Trends in the prescriptions of Kampo medicines over a six-year period

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Abstract

Changes in the prescriptions of Kampo medicines (Sino-Japanese traditional herbal medicines) issued at a university hospital over a six-year period were investigated. Prescriptions including a Kampo medicine (79,132 sheets) issued at Kitasato University Hospital in Kanagawa Prefecture, Japan, over a 6-year period from 1994 to 1999 were analyzed. We found that Kampo medicines were mainly prescribed for patients of ages 30-39 yr and 50-59 yr, and were most frequently prescribed by the department of Obstetrics & Gynecology, followed by Internal Medicine and Dermatology. Ninety-six percent of the prescriptions were combined with modern medicine, and the percentage of Kampo medicines with instructions about its combination with western medicines in the package insert was approximately 1%. Among the prescriptions that combined a Kampo medicine with western medicine, the most frequently prescribed combination was a xanthine derivative and a Mao (麻黄, Ephedrae herba, *Ephedra sinica* STAPF)-containing Kampo medicine, especially theophylline and Kakkon-to. Regarding such combinations, the monitoring of adverse effects and a check of the prescription seemed to be important. The use of Toki-shakuyaku-san and Dai-kenchu-to rapidly increased and the use of Sho-saiko-to, Ninjin-yoei-to, Go-rei-san, and Hochu-ekki-to decreased over the study period. From these trends in the prescriptions, it is believed that the demand for Kankyo (乾姜), Zingiberis siccatum rhizoma, *Zingiber officinale* ROSCOE, Koi (膠飴), Saccharum granorum, Sansho (山椒), Zanthoxyli Fructus, *Zanthoxylum piperitum* DE CANDOLLE, Shakuyaku (芍薬), Paeoniae Radix, *Paeonia lactiflora* PALLAS, and Botampi (牡丹皮), Moutan cortex, *Paeonia suffruticosa* ANDREWS, will increase rapidly in the future. It is important to carry out similar investigations at a wide variety of hospitals and clinics including emergency hospitals and sanatoria to clarify the future balance of the supply and demand of Kampo medicines and their constituent herbs.

Key words Trends in prescriptions, Kampo medicine.

Abbreviations OBGY, The Department of Obstetrics and Gynecology; IM, The Department of Internal Medicine.

Introduction

Kampo medicines for ethical use (hereafter, Kampo medicines) have been widely used in clinics in Japan since they were covered by health insurance in 1967. According to a study on Kampo medicine conducted in Japan 2000,[1)] 72.0% of physicians who worked at a clinic or hospital replied that they were prescribing Kampo medicines to their patients at present. In addition, when physicians who had prescribed Kampo medicines in the past were included, it was 86.1%. The use of Kampo medicines has widely expanded and is a fixture in modern medical treatment in Japan. However, after the report of two cases of interstitial pneumonia upon treatment with the Kampo medicine, Sho-saiko-to, in the Information on Adverse Reactions to Drug No. 107[2)] published by the Ministry of Health and Welfare of Japan, many adverse effects of Kampo medicines have been reported, and instructions on the proper use of

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Kampo medicines are required. In addition, the review entitled, "For the Proper Use of Kampo Medicines", was distributed in the Information on Adverse Reactions to Drug No. 143,[3] and medical workers have begun to think about the indications for Kampo medicines. In such a background and in order to obtain basic data on the proper use of Kampo medicines, all prescriptions containing a Kampo medicine that were issued during a six-year period at a university hospital were analyzed.

Subject and Methods

This study included 79,132 sheets of prescriptions that contained a Kampo medicine and that were issued at Kitasato University Hospital in Kanagawa Prefecture, Japan, over a six-year period from January, 1994 to December, 1999.

Six items including the patients' background, number of prescriptions issued by each clinical department, number of prescriptions of each Kampo medicine, length of the prescribed period of each Kampo medicine, number of prescriptions of each Kampo medicine per year and its annual change, and their combined use with modern medicines were surveyed. As to the combined use of Kampo medicines with modern western medicines, combinations to which special attention should be paid as described in the package inserts were investigated. The length of the prescribed period of each Kampo medicine, the number of prescriptions of each Kampo medicine per year and its annual change, were studied. In addition, the quantity of each constituent herb that was necessary for preparing the prescriptions of the ten most frequently prescribed Kampo medicines each year, was estimated.

Results

1) Background of patients and prescriptions

The total number of prescriptions containing a Kampo medicine issued during the six-year study period was 79,132. Among them, the number of prescriptions for male patients was 27,648 sheets (34.9%) and that of female patients was 51,484 sheets (65.1%). The prescriptions were issued to a total of 8,738 patients [2,640 males (30.2%) and 6,098 females (69.8%)]. The mean number of prescription sheets per patient was 9.1 (males, 10.5; females, 8.5). The percentage of prescription sheets including a Kampo medicine out of the total number of prescriptions sheets issued at the hospital was 2.6% during the study period. The percentage of prescription sheets containing a Kampo medicine out of the total number of prescriptions issued each year between 1994 and 1999 was 3.1% (16,049/524,420), 3.1% (15,622/505,818), 2.7% (14,745/542,811), 2.3% (11,672/498,962), 2.2% (11,210/510,125), and 1.9% (9,834/516,542), respectively, this showed that it decreased throughout the study period (Fig.1). This decline tended to be associated with the reduction in the proportion of total sales of Kampo medicines to those of all pharmaceutical drugs (Fig. 1). As to the age of the patients, Kampo medicines were most frequently prescribed to patients aged 30-39 yr and 50-59 yr (Fig. 2).

2) Number of prescriptions issued by each clinical department

As a result of surveying the sheets from each clini-

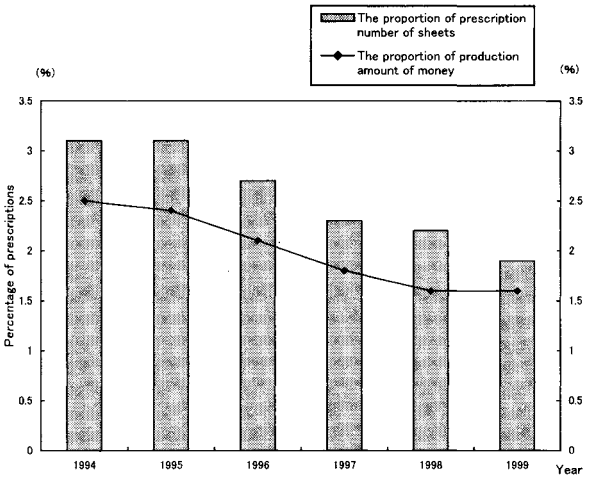

Fig. 1 Annual proportion of prescription sheets containing a Kampo medicine out of the total number of prescription sheets issued at a university hospital between 1994 and 1999.

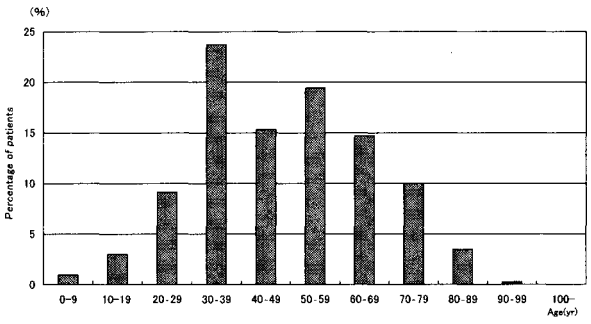

Fig. 2 Age distribution of the patients who were prescribed a Kampo medicine during the study period.

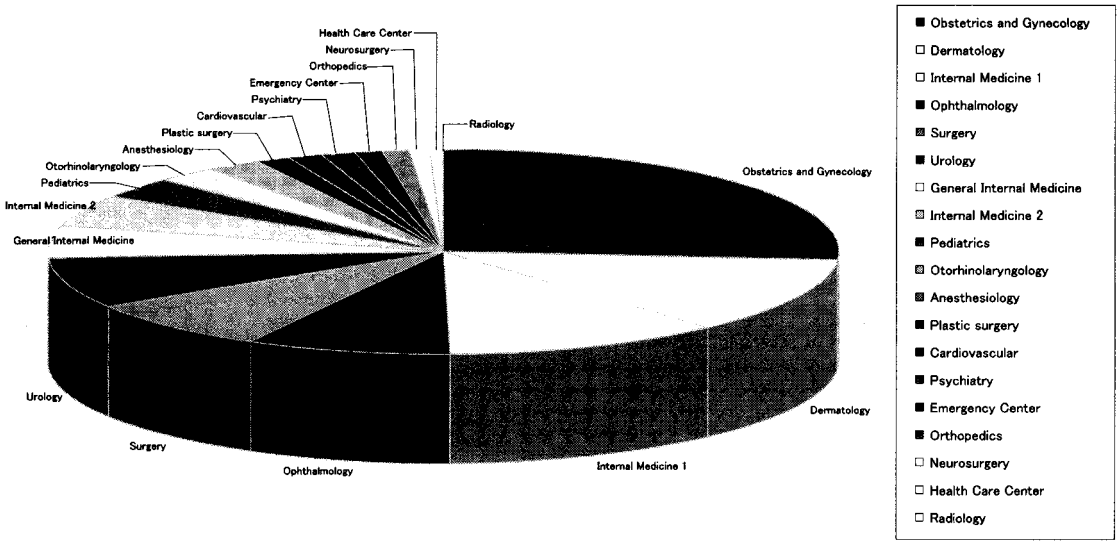

Fig. 3 Proportion of prescriptions including a Kampo medicine issued by each clinical department in the hospital

cal department, we found that the Department of Obstetrics and Gynecology (OBGY) prescribed the largest number of prescriptions containing a Kampo medicine, corresponding to over one-fourth of all prescriptions containing a Kampo medicine issued at the hospital, as shown in Fig. 3. The Department of Internal Medicine (IM) consists of three divisions (First Department of IM ; Second Department of IM; General IM) and the total number of prescriptions containing a Kampo medicine issued by IM ranked second, comprising over one-fifth of the total number of prescriptions containing a Kampo medicine. The First Department of IM which covers the fields of neurology, circulation, collagen disease and infection prescribed 11.3% of the total number of prescriptions containing a Kampo medicine, and the Second Department of IM which covers the fields of respiration, digestion, endocrinology and metabolism, nephrology, and hematology prescribed 4.8%. The Department of General IM prescribed 5.0% of the total number of prescriptions containing a Kampo medicine. Kampo medicines were prescribed by all clinical departments in the hospital, although there were large differences in the number of prescriptions issued by each department.

3) Number of prescriptions of each Kampo medicine

The number of prescriptions of each Kampo medicine and its percentage among the total number of prescriptions containing a Kampo medicine are shown in Table I. Although all 63 Kampo medicines employed in the hospital were prescribed, there were large differences in the number of prescriptions of each Kampo medicine. The ratio of the number of prescriptions of the most frequently prescribed to that of the least frequently prescribed Kampo medicine was over 1,000. Three Kampo medicines were prescribed over 10,000 times during the study period, and they were Sairei-to, Sho-saiko-to and Dai-kenchu-to.

Because Sairei-to (the most frequently prescribed), Saiboku-to (the 18th most frequently prescribed), Saiko-keishi-to (the 33rd), Saiko-ka-ryukotsu-borei-to (the 39th), Saiko-keishi-kankyo-to (the 42nd) and Sho-saiko-to-ka-kikyo-sekko (the 51st) are combinations of Sho-saiko-to (the second) and another formula or additional herbs, the prescribed number of medicines containing all of the component herbs of Sho-saiko-to was 25,311 (32.0%). In addition, Otsuji-to (the fifth most frequently prescribed), Hochu-ekki-to (8th), Kami-shoyo-san (14th), Keigai-rengyo-to (27th), Kami-kihi-to (30th), Jumihaidoku-to (34th), Dai-saiko-to (48th), Yoku-kan-san (56th) and Shigyaku-san (61st) are Saiko-zai, i.e., medicines containing Saiko (柴胡), Bupleuri radix, *Bupleurum falcatum* LINNÉ. As a result, the total number of Saiko-containing medicines was 16(25.4%) out of the 63 formulae, and a Saiko-containing medicine was included in 35,804 prescriptions (39.2%). A large number of Saiko-containing medicines was prescribed throughout the study period.

Kanzo (甘草), Glycyrrhizae radix, *Glycyrrhiza*

Table I. Number of prescriptions of each formula of Kampo medicines.

Ranking	Formula	Number of prescription	Proportion (%)*	Accumulation (%)**			
1	Sairei-to (柴苓湯)	11511	12.62	12.62	**31**	Tokaku-joki-to (桃核承気湯)	509
2	Sho-saiko-to (小柴胡湯)	11445	12.54	25.16	**32**	Toki-shigyaku-ka-goshuyu-shokyo-to (当帰四逆加呉茱萸生姜湯)	458
3	Dai-kenchu-to (大建中湯)	10142	11.12	36.27	**33**	Saiko-keishi-to (柴胡桂枝湯)	396
4	Kakkon-to (葛根湯)	8170	8.95	45.23	**34**	Jumi-haidoku-to (十味敗毒湯)	371
5	Otsuji-to (乙字湯)	3868	4.24	49.47	**35**	Chorei-to-go-shimotsu-to (猪苓湯合四物湯)	333
6	Keishi-bukuryo-gan (桂枝茯苓丸)	3793	4.16	53.62	**36**	Hange-koboku-to (半夏厚朴湯)	333
7	Sho-seiryu-to (小青竜湯)	3184	3.49	57.11	**37**	Bofu-tsusho-san (防風通聖散)	320
8	Hochu-ekki-to (補中益気湯)	2813	3.08	60.20	**38**	Rikkunshi-to (六君子湯)	283
9	Toki-shakuyaku-san (当帰芍薬散)	2776	3.04	63.24	**39**	Saiko-ka-ryukotsu-borei-to (柴胡加竜骨牡蛎湯)	276
10	Bakumondo-to (麦門冬湯)	2769	3.03	66.27	**40**	Eppi-ka-jutsu-to (越婢加朮湯)	270
11	Gorei-san (五苓散)	2506	2.75	69.02	**41**	Unkei-to (温経湯)	270
12	Choto-san (釣藤散)	2292	2.51	71.53	**42**	Saiko-keishi-kankyo-to (柴胡桂枝乾姜湯)	251
13	Gosha-jinki-gan (牛車腎気丸)	2010	2.20	73.74	**43**	Keishi-ka-jutsubu-to (桂枝加朮附湯)	245
14	Kami-shoyo-san (加味逍遥散)	1978	2.17	75.90	**44**	Mashi-nin-gan (麻子仁丸)	220
15	Oren-gedoku-to (黄連解毒湯)	1727	1.89	77.80	**45**	Keishi-ka-shakuyaku-to (桂枝加芍薬湯)	213
16	Hachimi-jio-gan (八味地黄丸)	1633	1.79	79.59	**46**	Ryo-kei-jutsu-kan-to (苓桂朮甘湯)	207
17	Ninjin-yoei-to (人参養栄湯)	1350	1.48	81.07	**47**	Goshuyu-to (呉茱萸湯)	207
18	Saiboku-to (柴朴湯)	1256	1.38	82.44	**48**	Dai-saiko-to (大柴胡湯)	201
19	Chorei-to (猪苓湯)	1218	1.33	83.78	**49**	Toki-inshi (当帰飲子)	195
20	Shakuyaku-kanzo-to (芍薬甘草湯)	948	1.04	84.82	**50**	Rokumi-gan (六味丸)	188
21	Byakko-ka-ninjin-to (白虎加人参湯)	942	1.03	85.85	**51**	Sho-saiko-to-ka-kikyo-sekko (小柴胡湯加桔梗石膏)	176
22	Unsei-in (温清飲)	892	0.98	86.83	**52**	Seijo-bofu-to (清上防風湯)	157
23	Shofu-san (消風散)	848	0.93	87.76	**53**	Shimotsu-to (四物湯)	157
24	Goshaku-san (五積散)	735	0.81	88.56	**54**	Sho-kenchu-to (小建中湯)	151
25	Juzen-taiho-to (十全大補湯)	609	0.67	89.23	**55**	Shimbu-to (真武湯)	151
26	Hange-shashin-to (半夏瀉心湯)	603	0.66	89.89	**56**	Yoku-kan-san (抑肝散)	138
27	Keigai-rengyo-to (荊芥連翹湯)	596	0.65	90.54	**57**	Sammotsu-ogon-to (三物黄芩湯)	126
28	Boi-ogi-to (防已黄耆湯)	590	0.65	91.19	**58**	Keishi-ka-ryukotsu-borei-to (桂枝加竜骨牡蛎湯)	107

29	Seishin-renshi-in (清心蓮子飲)	521	0.57	91.76	**59**	Yokuinin-to (薏苡仁湯)	50
30	Kami-kihi-to (加味帰脾湯)	515	0.56	92.32	**60**	Koso-san (香蘇散)	19
					61	Shigyaku-san (四逆散)	13
					62	Bukuryo-in-go-hange-koboku-to (茯苓飲合半夏厚朴湯)	6
					63	Inchin-ko-to (茵蔯蒿湯)	6
						TOTAL	91,243

*The percentage of prescriptions for the indicated formula out of the total number of prescriptions for all formulae.
**The sum of the proportion of prescriptions for the indicated formula and those of all higher-ranked formulae.

uralensis FISCHER or *Glycyrrhiza glabra* LINNÉ, is also a popular herb in Kampo medicine; the number of Kanzo-containing medicines was 42 (66.7%) out of the 63 formulae, and a Kanzo-containing medicine was included in 62,342 prescriptions (68.3%).

Mao (麻黄), Ephedrae herba, *Ephedra sinica* STAPF, is an important herb as a constituent of Mao-containing medicines, which are widely used for treatment of the common cold, allergic rhinitis, asthma, *etc*. The number of Mao-containing medicines was six (9.5%) out of the 63 formulae, and a Mao-containing medicine was included in 12,729 prescriptions (14.0%).

4) Mean number of prescription days of each medicine

The length of the prescribed period of all Kampo medicines was 91.9 ± 37.1 (mean ± S.D.) days. The mean length of the prescribed period of each Kampo medicine is shown in Table II. The shortest mean prescribed period of a Kampo medicine was 16.3 days for Koso-san, which greatly differed from the longest mean prescribed period of 207.3 days for Toki-inshi. The Kampo medicines with a shorter mean number of prescription days such as Koso-san, Kakkon-to and Sho-seiryu-to were effective during the acute phase of infectious illnesses such as the common cold. However, several Kampo medicines that are usually prescribed for a short period of time, were prescribed for a long period of time in some cases. For Koso-san, the longest prescribed period of Koso-san was 28 days. On the other hand, the longest prescribed period of Kakkon-to and Sho-seiryu-to was 1,456 and 644 days, respectively. The mean (±S.D.) of the largest number of prescription days for each Kampo medicine was 866.1 (±456.6) days. The proportion of prescriptions with a short prescribed period of 14 days or less against the total number of prescriptions of that medicine was the highest for Sho-seiryu-to (75.9%), followed by Bukuryo-in-go-hange-koboku-to (75.0%), Bakumondo-to (73.7%), Koso-san (66.7%), Kakkon-to (65.7%) and so on as shown in Table Ⅱ.

On the other hand, some Kampo medicines were prescribed on average for long periods of time such as Toki-inshi, Dai-saiko-to, and Saiko-ka-ryukotsu-borei-to. Those Kampo medicines that were prescribed for longer periods of time on average, were mainly issued to patients with dermatologic problems, and they included Toki-inshi, Unsei-in, Boi-ogi-to, Shofu-san, Byakko-ka-ninjin-to, and Jumi-haidoku-to. The percentage of prescriptions containing a Kampo medicine for a prescribed period of 14 days or less out of the total number of prescriptions issued for that medicine was the lowest for Unsei-in and Shimotsu-to (13.4%), followed by Eppi-ka-jutsu-to (15.8%) and Dai-saiko-to (16.0%). However, the length of prescribed period for a Kampo medicine greatly varied by case, and 68 cases (0.6%) were administered a Kampo medicine for over 1,000 days. These cases were found in the groups administered Sairei-to (11 cases), Dai-kenchu-to (11 cases), Hochu-ekki-to (six cases), Otsuji-to (five cases), Hachimi-jio-gan (four cases), Boi-ogi-to (four cases), Ninjin-yoei-to (three cases), Unsei-in (three cases), Bakumondo-to (two cases), Shofu-san (two cases), Keishi-bukuryo-gan (two cases), Kakkon-to (one case), Ryo-kei-jutsu-kan-to (one case), Goshaku-san (one case), Kami-shoyo-san (one case), Sho-saiko-to (one case), Gorei-san (one case), Toki-inshi (one case), Jumi-haidoku-to (one case), Juzen-taiho-to (one case), Mashi-nin-gan (one case), Saiboku-to (one case), Dai-saiko-to (one case), Saiko-

Table II. Mean number of prescription days for each formula.

Ranking	Formula	Mean number of prescription days (day)	Proportion of prescriptions that were for 14 days or less (%)	Proportion of prescriptions that were for over 183 days (%)	Proportion of prescriptions that were for over 366 days (%)	Minimum number of prescription days (day)	Maximum number of prescription days (day)
1	Koso-san (香蘇散)	16.3	66.7	0	0	7	8
2	Sho-seiryu-to (小青竜湯)	24.9	75.9	2.7	0.4	3	644
3	Kakkon-to (葛根湯)	26.4	65.7	2.1	0.7	1	1456
4	Bukuryo-in-go-hange-koboku-to (茯苓飲合半夏厚朴湯)	26.5	75.0	0	0	1	64
5	Yokuinin-to (薏苡仁湯)	38.5	37.5	0	0	14	112
6	Bakumondo-to (麦門冬湯)	40.9	73.7	5.9	2.1	1	1309
7	Keishi-ka-ryukotsu-borei-to (桂枝加竜骨牡蛎湯)	41.6	29.4	0	0	7	98
8	Saiboku-to (柴朴湯)	43.4	62.1	3.1	2.1	1	1008
9	Hange-shashin-to (半夏瀉心湯)	51.6	40.0	5.6	2.2	3	394
10	Goshuyu-to (呉茱萸湯)	52.7	37.0	7.4	3.7	3	466
11	Seijo-bofu-to (清上防風湯)	56.3	30.0	0	0	7	294
12	Chorei-to-go-shimotsu-to (猪苓湯合四物湯)	57.0	41.2	5.9	0	7	233
13	Keishi-ka-shakuyaku-to (桂枝加芍薬湯)	60.5	39.4	12.1	3.0	3	378
14	Chorei-to (猪苓湯)	60.6	44.3	9.8	2.7	2	574
15	Ryo-kei-jutsu-kan-to (苓桂朮甘湯)	64.3	22.6	6.5	0	14	308
16	Sho-saiko-to-ka-kikyo-sekko (小柴胡湯加桔梗石膏)	64.7	45.5	13.6	0	3	364
17	Choto-san (釣藤散)	67.2	32.6	7.0	4.7	2	434
18	Sammotsu-ogon-to (三物黄芩湯)	70.0	63.0	18.8	0	14	322
19	Shakuyaku-kanzo-to (芍薬甘草湯)	74.5	34.3	10.7	3.6	1	782
20	Yoku-kan-san (抑肝散)	74.9	30.0	10.0	5.0	14	675
21	Dai-kenchu-to (大建中湯)	77.1	32.9	10.9	4.9	1	1628
22	Saiko-keishi-kankyo-to (柴胡桂枝乾姜湯)	78.0	31.4	17.1	8.6	3	672
23	Seishin-renshi-in (清心蓮子飲)	78.5	42.9	13.0	3.9	5	686
24	Otsuji-to (乙字湯)	80.3	37.3	10.9	5.0	2	1512
25	Toki-shakuyaku-san (当帰芍薬散)	82.0	32.0	12.2	4.9	3	1206
26	Sho-saiko-to (小柴胡湯)	82.6	35.5	11.0	5.2	1	1505
27	Saiko-keishi-to (柴胡桂枝湯)	84.7	42.3	11.5	7.7	2	1134
28	Unkei-to (温経湯)	86.3	17.9	12.8	5.1	7	602
29	Gorei-san (五苓散)	87.0	28.8	13.9	6.6	1	1119
30	Mashi-nin-gan (麻子仁丸)	88.8	45.2	9.8	3.2	1	1526
31	Hange-koboku-to (半夏厚朴湯)	90.4	44.7	10.6	4.3	1	1519
32	Sho-kenchu-to (小建中湯)	92.1	47.8	8.7	0	7	238
33	Kami-shoyo-san (加味逍遥散)	93.1	30.3	12.5	5.2	7	1092
34	Shimotsu-to (四物湯)	94.3	13.4	13.6	9.1	14	615
35	Rikkunshi-to (六君子湯)	94.8	26.2	14.3	7.1	3	840
36	Sairei-to (柴苓湯)	95.4	28.2	14.8	6.6	1	1442
37	Shimbu-to (真武湯)	99.4	36.4	13.6	13.6	1	728
38	Kami-kihi-to (加味帰脾湯)	100.8	24.1	16.5	7.6	14	805
39	Toki-shigyaku-ka-goshuyu-shokyo-to (当帰四逆加呉茱萸生姜湯)	100.9	22.6	16.1	14.5	7	714
40	Juzen-taiho-to (十全大補湯)	101.8	26.9	13.5	7.9	3	1232
41	Goshaku-san (五積散)	106.4	26.3	15.8	15.8	14	791
42	Rokumi-gan (六味丸)	108.4	32.0	12.0	12.0	4	969
43	Ninjin-yoei-to (人参養栄湯)	109.6	30.2	14.4	5.4	2	1470
44	Inchin-ko-to (茵蔯蒿湯)	110.5	25.0	25.0	0	7	182

45	Keigai-rengyo-to（荊芥連翹湯）	111.5	22.6	17.6	9.5	5	924
46	Oren-gedoku-to（黄連解毒湯）	111.8	22.5	21.3	7.1	3	966
47	Eppi-ka-jutsu-to（越婢加朮湯）	112.2	15.8	23.7	5.3	14	728
48	Keishi-ka-jutsubu-to（桂枝加朮附湯）	112.4	18.2	18.2	6.1	7	728
49	Gosha-jinki-gan（牛車腎気丸）	113.4	21.5	17.8	10.3	2	889
50	Keishi-bukuryo-gan（桂枝茯苓丸）	114.9	21.8	17.3	10.7	7	1282
51	Jumi-haidoku-to（十味敗毒湯）	118.2	23.5	21.6	13.7	1	1078
52	Tokaku-joki-to（桃核承気湯）	119.8	31.5	17.8	12.3	2	1470
53	Bofu-tsusho-san（防風通聖散）	122.8	25.6	18.6	11.6	3	777
54	Hachimi-jio-gan（八味地黄丸）	129.9	30.1	21.2	12.4	5	1555
55	Byakko-ka-ninjin-to（白虎加人参湯）	133.2	23.8	30.0	13.1	3	980
56	Hochu-ekki-to（補中益気湯）	133.3	21.8	23.1	11.4	2	1400
57	Shofu-san（消風散）	140.5	27.3	25.6	11.6	8	1287
58	Shigyaku-san（四逆散）	152.5	25.0	50.0	0	8	194
59	Boi-ogi-to（防已黄耆湯）	153.8	24.7	19.8	16.0	2	1330
60	Unsei-in（温清飲）	155.3	13.4	30.3	11.8	14	1302
61	Saiko-ka-ryukotsu-borei-to（柴胡加竜骨牡蛎湯）	158.3	26.5	29.7	18.9	7	1316
62	Dai-saiko-to（大柴胡湯）	165.9	16.0	32.0	20.0	10	1084
63	Toki-inshi（当帰飲子）	207.3	17.9	35.7	25.0	8	1103
	Average	—	—	—	—	5.2±4.3	866.1±456.6

Table III. The three most frequently prescribed formulae issued in each clinical department

Department Number of cases	1st	2 nd	3 rd
Obstetrics & Gynecology [27.1%] 2366（100.0%）	Sairei-to 562（23.8%）	Keishi-bukuryo-gan 376（15.9%）	Toki-shakuyaku-san 252（10.7%）
Dermatology [11.6%] 1016（100.0%）	Oren-gedoku-to 218（21.5%）	Sairei-to 107（10.5%）	Byakko-ka-ninjin-to 80（7.9%）
Internal Medicine 1 [10.9%] 953（100.0%）	Kakkon-to 252（26.4%）	Bakumondo-to 104（10.9%）	Sho-saiko-to 62（6.5%）
Ophthalmology [8.3%] 728（100.0%）	Sairei-to 449（61.7%）	Gorei-san 161（22.1%）	Keishi-bukuryo-gan 35（4.8%）
Surgery [8.3%] 725（100.0%）	Otsuji-to 319（44.0%）	Dai-kenchu-to 129（17.8%）	Hochu-ekki-to 60（8.3%）
Urology [8.2%] 719（100.0%）	Chorei-to 178（24.8%）	Hochu-ekki-to 147（20.4%）	Hachimi-jio-gan 109（15.2%）
General Internal Medicine [5.3%] 461（100.0%）	Kakkon-to 156（33.8%）	Bakumondo-to 66（14.3%）	Sho-seiryu-to 44（9.5%）
Internal Medicine 2 [4.4%] 384（100.0%）	Sho-saiko-to 228（59.4%）	Kakkon-to 108（28.1%）	Bakumondo-to 28（7.3%）
Pediatrics [3.2%] 279（100.0%）	Bakumondo-to 93（33.3%）	Sairei-to 46（16.5%）	Gorei-san 16（5.7%）
Otorhinolaryngology [2.7%] 237（100.0%）	Saiboku-to 145（61.2%）	Sho-seiryu-to 20（8.4%）	Ryo-kei-jutsu-kan-to 15（6.3%）
Anesthesiology [2.1%] 182（100.0%）	Kakkon-to 18（9.9%）	Byakko-ka-ninjin-to 17（9.3%）	Sho-seiryu-to 12（6.6%）
Plastic surgery [1.6%] 136（100.0%）	Shofu-san 50（36.8%）	Boi-ogi-to 38（27.9%）	Sairei-to 31（22.8%）
Cardiovascular [1.3%] 114（100.0%）	Kakkon-to 91（79.8%）	Otsuji-to 5（4.4%）	Keishi-bukuryo-gan 4（3.5%）
Emergency [1.3%] 111（100.0%）	Kakkon-to 31（27.9%）	Dai-kenchu-to 19（17.1%）	Sho-seiryu-to 10（9.0%）

Orthopedics [1.3%] 111 (100.0%)	Gosha-jinki-gan 36 (32.4%)	Kakkon-to 21 (18.9%)	Shakuyaku-kanzo-to 15 (13.5%)
Psychiatry [1.2%] 105 (100.0%)	Keigai-rengyo-to 16 (15.2%)	Sho-seiryu-to 14 (13.3%)	Saiko-ka-ryukotsu-borei-to 12 (11.4%)
Neurosurgery [0.6%] 55 (100.0%)	Kakkon-to 25 (45.5%)	Hachimi-jio-gan 7 (12.7%)	Ninjin-yoei-to 5 (9.1%)
Health Care Center [0.5%] 48 (100.0%)	Sho-seiryu-to 27 (56.3%)	Kakkon-to 9 (18.8%)	Sho-saiko-to 7 (14.6%)
Radiology [0.1%] 8 (100.0%)	Kakkon-to 3 (37.5%)	Ninjin-yoei-to 2 (25.0%)	Juzen-taiho-to 2 (25.0%)
TOTAL [100.0%] 8,738			

keishi-to (one case), Tokaku-joki-to (one case) and Hange-koboku-to (one case). The number of cases which prescribed a Kampo medicine for longer than six months (183 days) or longer than one year (365 days) was 1,393 (15.9%) and 648 (7.4%) cases, respectively. The number of formulae in which the proportion of prescriptions with a prescribed period longer than 6 months exceeded 10% or 20% of the total number of prescriptions was 46 (73.0%) and 13 (20.6%) , respectively. Similarly, the number of formulae in which the proportion of prescriptions with a prescribed period longer than one year exceeded 10% of the total number of prescriptions was 18 (28.6%). The largest number of prescription days for each Kampo medicine was distributed between 28 days (for Koso-san) and 1,628 days (for Dai-kenchu-to) (mean ±S.D., 866.1±456.6 days), and the fewest number of prescription days ranged from one day (for 13 formulae) to 14 days (for nine formulae) (mean±S.D., 5.2±4.3 days), as shown in Table Ⅱ.

5) The number of prescriptions of each Kampo medicine issued by each department

Among all the prescriptions containing a Kampo medicine issued by OBGY, which corresponded to over one-fourth of the prescriptions containing Kampo medicines issued by the entire hospital, the most frequently prescribed formula was Sairei-to (Table Ⅲ). Sairei-to was included in 23.8% of all OBGY prescriptions containing a Kampo medicine. The Kampo medicines that were the second and third most frequently prescribed in OBGY were Keishi-bukuryo-gan (15.9%) and Toki-shakuyaku-san (10.7%), which both belong to Ku-oketsu-zai (駆瘀血剤) . The age distribution of patients who received the three most frequently prescribed formulae among OBGY prescriptions is shown in Fig. 4. Sairei-to was most frequently prescribed to women aged 30-39 yr (50.3%, 284 persons among 565 Sairei-to-prescribed patients from OBGY), but the other two Ku-oketsu-zai, which showed a similar distribution pattern, were most frequently prescribed to women aged 50-59 yr [169 persons among 376 Keishi-bukuryo-gan-administered OBGY patients (44.9%) and 116 persons among 252 Toki-shakuyaku-san-administered OBGY patients (46.3 %)]. Sairei-to was the most frequently prescribed Kampo medicine not only in OBGY, but also in the Department of Ophthalmology (61.7% of the total number of prescriptions issued by this Department), the second most frequently prescribed Kampo medicine in both Dermatology (10.5%) and Pediatrics (16.5%), and the third most frequently prescribed Kampo medicine in Plastic Surgery (22.8%).

Sho-saiko-to was mainly prescribed to patients seen in IM. In the Second Department of IM which treats hepatic and respiratory diseases, the Kampo medicine pre-

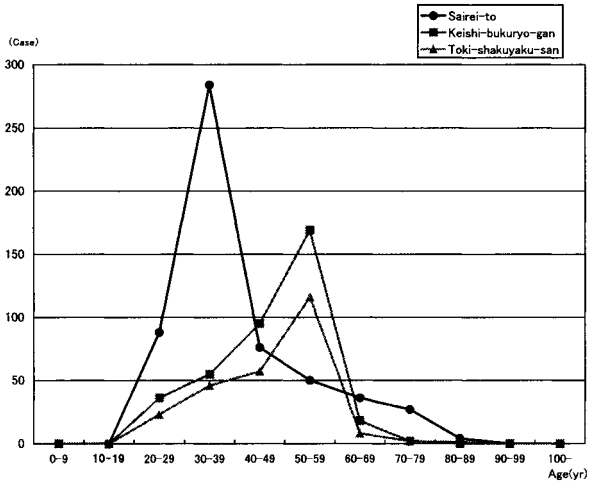

Fig. 4 Age distribution of the patients who were given a prescription containing Sairei-to, Keishi-bukuryo-gan or Toki-shakuyaku-san by the Obstetrics and Gynecology

scribed in nearly 60% of the prescriptions containing a Kampo medicine was Sho-saiko-to and this Kampo medicine was the third most frequently prescribed Kampo medicine in the First Department of IM which covers the fields of collagen disease, infections, *etc.*, and in the Health Care Center. Bakumondo-to was also widely used in the Departments of IM and was the most frequently prescribed Kampo medicine in Pediatrics. One-third of the pediatric patients who were treated with a Kampo medicine received this formula.

Bakumondo-to was the second most frequently prescribed Kampo medicine in both the Departments of First (10.9%) and General (14.3%) IM, and the third most frequently prescribed Kampo medicine in the Second Department of IM (7.3%). Kakkon-to was widely used in various departments and was the most frequently prescribed Kampo medicine in seven departments (37%) and the second most frequently prescribed in three departments (16%) among the 19 clinical departments.

6) Annual change in the prescribed dose of each Kampo medicine

The change in the annual prescribed dose of the ten most frequently prescribed medicines in quantity base is shown in Fig.5. There was no large change in prescribed dose nor ranking of each medicine from 1994 to 1995. However, the quantity of prescriptions of Sho-saiko-to which had been the most frequently prescribed medicine in 1994 and 1995, greatly decreased in 1996 and this tendency continued after 1997. Sho-saiko-to, however, was the third most frequently prescribed medicine even in 1998, the year in which the fewest number of prescriptions containing a Kampo medicine were written, and the number of prescriptions containing Sho-saiko-to tended to increase in 1999. The annual prescribed dose of Kuoketsu-zai, which includes medicines that improve the blood flow such as Keishi-bukuryo-gan, Toki-shakuyaku-san and Kami-shoyo-san, showed no obvious changes over the study period and it tended to be relatively more frequently prescribed as time elapsed. Hochu-ekki-to and Ninjin-yoei-to are Ho-zai (補剤), which strengthens the physical fitness and has sthenia action; these two medicines were among the 10 most frequently prescribed medicines in 1994, but the number of prescriptions and ranking of both medicines tended to decrease thereafter. During the study period, Hochu-ekki-to fell from fourth to fifth and then dropped out of the ten most frequently prescribed medicines, and Ninjin-yoei-to fell from tenth to outside the top ten (18th) during the study period. Kampo medicines that were prescribed at relatively high levels throughout the study period were Sai-rei-to, Dai-kenchu-to and Toki-shakuyaku-san (Fig. 5).

7) Combined prescription with western medicine

The number of prescriptions in which a Kampo medicine was prescribed independently from newly developed western drugs was only 3,181 sheets (4.0%), and the remaining (> 95%) were combined with western drugs. Among them, the number of combined prescriptions with indications of warnings or precautions described in the package inserts for the Kampo medicines was 801 sheets (1.1% of the total number of combined prescriptions) (Fig.6). Each combination of a Kampo medicine and western drug had been written on the same prescription sheet, and there was no case of combined use resulting from prescriptions issued by different departments.

The number of prescriptions of a combination of a Mao-containing Kampo medicine and a xanthine derivative or ephedrine-containing medicine was 678. Of those, 617 (91.0%) were with a xanthine-derivative and the remaining 61 (9.0%) were with an ephedrine-containing

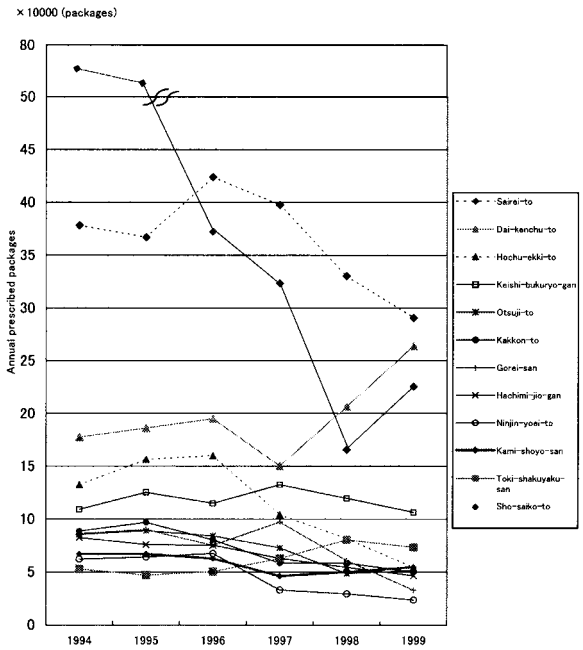

Fig. 5 Change in the annual total dose (packages) of 12 Kampo medicines between 1994 and 1999.

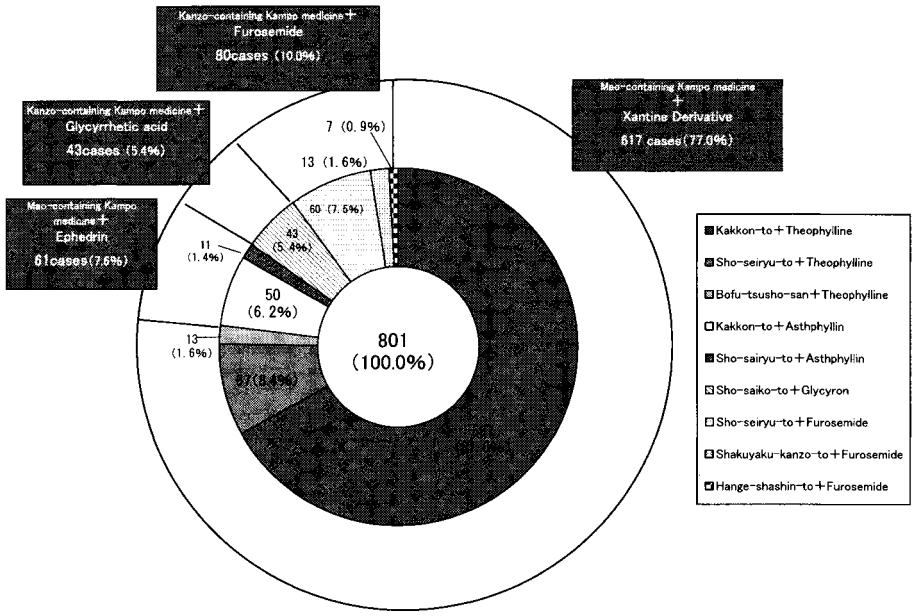

Fig. 6 Prescriptions of combinations of a Kampo medicine and western drug of which possible interactions were written in the package insert.

medicine (Fig. 6). The most frequently prescribed combination was Kakkon-to and a xanthine derivative. The combined use of a Mao-containing Kampo medicine and thyroid preparation or catecholamine derivative was not found.

On the other hand, the number of prescriptions of the combination of a Kampo medicine containing Kanzo with a daily dose over 2.5 g and a glycyrrhizin-containing medicine or diuretic was 123 and, among them, 80 (65.0%) were the combined use with a glycyrrhizin-containing drug and 43 (35.0%) were with a diuretic. The most frequently prescribed combination of a Kanzo-containing Kampo medicine with a western drug was that of Sho-seiryu-to and furosemide (Fig. 6).

8) Annual change in the demand of each constituent herb of major Kampo medicines

In order to obtain information on the demand for the constituent herbs of Kampo medicines, the ten most frequently prescribed formulae each year and throughout the six-year period were investigated. The ten most frequently prescribed medicines over the six-year study period were Sai-rei-to, Sho-saiko-to, Dai-kenchu-to, Keishi-bukuryo-gan, Toki-shakuyaku-san, Kami-shoyo-san, Hochu-ekki-to, Otsuji-to, Kakkon-to and Bakumondo-to. The number of prescriptions of the ten most frequently prescribed or 20 most frequently prescribed Kampo medicines comprised 67.3% and 83.8%, respectively, of all prescriptions issued over the study period, and there was a large difference in prescription quantity between formulae that were ranked in the upper and lower positions. The ten formulae that showed the greatest percentage increase in prescription quantity between 1994 and 1999 were Yoku-kan-san, Unkei-to, Byakko-ka-ninjin-to, Choto-san, Goshuyu-to, Shimbu-to, Hange-shashin-to, Bakumondo-to, Toki-shakuyaku-san and Orengedoku-to. Six of the 10 most frequently prescribed Kampo medicines at our hospital over the study period, i.e., Sairei-to, Dai-kenchu-to, Sho-saiko-to, Toki-shakuyaku-san, Kami-shoyo-san and Kakkon-to, were among the top 10 formulae that were available in the largest quantity in Japan through production and importation in 1999, according to the Annual Report of Statistical Survey on Trends in Pharmaceutical Production.[4] Before 1998, there were no data on the produced quantity of Sairei-to, Dai-kenchu-to and Gosha-jinki-gan in the Annual Report, because only one or two companies produced each formula. Among the 20 most frequently prescribed formulae at our hospital over the study period, 13 were among the most frequently prescribed formulae in Japan. Among the ten most frequently prescribed Kampo medicines in 1999, the prescription quantity of only two formulae, Dai-kenchu-

Table IV. Calculated demand for the constituent herbs of the ten most frequently prescribed formulae in quantity of prescriptions (Kg).

	1994	1995	1996	1997	1998	1999	1999/1994 (%)
Saiko (柴胡), Bupleuri radix, *Bupleurum falcatum* LINNÉ	2851.0	2806.0	1236.5	1118.5	875.0	855.0	29.99
Ninjin (人参), Ginseng radix, *Panax ginseng* C.A.MEYER	1884.7	1396.1	802.6	611.5	542.5	495.1	26.27
Hange (半夏), Pinelliae tuber, *Pinellia ternate* BREITENBACH	1871.4	1823.9	706.6	662.5	550.4	484.5	25.89
Taiso (大棗), Zizyphi fructus, *Zizyphus jujuba* MILLER var. *inermis* REHDER	1796.3	1295.5	611.2	526.4	443.4	376.7	20.97
Ogon (黄芩), Scutellariae radix, *Scutellaria baicalensis* GEORGI	1704.8	1183.3	508.4	470.4	330.3	342.2	20.07
Kanzo (甘草), Glycyrrhizae radix, *Glycyrrhiza uralensis* FISCHER, *Glycyrrhiza glabra* LINNÉ	931.1	931.7	495.1	409.3	325.2	315.9	33.93
Takusha (沢瀉), Alismatis rhizoma, *Alisma orientale* JUZEPCZUK	828.1	807.7	882.4	939.1	793.4	628.8	75.93
Bukuryo (茯苓) Hoelen, *Poria cocos* WOLF	656.5	658.2	779.8	774.3	722.6	596.1	90.80
Keihi (桂皮), Cinnamomi cortex, *Cinnamomum cassia* BLUME	491.4	504.9	570.4	506.8	427.6	348.9	71.00
Sojutsu (蒼朮), Atractylodis lanceae rhizoma, *Atractylodes lancea* DE CANDOLLE	464.5	457.0	499.4	578.6	548.5	443.2	95.41
Chorei (猪苓), Polyporus, *Polyporus umbellatus* FRIES	464.5	457.0	499.4	494.7	391.3	290.7	62.58
Shokyou (生姜), Zingiberis rhizoma, *Zingiber officinale* ROSCOE	455.6	455.5	221.7	189.5	179.3	157.4	34.55
Toki (当帰), Angelicae radix, *Angelica acutiloba* KITAGAWA	303.7	334.5	418.9	312.9	212.1	285.3	93.94
Koi (膠飴), Saccharum granorum	295.9	310.2	324.9	250.4	344.4	440.0	148.95
Botampi (牡丹皮), Moutan cortex, *Paeonia suffruticosa* ANDREWS	178.2	188.6	177.7	185.2	198.3	181.7	101.96
Ogi (黄耆), Astragali radix, *Astragalus membranaceus* BUNGE	176.7	208.7	247.2	138.9	108.9	72.4	40.97
Byakujutsu (白朮), Atractylodis rhizoma, *Atractylodes japonica* KOIDZUMI ex KITAMURA	176.7	280.7	303.6	138.9	108.9	72.4	40.97
Shakuyaku (芍薬), Paeoniae Radix, *Paeonia lactiflora* PALLAS	168.5	189.9	213.7	256.1	316.0	292.1	173.35
Jio (地黄), Rehmanniae radix, *Rehmannia glutinosa* LIBOSCHITZ var. *purpurea* MAKINO	165.3	151.9	240.8	126.2	108.8	93.1	56.32
Kankyou (乾姜), Zingiberis siccatum rhizoma, *Zingiber officinale* ROSCOE	148.0	155.1	162.4	125.2	172.2	220.0	148.65
Kakkon (葛根), Puerariae radix, *Pueraria lobata* OHWI	118.3	129.2	107.8	79.2	78.1	66.4	56.13
Tonin (桃仁), Persicae semen, *Prunus persica* BATSCH	109.3	125.3	114.9	132.6	119.7	106.4	97.35
Mao (麻黄), Ephedrae herba, *Ephedra sinica* STAPF	88.8	96.9	80.5	59.4	58.6	49.8	56.08
Chinpi (陳皮), Aurantii nobilis pericarpium, *Citrus unshiu* MARKOVICH	88.3	104.3	151.8	69.5	54.5	36.2	41.00
Shoma (升麻), Cimicifugae rhizoma, *Cimicifuga simplex* WORMSKJORD	87.0	96.7	95.5	71.2	27.2	43.8	50.34
Sanshuyu (山茱萸), Corni fructus, *Cornus officinalis* SIEBOLD et ZUCCARINI	82.7	75.9	75.3	63.1	54.4	46.5	56.23

Sanyaku (山薬), Dioscoreae Rhizoma, *Dioscorea japonica* THUNBERG	82.7	75.9	75.3	63.1	54.4	46.5	56.23
Sansho (山椒), Zanthoxyli Fructus, *Zanthoxylum piperitum* DE CANDOLLE	59.2	62.0	65.0	50.1	68.9	88.0	148.65
Daio (大黄), Rhei rhizoma, *Rheum palmatum* LINNÉ, *Rheum tanguticum* MAXIMOWICZ, *Rheum officinale* BAILLON, *Rheum coreanum* NAKAI	28.5	29.7	28.1	24.3	0	17.2	60.35
Bushi (附子), Aconiti tuber, *Aconitum carmichaeli* DEBEAUX	13.8	12.7	12.6	10.5	9.1	7.8	56.52
Onji (遠志), Polygalae radix, *Polygala tenuifolia* WILLDENOW	0	0	45.1	0	0	0	–
Gomishi (五味子), Schisandrae fructus, *Schisandra chinensis* BAILLON	0	0	22.6	0	0	0	–
Sanshishi (山梔子), Gardeniae fructus, *Gardenia jasminoides* ELLIS	0	0	0	0	33.3	36.5	–
Senkyu (川芎), Cnidii rhizoma, *Cnidium officinale* MAKINO	0	0	0	62.9	80.5	73.4	–
Hakka (薄荷), Menthae herba, *Mentha arvensis* LINNÉ var.*piperascens* MALINVAUD	0	0	0	0	16.6	18.2	–

(Kg)

to (148.7%) and Toki-shakuyaku-san (138.8%), had increased in comparison with the respective quantity in 1994. Kampo medicines for which there was a remarkable percentage decrease in prescription quantity between 1994 and 1999, were Sho-saiko-to (30.3%), Ninjin-yoei-to (38.0%), Gorei-san (38.3%) and Hochu-ekki-to (41.0%).

The total amounts of herbal drugs necessary for production of the ten most frequently prescribed formulae each year are shown in Table Ⅳ. The consumption of each of the following herbs at our hospital exceeded 300 kg in 1999 Saiko, Takusha (沢瀉), Alismatis rhizoma, *Alisma orientale* JUZEPCZUK, Bukuryo (茯苓), Hoelen, *Poria cocos* WOLF, Ninjin (人参), Ginseng radix, *Panax ginseng* C.A.MEYER, Hange (半夏), Pinelliae tuber, *Pinellia ternate* BREITENBACH, Sojutsu (蒼朮), Atractylodis lanceae rhizoma, *Atractylodes lancea* DE CANDOLLE, Koi, Taiso (大棗), Zizyphi fructus, *Zizyphus jujuba* MILLER var. *inermis* REHDER, Keihi (桂皮), Cinnamomi cortex, *Cinnamomum cassia* BLUME, Ogon (黄芩), Scutellariae radix, *Scutellaria baicalensis* GEORGI, and Kanzo. The quantities of these herbs required in 1999 were lower than those required in 1994 with the exception of Saccharum granorum. On the other hand, the required quantities of five herbs increased from 1994 to 1999; these were Shakuyaku (芍薬), Paeoniae Radix, *Paeonia lactiflora* PALLAS (173.4%), Kankyo (乾姜), Zingiberis siccatum rhizoma, *Zingiber officinale* ROSCOE (148.6%), Koi (膠飴), Saccharum granorum (148.7%), Sansho (山椒), Zanthoxyli Fructus, *Zanthoxylum piperitum* DE CANDOLLE (148.6%), and Botampi (牡丹皮), Moutan cortex, *Paeonia suffruticosa* ANDREWS (102.0%). These herbs are components of Toki-shakuyaku-san, Dai-kenchu-to and Keishi-bukuryo-gan, and the prescription doses of these medicines increased over the study period.

Discussion

1) Characteristics of the hospital and reliability of the data

Kampo medicines have been widely used in Japan and have largely contributed to the maintenance of the health and welfare, as well as to the treatment and care of diseases in the Japanese. However, after the report of interstitial pneumonia presumably induced by Sho-saiko-to in 1996, the use of Kampo medicines which had been thought to be stable in our medical system, suddenly decreased. In order to assess the trends and problems of recent usage of Kampo medicines, we analyzed all prescriptions containing a Kampo medicine that were issued at one general hospital over a six-year period. Many reports that have analyzed the trend of prescriptions at a medical facility have been published[5,6] and through these studies, the nationwide trend can be estimated. The hospital chosen for the present study is a university hospital in a metropolitan area and plays an important role as one of the registered advanced treatment hospitals in Japan

(there were a total of 81 such hospitals in Japan in 1999). This hospital has 19 clinical departments, and the mean daily number of outpatients and mean daily number of hospitalized patients were 3,047 and 922, respectively, in 1998. The trend of Kampo medicine usage might become clear by analyzing the prescriptions issued at an advanced treatment hospital. In addition, our hospital has comparatively greater numbers of doctors and pharmacists with an interest, knowledge and actual history of using Kampo medicine than other university hospitals, although there are differences within our hospital according to the department.

At present, 148 Kampo medicines for ethical usage are available in Japan, although the number of hospitals and clinics that use all formulae is very small. Our hospital has adopted only approximately half of the available Kampo medicines, i.e., 63 formulae, but this figure is relatively not small. Although the adopted 63 formulae were all prescribed during the study period, the prescriptions for the ten most frequently prescribed formulae comprised 66.3%, and those for the 20 most frequently prescribed formulae comprised 84.8% of all prescriptions containing a Kampo medicine. This finding suggests that only a limited number of formulae were prescribed frequently. This trend is the same as the nationwide trend. Oikawa *et al.*[7] analyzed the combined use of Kampo medicine with western medicine at a hospital that had adopted 25 formulae, and the report provided guidelines on the proper use of Kampo medicine by finding inadequate combinations. The number of adopted formulae is not simply thought to reflect the actual nationwide condition of Kampo usage.

During the six-year study period, 2.6% of the prescriptions issued at our hospital contained a Kampo medicine and this value seems to be in agreement with the proportion of Kampo medicines out of all pharmaceutical products in the nationwide survey, although it was not possible to simply compare them. The number and the proportion of prescriptions including a Kampo medicine decreased throughout the study period, and the reduction after 1996 was especially obvious. This sudden decrease was thought to be related to the report on the so-called adverse effect of Sho-saiko-to in March, 1996. The reduction in the usage of Kampo medicines at our hospital correlated well with the reduced usage of Kampo medicine reported in the nationwide survey of pharmaceutical products. Our results showed that the prescribed quantity at our hospital was in agreement with the sales amount from the manufacturer. In 1999, the proportion of Kampo medicines out of all pharmaceutical products produced in Japan stopped decreasing and there was a slight increase in 1999, according to the nationwide survey. The total prescribed amount of Sho-saiko-to also increased at our hospital in 1999 and showed a similar tendency as the nationwide trend. These results suggest that analysis of the trend of Kampo medicine prescriptions at this hospital might be useful for detecting the nationwide trend of use.

2) Trends in the prescriptions of Kampo medicines and the impact of the adverse reaction report

We found that there were large differences in the number of prescribed patients and in the mean number of prescription days among the 63 formulae. Three formulae were each prescribed more than 10,000 times during the study period, and they were Sairei-to, Sho-saiko-to and Dai-kenchu-to. These formulae were among the five most frequently prescribed Kampo medicines in the nationwide survey, and were in good agreement. As the most frequently prescribed formula at our hospital was Sairei-to, which is a combination of Sho-saiko-to and Gorei-san, and the second most frequently prescribed formula was Sho-saiko-to, those formulae that contain all of the constituent herbs of Sho-saiko-to play an important role in Kampo treatment. Seven formulae belonging to the Sho-saiko-to family have been adopted at our hospital and comprised approximately one-third of the total number of prescriptions containing a Kampo medicine. However, after the report of an adverse effect due to Sho-saiko-to, its use decreased sharply. As a result of a slight increase in 1996, Sairei-to became the most frequently prescribed Kampo medicine at our hospital, although its usage also decreased suddenly after 1996 similar to Sho-saiko-to. This result suggested that the doctors at our hospital knew that Sairei-to is a Sho-saiko-to-containing formula. Formulae in which the name of the medicine includes "Sho-saiko-to" such as Sho-saiko-to-ka-kikyo-sekko, would be easily recognized as being in the same group, and their prescribed amount also decreased during this period. On the other hand, 16 formulae containing Saiko as a constituent have been adopted at our hospital. These prescriptions comprised approximately 40% of the total number of prescriptions and the

demand for Saiko-containing formulae was extremely large. There are many Saiko-containing formulae whose name does not contain "Saiko" such as Hochu-ekki-to or Kami-shoyo-san, and there was no obvious change in the number of prescriptions for such formulae around 1996.

There was no significant change in the number of prescriptions for formulae containing Ogon, which is a constituent herb of Sho-saiko-to[8] and is suspected of having caused the interstitial pneumonia. These results suggest that physicians' knowledge of the constituent herbs of each formula was sometimes insufficient even among physicians who use Kampo medicines usually with the knowledge of their indication and efficacy. In 1999, the number of prescriptions for Sho-saiko-to increased again. In the background of this increase, physicians seemed to have learned the usefulness and safety of this formula. One reason could be the pharmacoepidemiological evidence[9] that stopping the use of Sho-saiko-to brought about an increase in the serum aminotransferase levels and aggravation of liver function. On the other hand, the frequency of interstitial pneumonia among patients who received Sho-saiko-to was less than 0.01%.[10] Therefore, balancing the efficacy and adverse effects, the use of Sho-saiko-to has become accepted again. At the same time, because it is known that not only Sho-saiko-to but also other Saiko-containing formulae have anti-inflammatory and anti-fibrotic effects, Saiko-containing medicines have become widely used according to each patient's indication, Sho (証), on the one hand, and, on the other hand, Sho-saiko-to started to be used again in indication-adapted patients. Because formulae belonging to the Sho-saiko-to family are now widely used, the adequate use according to patient's indication and the detailed observation of prescribed patients should become more important. In 1998, Otsuji-to disappeared from among the ten most frequently prescribed formulae. This was thought to be the result of the report on interstitial pneumonia due to Otsuji-to.

These changes in prescriptions including those for Sho-saiko-to-family formulae and Otsuji-to suggested that physicians responded rapidly to information on the safety of the drugs. As a result, not only the release of information on drug safety, but also the results of epidemiological and pharmacotoxicological studies on the causal relationship, establishment of guidelines for appropriate use, and training in making judgments on the safety and adverse reactions of Kampo medicines, are important.

3) Combination of Kampo medicines and new western drugs

From the viewpoint of safety, the potential interaction of Kampo medicine with new western drugs is an important problem. Approximately 96% of the Kampo medicines were prescribed together with a western drug and, among them, 1.1% were combinations to which attention should be paid according to the package inserts. Because each combined prescription was written on the same prescription sheet, there was a possibility that the combination of drugs written on the prescription sheet was not checked carefully. It is important to pay particular attention to the constituent herbs of each Kampo medicine both at the time of writing the prescription and at the time of the prescription check. On the other hand, not only the names of herbs with which a western drug may interact, but also the names of formulae containing such herbs as constituents should be written in the package insert of western drugs. In addition, it is important to pay attention to other combinations that are not written in the package insert such as the combinations of Dai-saiko-to or other Kijitu- or Chimpi-containing formulae and Nifedipine or other CYP 3A4-dependent drugs;[11] Dai-kenchu-to and Acarbose or other α-glycosidase inhibitors;[12] and so on.

4) The role of Kampo medicines in each clinical department, especially in obstetrics and gynecology

Kampo medicines were used to treat a limited number of symptoms or diseases in each clinical department. The patients who were prescribed Kampo medicines consisted of a greater percentage of females than males. This is due to the fact that the OBGY issued the largest number of prescriptions among all departments. One reason that the OBGY frequently prescribed Kampo medicines is that many herbal medicines are suitable for symptoms and diseases specific to females such as menopausal symptoms. Another reason is that Kampo medicines are comparatively safer than new drugs for pregnant women. The number of prescriptions containing Kampo medicines that were issued by OBGY corresponded to about one-fourth of all prescriptions containing Kampo medicines issued by the hospital and there were large differences in the number of prescriptions issued in the various clinical fields. The age distribution of patients in all clinical departments who were prescribed

a Kampo medicine was similar to that from OBGY, and showed two peaks in patients aged 30-39 yr and those aged 50-59 yr. The two peaks were thought to reflect the ages of pregnancy and menopause, respectively. The most frequently prescribed Kampo medicine for patients of 30-39 yr was Sairei-to, and those for patients of 50-59 yr were Toki-shakuyaku-san and Keishi-bukuryo-gan. These formulae are appropriate for the treatment of toxemia and other minor troubles in pregnancy and menopausal syndromes, respectively.

On the other hand, the number of prescription sheets per patient and the number of prescription days per sheet were smaller in the female patients in comparison with those in the male patients. This may be due to the fact that the Kampo medicines used in OBGY sometimes exerted a faster effect. In addition, the prescriptions for pregnant women tended to be issued for a fewer number of days.

These results indicate that Kampo medicines are not simply drugs for elderly persons and are not used over long periods of time, but are medicines suitable for the younger generation and have a rather quick effect. As a result, wider application of Kampo medicines is expected.

5) Length of the prescribed period and clinical role of each Kampo medicine

The mean length of the prescribed period of each formula varied greatly. Also, for a particular formula, the length of the prescribed period among patients showed large variations. Although the length of the prescribed period did not simply reflect the length of time until the disease or symptom was cured, it reflected the nature and specificity of each formula. The length of the prescribed periods of formulae that are frequently used for the treatment of inflammation of the upper respiratory tract such as Kakkon-to, Sho-seiryu-to, Koso-san, *etc.*, was usually short, but for a particular percentage of cases the length of the prescribed period was extremely long. The patient who received Kakkon-to for 1,456 days during the duration of cancer therapy, received this Kampo medicine for pain and shoulder discomfort after the irradiation. The patient who was prescribed Sho-seiryu-to for 644 days was receiving therapy for perennial nasal allergy. Because Kampo medicines are believed to be relatively safe and are sometimes prescribed for long periods of time at the request of the patient, it is important to pay attention to prescriptions containing the same medicine. The Health Care Center, which mainly treats the staff of the hospital, also issued a large number of prescriptions for Sho-seiryu-to at the request of the staff members. Three-fourths of the prescriptions issued by the Health Care Center were for a prescribed period of 14 days or less, and it was thought that the majority of these were prescribed for influenza and the common cold syndrome. The majority of the prescriptions were for Mao-containing medicines and it is possible that they were used as a cold remedy without the side effects of sleepiness and central nervous system suppression. However, since long-term use of Mao-containing medicines may lead to addiction, these medicines need to be investigated further.

On the other hand, formulae that were used for intractable dermatological diseases such as Toki-inshi, Unsei-in, Byakko-ka-ninjin-to, *etc.*, tended to be prescribed for long periods of time. One reason that many prescriptions in the present study had a long prescribed period, is that a high proportion of patients with an intractable disease were referred to our hospital by other clinics and hospitals, because the university hospital plays a role as an advanced treatment hospital. Generally, formulae with a high percentage of prescribed periods of 14 days or less, tended to have a shorter mean prescribed period. However, there were formulae such as Sammotsu-ogon-to that had a long mean prescribed period, although a large percentage of cases had a prescribed period of less than 14 days. Sammotsu-ogon-to was mainly used for the flush of atopic dermatitis. It was usually prescribed for a short period of time, but if the symptoms persisted, the formula was prescribed repeatedly. One of the reasons for the case-to-case variation in the length of the prescribed period was thought to be repeated observation and assessment of each patient and change of prescription. The mean length of the prescribed period of Ho-zai such as Juzen-taiho-to, Hochu-ekki-to, and Ninjin-yoei-to, was over 100 days, and the reason was thought to be that these formulae were mainly used for recovery from damage during cancer chemotherapy, or during the postoperative period. Because Gosha-jinki-gan and Hachimi-jio-gan were mainly prescribed to patients with peripheral neuropathy due to diabetes mellitus which is not easily treatable, the prescribed period of these formulae became prolonged.

Similarly, the prescribed periods of Eppi-ka-jutsu-to and Keishi-ka-jutsubu-to which were frequently given to patients with chronic rheumatoid arthritis, tended to be long due to the long history and course of the primary disorder.

6) Trend in the prescriptions of major Kampo medicines and the effect of newly developed western medicine and therapeutic method

Analysis of the ten most frequently prescribed formulae each year may clarify the trends of treatment. There were only two formulae for which the number of prescriptions issued in 1999 was greater than that in 1994, Dai-kenchu-to and Toki-shakuyaku-san. These formulae have unique effects that cannot be found among western drugs.

Dai-kenchu-to was extensively used during surgery for protection and treatment of postoperative ileus. There is a possibility that Dai-kenchu-to worsens the ileus-like syndrome due to α-glycosidase inhibitors.[12] In order to protect against such iatrogenic effect, adequate information on the proper use of Kampo medicines should be disseminated widely. After such efforts, Dai-kenchu-to would be prescribed more often.

As to Toki-shakuyaku-san, we previously carried out a retrospective study on its efficacy and safety, in which we analyzed the cost-benefit balance and assessed its prophylactic effect and usefulness for the treatment of iron deficiency anemia at this hospital.[13] As a result, the usefulness of Toki-shakuyaku-san was well known at our hospital and the prescribed dose increased after our results were published.

On the other hand, the prescribed amount of Ho-zai decreased over the study period, and fell out of the ten most frequently prescribed Kampo medicines after 1996. Possible reasons for this may be the popularization of G-CSF for the treatment of cancer starting in 1991, the development of Viagra in 1998, advances in new techniques for infertility treatment, introduction of the critical path, efforts to shorten the length of inpatient stays by the hospital, and so on.

The quantity of prescriptions of some formulae such as Yoku-kan-san, Unkei-to, Byakko-ka-ninjin-to, Choto-san, Goshuyu-to, Shimbu-to, Hange-shashin-to, Bakumondo-to, Toki-shakuyaku-san and Oren-gedoku-to tended to increase throughout the study period. The usefulness of many of these formulae for intractable diseases such as lifestyle diseases and atopic dermatitis or for the prevention and treatment of adverse effects of anti-cancer drugs, has been reported.

These results suggest that not only the classical knowledge, but also recent pharmacological evidences and clinical findings were dynamically employed. Similarly, the use of Kampo medicine is easily influenced by many factors such as the development of western drugs and technologies and reports on their adverse effects. However, there are unique Kampo medicines for which there are no alternative western drugs such as Kuoketsu-zai and Dai-kenchu-to, and the usage of these Kampo medicines was relatively stable over the study period and not affected by such factors.

7) Trend in the prescriptions of Kampo medicine and supply of constituent herbs

Although the quantity of prescriptions of each Kampo medicine changed every year, the usage of several important formulae increased over the study period. As a result, it is important to maintain a stable supply of their constituent herbs. It is necessary to develop a plan. Kanzo and Mao were major constituents of the formulae in this study, and were included in 67% and 14% of the formulae, respectively. The present study pointed out the importance of maintaining the supply of the constituent herbs of the ten most frequently prescribed formulae, which corresponded to approximately two-thirds of the total number of prescriptions and could assess the trend of the herbal supply needed. Since the annual amount of consumption of some constituent herbs such as Saiko and a few other herbs exceeded 1,000 kg over a few years only at this hospital, the demand for these herbs in Japan and in the world in the future was estimated to be enormous. Among the herbs with a mean annual consumption of over 300 kg, Koi was the only herb whose demand increased over the study period, and this reflected the increasing usage of Dai-kenchu-to. Besides Koi, the demand for the constituent herbs of Dai-kenchu-to, Toki-shakuyaku-san and Keishi-bukuryo-gan such as Shakuyaku, Kankyo, Sansho and Botampi tended to increase. As a matter of course, the increased demand for these herbs was the result of increased usage of Kampo medicines and reflected the problems with western drugs including appearance of adverse effects. The report of the Japan Specialty Agriculture Products Association estimated that the annual production of Kampo medicines

would reach 200 billion yen in 2010, while the entire demand for crude drugs was estimated to increase by 5% over the five-year period from 2006 to 2010.[14] However, among the constituent herbs of Kampo medicines, Ogon, Onji (遠志), Polygalae Radix, *Polygala tenuifolia* WILLDENOW, Kankyo, Kanzo, Kyonin (杏仁), Armeniacae Semen, *Prunus armeniaca* LINNÉ, Keigai (荊芥), Schizonepetae Spica, *Schizonepeta tenuifolia* BRIQUET, Gomishi (五味子), Schisandrae Fructus, *Schisandra chinensis* BAILLON, Saishin (細辛), Asiasari Radix, *Asiasarum sieboldi* F. MAEKAWA, Sansonin (酸棗仁), Zizyphi Spinosi Semen, *Zizyphus jujuba* MILLER, Chimo (知母), Anemarrhenae Rhizoma, *Anemarrhena asphodeloides* BUNGE, Chotoko (釣藤鉤), Uncariae Uncis Cum Ramulus, *Uncaria rhynchophylla* MIQUEL, Tonin (桃仁), Persicae Semen, *Prunus persica* BATSCH, Hange, Bushi (附子), Aconiti Tuber, *Aconitum carmichaeli* DEBEAUX and Mao are not produced domestically and need to be imported. Takido[15] reported that a countermeasure to maintain the supply of herbs is necessary due to reduced herbal production in Japan. Satake[16] also pointed out that importation of herbs from countries around China would be necessary, because there was no prospect for the release of Chinese restrictions on the export of Kanzo and Mao. Although it is well known that Kanzo is widely used as a low-calorie sweetener,[17,18] drastic conversion to medical use would be necessary. Such surveys to clarify the demand for Kampo medicines and their constituent herbs would be useful for obtaining basic data to assess and develop a plan for maintaining an adequate supply and, if necessary, planting or development of alternative herbs or materials.

This survey was carried out at an advanced treatment hospital and the results are thought to reflect the nationwide trends of prescriptions of Kampo medicines. In the present investigation, the tendency of usage of various Kampo medicines, influence of trends in newly developed drugs and medical technologies, possible interaction resulting from combination with western drugs, and demand for herbs, became clear. A similar type of survey conducted at other types of hospitals and clinics will be useful for obtaining more accurate data. In addition, changes in the prescriptions for Kampo medicines over a six-year period were analyzed in this study and it would be helpful to follow the time-dependent trend at the same hospital.

Part of the results of this investigation was reported orally at the 52nd Annual Meeting of the Japanese Society of Oriental Medicine, held in Sapporo in 2001.

和文抄録

医療用漢方エキス製剤（以下，漢方エキス製剤）の処方動向および問題点の抽出を目的に，首都圏の特定機能病院において使用実態調査を行った。1994年から1999年までの6年間に発行された漢方エキス製剤を含む79,132枚の処方箋を解析した。調査対象施設では63品目の漢方エキス製剤が採用されていた。年齢別処方動向は，30代から60代の年齢層の患者に多く処方される傾向があり，診療科別では婦人科，内科，皮膚科などで多く処方されていた。方剤別では，柴苓湯，小柴胡湯，大建中湯などの品目が処方件数が多く，上位20品目で全体の84.8%を占めていた。経年的な処方実績を観察することによって，大建中湯，当帰芍薬散の需要が急速にのびていたことが明らかになった。一方，処方量の著しい減少が観察された方剤は，小柴胡湯，人参養栄湯，五苓散，補中益気湯などであった。西洋薬との併用に関しては，96.0%が西洋薬との併用処方であり，医療用医薬品添付文書に記載されている併用注意に該当する併用は1.1%であった。その中では，麻黄含有漢方エキス製剤とキサンチン製剤との併用が多く，特に葛根湯とテオフィリンとの併用が最も多く処方監査の充実や有害作用発現に関するモニターが必要であると考えられた。また，1999／1994比により将来的に必要とされる生薬を調査したところ，芍薬（173.4%），膠飴（149.0%），乾姜（148.7%），山椒（148.7%），牡丹皮（102.0%）などの需要が伸びていた。本調査によって，漢方エキス製剤の使用状況の一端が明らかになったが，今後は急性期および療養型の病床において同様の調査を継続して行うことによって，日本における漢方エキス製剤の使用状況がより明確になると考えられた。

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