampo medicine alone	96	Patients
Combined with DMARDs	5	Patients
Combined with NSAIDs	63	Patients
Combined with NSAIDs+steroid	37	Patients
Combined with NSAIDs+DMARDs	2	Patients
Combined with NSAIDs+steroid+DMARDs	5	Patients
Combined with steroid	11	Patients
Combined with steroid+DMARDs	2	Patients

NSAIDs, non-steroidal anti-inflammatory drugs;
DMARDs, disease modifying antirheumatic drugs.

Table III Endoscopic findings in rheumatoid arthritis

Active ulcer	10	(4.5%)
GU	9	
DU	3	
Ulcer scar	21	(9.5%)
GU scar	16	
DU scar	5	
Gastritis		
superficial	23	(10.4%)
erosive	12	(5.4%)
verrucous	4	(1.8%)
atrophic	62	(28.0%)
Carcinoma	6	(2.7%)
gastric(early)	4	
gastric(advanced)	1	
duodenal	1	

GU, gastric ulcer; DU, duodenal ulcer

The examination of the patients complicated with gastroduodenal ulcer (Table IV)

The mean age of the 12 patients (5 males and 7 females) who had complicated gastroduodenal ulcer was 55.4±10.0. One patient had multiple ulcers. All ulcers were within 2 cm in width. Ten of the 12 patients were treated with NSAIDs. Four patients were treated with both steroid and NSAIDs. The dose of steroid was 2.5mg to 5.0mg as prednisolone per day. Six patients were administered anticholinergic agents for prevention. Gastroduodenal ulcers in all patients were healed by H2-blockers.

The influences of preventive administration of conventional anti-ulcer drugs

Fifty-eight patients and 18 patients were treated with conventional anti-ulcer drugs like anti-cholinergic drugs and H2-blockers for prevention of gastroduodenal ulcer, respectively. Twelve patients were treated with both conventional anti-ulcer drugs and H2-blockers for prevention of gastroduodenal ulcer. Of 58 patients treated with conventional anti-ulcer drugs, 5 patients were indicated having peptic ulcers. On the other hand, 6 of 133 patients who were not treated with conventional anti-ulcer drugs were indicated having peptic ulcers. There was no significant difference between these two groups. One of the 12 patients who received both conventional anti-ulcer drugs and H2-blockers had peptic ulcer.

The comparison of the Kampo medicine group and the NSAIDs group

We compared the group that was treated with Kampo medicine alone (Kampo medicine group) with the group that was treated with NSAIDs (NSAIDs group). Table V and VI show the results of evaluation for the disease activity at the time of 4 weeks before endoscopic study. As for the male and female ratio, age and duration of disease, there was no significant difference between these two groups. Lansbury Index, joint counts and ESR were significantly higher in NSAIDs group than those in the Kampo medicine group (Table V). RBC, Hb and albumin were significantly lower in

Table IV Occurrences of peptic ulcer

No	Age	Gender	Sympton	Stage	Location	NSAIDs	Steroid	DMARDs	antiulcer drugs
1	62	F	tarry stool	H1	antrum lesser curvature	(−)	(−)	(−)	(−)
2	62	F	anemia	H1	antrum lesser curvature	dicl (po) indo (sup)	PSL 2.5 mg	(−)	(−)
3	43	F	occult blood	H1	angulus	indo (po)	(−)	(−)	anticholinergic agents
4	48	M	none	H2	corpus posterior wall	indo (po)	(−)	(−)	anticholinergic agents
5	52	M	epigastralgia	H1	angulus	indo (sup)	(−)	(−)	(−)
6	47	M	epigastralgia	A1	angulus	tiap (po) indo (sup)	(−)	(−)	(−)
7	61	M	epigastralgia	H1	angulus	aspi (po) indo (sup)	PSL 2.5 mg	(−)	anticholinergic agents
8	44	M	epigastralgia	A2	duodenal bulbus	napr (po) indo (sup)	PSL 5.0 mg	(−)	(−)
9	69	F	anemia	A2	duodenal bulbus	(−)	(−)	(−)	(−)
10	69	F	anemia	A1	corpus anterior wall	napr (po)	(−)	(−)	anticholinergic agents
11	66	F	occult blood	H2	duodenal bulbus	indo (sup)	(−)	(−)	anticholinergic agents
12	48	F	none	A1	angulus	ampir (po)	PSL 5.0 mg	gold	anticholinergic agents H2-blockers

po, peros; sup, suppository; dicl, diclofenac; tiap, tiaprofenac acid; napr, naproxen; PSL, prednisolone; aspi, aspirin; indo, indomethacin; ampir, ampiroxicam; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease modifying anti-rheumatic drugs.

Table V Treatment of rheumatoid arthritis with NSAIDs vs. without NSAIDs

		NSAID group (107 cases)	Kampo medicine alone (96 cases)
RA class	1	9	18
	2	57	60
	3	36	16
	4	5	2
RA stage	1	11	13
	2	19	32
	3	19	18
	4	58	33
ESR(mm/hr.)	(mean±SD)	83.5±38.8**	54.5±38.5
Joint count	(mean±SD)	64.1±46.3*	49.2±44.8
Lansbury index	(mean±SD)	59.3±27.2**	38.8±27.2

*$p<0.05$ **$p<0.01$ vs. other group (t test)
NSAID, npn-steroidal anti-inflammatory drug; ESR, erythrocyte sedimentation rate.

Table VII Endoscopic findings in two groups

	NSAID group (107 cases)	Kampo medicine alone (96 cases)
Active ulcer	10 (9.3%)*	2 (2.1%)
GU	8	1
DU	2	1
Ulcer scar	15 (14.0%)	7 (7.3%)
GU scar	14*	4
DU scar	1	3
Gastritis**		
superficial	15 (14.0%)	8 (8.3%)
erosive	8 (7.5%)	5 (5.2%)
verrucous	2 (1.9%)	2 (2.1%)
atrophic	33 (30.8%)	28 (29.1%)

*$p<0.05$ vs. other group; x^2 test
**: The cases in which overlaps are contained.
NSAIDs, nonsteroidal anti-inflammatory drugs; GU, gastric ulcer; DU, duodenal ulcer.

Table VI Blood test results in two groups

		NSAID group (107 cases)	Kampo medicine alone (96 cases)
WBC	/μl	6898.6±2004.3**	6001.2±1626
RBC	10^4/μl	387.2±48.7**	412.0±43.8
Hb	g/dl	10.3±1.7**	12.0±1.6
Ht	%	32.3±5.2	36.2±4.5
MCV	fl	83.7±8.3	88.4±4.4
MCH	pg	26.6±3.5	29.0±2.0
MCHC	g/dl	31.6±2.2	32.7±1.3
Plt	/μl	33.7±12.1**	26.3±7.8
ESR	mm/hr	83.3±41.6	58.1±42.7
T-P	g/dl	7.0±0.7	7.2±0.7
Alb	g/dl	3.5±0.5**	3.9±0.5
alb	%	52.1±7.9	57.4±6.8
α1-glb	%	3.8±0.9	3.4±1.2
α2-glb	%	12.4±8.5	10.3±1.8
β-glb	%	9.8±1.6	9.3±1.2
γ-glb	%	23.0±7.2**	19.8±6.1

**p-value <0.01 vs. other group; t test
WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; Plt, platelet; ESR, erythrocyte sedimentation rate; Alb, albumin; alb, albumin; glb, globulin; NSAID, non-steroidal anti-inflammatory drug.

NSAIDs group than those in the Kampo medicine group. On the other hand, platelet and gamma globulin were significantly higher in NSAIDs group than those in Kampo medicine group (Table VI). These findings indicated that the disease activity was higher in NSAIDs group. As for endoscopic findings, the incidence of gastroduodenal ulcer was significantly higher in NSAIDs group than that in the Kampo medicine group (Table VII). Gastric ulcer scar was seen significantly more frequently in NSAIDs group than that in Kampo medi-

Table VIII Occurrences of cancer

Age	Gender	RA stage	RA class	Tumor type	Tumor location	Histology
63	M	I	II	Borrmann III	corpus (greater curvature)	signet-ring-cell carcinoma
55	M	II	III	II c	angulus	moderately differentiated adenocarcinoma
55	F	IV	III	II c	angulus	signet-ring-cell carcinoma
61	M	II	III	II a	corpus (posterior wall)	well-differentiated tubular adenocarcinoma
62	M	II	II		duodenum	poorly differentiated adenocarcinoma
77	F	IV	II	II c	corpus (greater curvature)	well-differentiated tubular adenocarcinoma

RA, rheumatoid arthritis

cine group. There was no significant difference between these two groups in other findings like gastritis.

Cancer (Table VIII)

Cancer was found in 6 patients. In 6 patients 4 were males, aged 62.2±8.0 and 1 had duodenal cancer.

Discussion

The adverse gastrointestinal effects of NSAIDs currently used in treatment of arthritis have been studied extensively. In one study, the risk of bleeding, perforation, hospitalization, or death was found to be 3 times higher among NSAIDs users than among those not taking NSAIDs.[6] Concerning the prevalence of gastroduodenal ulcer inpatients with RA, Farah *et al.*[7] reported that 67 patients of 185 patients (36.2%) had complicated gastroduodenal ulcer. Shiokawa *et al.*[8] and Cheatum *et al.*[9] reported that 175 patients in 1008 patients (17.7%) and 239 patients in 1009 patients (23.6%) had complicated gastroduodenal ulcer, respectively. These facts taken together, shows it is suitable that the prevalence of gastroduodenal ulcer in patients with RA is 18% to 35%. Comparison of the results of our study with the results of other studies is difficult because patient groups, doses of NSAIDs and use conditions of anti-ulcer drug may vary between different studies. In our study, the prevalence of gastroduodenal ulcer in patients with RA was 12 patients in 221 patients (5.4%) which was relatively low compared with other studies. Even in NSAIDs group, the incidence of gastroduodenal ulcer was 9.3% (10 patients in 107 patients) in our study. In the Kampo medicine group, it was 2 patients in 96 patients (2.1%). There are two possible reasons why patients treated with Kampo medicines had a lower risk for gastroduodenal ulcer. One is that in taking Kampo medicine, patients could keep good control of the disease and as a result, they needed fewer doses of NSAIDs. The other reason is that Kampo medicine might have a protective effect of gastric mucosa. These results indicate that Kampo medicine is useful for treatment of RA patients from the point of complication of gastroduodenal ulcer as well.

The relatively low complication rate (9.3% in NSAIDs group) in our study may be related to Kampo medicine which we are using for treatment of RA patients. Of course it might be argued that the design of our study has some limitations that are absent in randomized controlled clinical trials. On the other hand, clinical trials are generally performed in a selected group of patients. Therefore, it can always be questioned whether results of randomized, double blind trials can be generalized to clinical (daily) practice. The results of our observational study give insight into the preventive effects of Kampo medicine on NSAIDs gastropathy.

In this study, we compared NSAIDs group with Kampo medicine alone group (Table VI and VII). As a result, it was revealed that NSAIDs were used for RA patients who had higher activity of disease than in the Kampo medicine group. It is likely that patients who had lower activity of disease were well controlled by Kampo medicine alone and who those had higher activity of disease were not controlled enough. Although the patients who used NSAIDs complicated gastroduodenal ulcer significantly more than the patients who were treated by Kampo medicine alone, the incidence of gastroduodenal ulcer in NSAIDs group in our study was lower compared with other studies. This study suggested that in using Kampo medicine for treatment of RA patients, we could decrease the gastroduodenal complication induced by NSAIDs.

和文抄録

和漢薬治療中の関節リウマチ（RA）患者の胃十二指腸病変を検討した。

【方法】当科で和漢薬治療中のRA患者のうち，1980年1月から2000年10月までに上部消化管内視鏡検査を施行した221例について内視鏡所見とRAの活動度，治療内容との関連を検討した。

【結果】対象221例中，活動性の消化性潰瘍は10例（4.5%）。内訳は胃潰瘍9例，十二指腸潰瘍3例であった。潰瘍瘢痕は21例（9.5%）。内訳は胃潰瘍瘢痕16例，十二指腸瘢痕5例であった。その他，びらん性変化が12例（5.4%），早期胃癌が4例（1.8%）に認められた。非ステロイド性消炎鎮痛剤（NSAIDs）またはステロイド剤（ス剤）併用治療群（107例）と和漢薬単独治療群（96例）で比較検討すると，前者の活動性胃十二指腸潰瘍合併例が10例（9.3%）であるのに対し，後者では2例（2.1%）とNSAIDsまたはス剤併用群に有意に多く活動性潰瘍が合併していた。

【考察】1999年Cheatumらは NSAIDs服用中のRA患者の胃十二指腸病変を内視鏡検査で検討し，1009例中239例（23.6%）に胃または十二指腸潰瘍があったことを

報告している。RA患者の胃十二指腸潰瘍の合併頻度については，Farahらの185例中67例（1988年），塩川らの1008例中175例（1991年）などがあり，いずれもNSAIDs投与との関連性が指摘されている。今回の検討では，221例中10例とこれらの報告と比較して少ない傾向にあった。和漢薬を中心とした治療で，NSAIDs使用を最小限にとどめることにより，消化性潰瘍の合併を減らしうる可能性が示唆された。

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