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Impact of free magnolol excretions in asthmatic patients who responded well to Saiboku-To, a Chinese herbal medicine

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Abstract—Saiboku-To, a mixture of ten different herbal extracts, has been used in Japan and Czechoslovakia for corticosteroid-dependent severe asthma to reduce the maintenance doses of corticosteroid. Magnolol has been considered to be an active component of Saiboku-To as an inhibitor of 11β-hydroxysteroid dehydrogenase and T-lymphocyte proliferation resulting in corticosteroid-sparing. To investigate the relationship between magnolol and the clinical effects of Saiboku-To, urinary magnolol excretion was compared in responders and non-responders under long-term Saiboku-To treatment. The clinical outcome of the Saiboku-To treatment was evaluated in nine asthmatic patients at 52 weeks after the onset of the treatment, using individual fluctuation of asthmatic points obtained from the patients' diary cards. Three patients whose clinical conditions were improved by the treatment were termed responders and six others were termed non-responders. The difference in the amounts of the total magnolol excreted were not significant; however, free (or non-conjugated) amounts of magnolol excreted in the responders were 7 times those in the non-responders ($P < 0.05$). These results suggest that the magnolol might be responsible for the therapeutic effect of Saiboku-To, indicating practical bioavailability in the responders.

Traditional herbal remedies (Kampo medicine in Japan) have been used for treatment of patients with chronic diseases whose clinical symptoms cannot be improved satisfactorily by synthetic medicines (Phillipson & Anderson 1984; Harper et al 1990). However, there has not been detailed knowledge of what kinds and what amounts of chemical constituents are absorbed into the body. Since the individual responses to Kampo therapy are highly variable, the most important therapeutic question has been said to be how to select the subjects to be treated (Niwa et al 1990). To date, this issue has been left to empirical judgement based on oriental diagnostics to differentiate possible responders from non-responders according to constitutional characteristics of the individual patient. In western countries, pharmacokinetics is one of the most important therapeutic concepts in synthetic medicines (Rowland & Tozer 1989). If the individual responses to a specific Kampo medicine depend on the pharmacokinetic variations of its chemical constituents, our therapeutic procedures using Kampo medicines could be reconstructed according to the same concepts as synthetic medicines.

Magnolol is a major urinary product of asthmatic patients treated with prednisolone co-administered with Saiboku-To (Homma et al 1992). Anti-asthmatic pharmacological activities of magnolol include depression of the central nervous system (Watanabe et al 1983), anti-platelet aggregation (Teng et al 1988), suppression of lymphocyte proliferation induced by concanavalin A (Hirano et al 1991) and inhibition of 11β-hydroxysteroid dehydrogenase (Homma et al unpublished data). An additional knowledge of pharmacokinetic properties of magnolol in both responders and non-responders in Saiboku-To therapy may be useful for evaluation of magnolol as an important component of Saiboku-To. To confirm this hypothesis, we carried out preliminary pharmacokinetic analysis of urinary magnolol in asthmatic subjects classed as responders and non-responders to Saiboku-To.

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Materials and methods

Subjects and sample collection. Saiboku-To (TJ-96) used in this study was a commercially available Kampo remedy, consisting of brownish granules of the dry extracts (Tsumura Co, Tokyo, Japan). The herbal constituents and the major components are listed in Table 1.

Nine asthmatic patients participated in the study. The patients' profiles are indicated in Table 2. Informed consent was obtained from each patient and the study was approved by the Ethics Committee of the Tokyo Medical College Hospital. All patients were given 7·5 g Saiboku-To three times daily (each 2·5 g, 2 h after meals). Twenty-four-hour urine samples were collected from the patients from 12 to 20 weeks after starting the treatment. The patients had been treated by co-administration of bronchodilators such as theophylline and β-stimulants, oral and inhaled corticosteroids, and anti-allergic drugs. Changes in clinical status of these patients were examined as follows.

Disease stages of the patients were evaluated by monitoring of asthmatic points according to the criteria of the Japan Allergology Society. The asthmatic points of each patient for each two weeks were calculated from numbers of asthmatic attacks and coughs, amount of phlegm, night waking, and prescribed drugs for the treatment of asthma. The data were collected for 52 weeks before and after the onset of the Saiboku-To therapy using daily diary cards. Differentiation of the responders from non-responders was made by changes in the asthmatic points before and after the treatment. Patients whose asthmatic points declined significantly ($P < 0.05$) or showed a tendency to decline ($P < 0.1$) were judged to be the responders.

Determination of urinary magnolol by HPLC. Since magnolol exists in urine in both free and glucuronic acid conjugated forms (Homma et al 1992), urine samples for the determination of conjugated magnolol were pretreated with β-D-glucuronidase (Homma et al 1993).

Statistical analysis. All data are presented as mean ± standard deviation. The differences in daily excreted amounts of magnolol between the subject groups were analysed with the unpaired Student's *t*-test. Asthmatic points in each patient before and after the onset of the Saiboku-To treatment were compared with the paired Student's *t*-test.

Results

Changes in the mean asthmatic points before and after the onset of the Saiboku-To treatment were compared between the responders and non-responders as illustrated in Fig. 1. The individual data are shown in Table 2. Three patients whose asthmatic points decreased significantly ($P < 0.05$) or tended to decrease ($P < 0.1$) after the treatment were assigned to the responders and the others, the non-responders. There was no statistically significant difference in asthmatic points between the patient groups before the Saiboku-To treatment (Table 2). After the onset of the treatment, however, mean asthmatic points of

Table 1. Crude drug composition of Saiboku-To.

Plant name	Family	Composition (%, w/w)	Major components
Bupleurum falcatum Linne	Umbelliferae	20·6	Saikosaponin a, c, d, e
Pinellia ternata Breitenbach	Araceae	14·7	Homogentisic acid
Poria cocos Wolf.	Polyporaceae	14·7	Eburiconic acid, pachyman
Scutellaria baicalensis Georgi	Labiatae	8·8	Baicalin, baicalein
Zizyphus vulgaris Lamark	Rhamnaceae	8·8	Zizyphus saponin, betulinic acid
Panax ginseng C. A. Meyer	Araliaceae	8·8	Ginsenoside
Magnolia officinalis	Magnoliaceae	8·8	Magnolol, honokiol
Glycyrrhiza glabra L.	Leguminosae	5·9	Glycyrrhizin, liquiritin
Perillae frutescens Britton	Labiatae	5·9	Perillaldehyde
Zingiber officinale Roscoe	Zingiberaceae	3·0	Zingiberen, gingerol

Table 2. Differentiation of the responders from the non-responders on the basis of decreased diagnostic asthmatic points before and after Saiboku-To treatment.

			Asthmatic points**	
Case	Age/sex	Type*	Before	After
Non-responders				
1	27/M	A	339·5±72·2	348·7±48·3
2	67/M	A	167·8±32·5	162·6±39·0
3	76/M	A	340·4±82·8	404·9±69·9
4	34/F	NA	312·1±55·7	396·0±72·2
5	61/F	NA	285·1±97·5	320·3±48·1
6	66/F	NA	255·2±57·3	255·9±106·8
Responders				
7	47/M	A	179·9±35·6	143·6±14·3$^{\#\#}$
8	50/F	NA	278·7±99·9	241·3±34·0$^{\#}$
9	62/M	A	244·7±30·8	184·7±14·3$^{\#\#}$

* Two clinical types of the patients were characterized as atopic (A) and non-atopic (NA) asthma.

** Improvement of asthmatic points was statistically evaluated as; significantly improved ($^{\#\#}P<0·05$) and tended to improve ($^{\#}P<0·1$).

the responders were apparently lower than that of the non-responders as shown in Fig. 1.

Corticosteroid-sparing was successfully achieved in the responders resulting in successful stepwise withdrawal from oral and inhaled corticosteroid use. Two (cases 7 and 9) of the three responders became completely controlled at 38 and 42 weeks, respectively, following the onset of the treatment, with corticosteroid treatment no longer being necessary.

The daily dose of Saiboku-To contained 3·15 mg magnolol, which was administered equally to all patients. The daily dose of magnolol per body weight did not differ significantly between the patient groups (Table 3). Comparison of daily excretion of magnolol between the responders and non-responders is shown in Table 3. Differences in the total and conjugated magnolol excretion between the responders and non-responders were not statistically significant. Recovery of the total magnolol in 24-h urine was calculated as 16·7±8·2% based on the daily dose of magnolol. No statistically significant difference was observed in this recovery rate between the patient groups. However, the free magnolol excretion in the responders was significantly higher (7 times) than that of the non-responders ($P<0·05$).

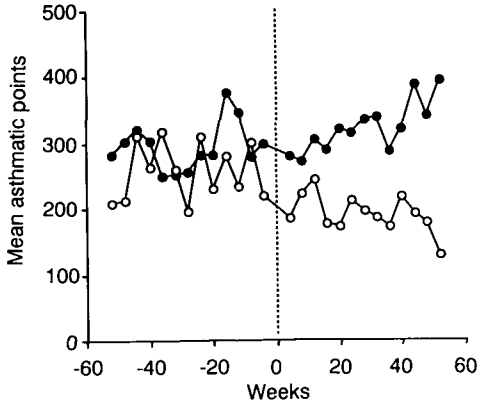

FIG. 1 Changes in mean asthmatic points of patients before and after the onset of Saiboku-To treatment in responders (○) and non-responders (●).

Discussion

Corticosteroid-sparing is the most important therapeutic goal in treating chronic severe asthma (Szefler 1990). Clinical approaches to this goal have been made by co-administration of corticosteroid metabolism inhibitors such as triacetyloleandomycin (Ong et al 1978) and glycyrrhetinic acid (Teelucksingh et al 1990), a split dosage regimen of corticosteroids (Reiss et al 1990), and targeting of T lymphocytes by immunosuppressive agents such as cyclosporin (Alexander et al 1992) and methotrexate (Mullarkey et al 1988). Under these circumstances, Saiboku-To has been extensively used in Japan (Nagano et al 1988) seeking corticosteroid-sparing effects on corticosteroid-dependent asthma.

Pharmacological properties of Saiboku-To, such as the inhibition of histamine release from mast cells (Toda et al 1988) and suppression of type I and type IV allergic reactions (Nishiyori et al 1983, 1985) have been reported. Other relevant pharmacological activities of the herbal constituents and chemical components may contribute to relief of the asthma symptoms; for example, the anti-allergic effects of *Bupleurum falcatum*, *Glycyrrhiza glabra*, *Panax ginseng*, *Magnolia officinalis*, and *Scutellaria baicalensis* (Koda et al 1982), and anti-tussive effect of glycyrrhizin, a component of *G. glabra* (Anderson & Smith 1961), stimulation effects on the hypothalamic-pituitary-adrenal axis by Saiko saponins isolated from *B. falcatum* (Hiai et al 1981) are listed. However, these pharmacological activities attained in animal experiments have not been uniformly confirmed in asthmatic patients. Pharmacokinetic variation of the chemical constituents in patients may cause the difference of therapeutic response to Saiboku-To.

Our interest was focused on the pharmacokinetic profile of magnolol in different disease stages under the Saiboku-To therapy, because this compound could be considered to play an important role in elevation of prednisolone blood level under Saiboku-To co-administration through inactivation of 11β-hydroxysteroid dehydrogenase (HSD) (Taniguchi et al 1992). Although glycyrrhizin, a known HSD inhibitor, is contained in Saiboku-To (Table 1), the amount is too small to alter prednisolone pharmacokinetics (Taniguchi et al 1992). Our preliminary observation that magnolol inhibited rat liver HSD

Table 3. Comparison of daily excreted amounts of urinary magnolol between responders and non-responders of asthmatic patients taking Saiboku-To.

	Daily dose ($\mu g\ kg^{-1}$)	Urinary excreted amounts ($\mu g\ day^{-1}$)		
		Free*	Conjugated	Total
Responders (n = 3)	49·5 ± 8·0	30·2 ± 19·3	601·6 ± 376·8	628·8 ± 353·6
Non-responders (n = 6)	57·5 ± 5·9	4·3 ± 2·3	470·8 ± 214·0	474·2 ± 214·5

* Significant difference was observed between responders and non-responders ($P < 0.05$).

(unpublished data) suggested that the inhibitory effect of Saiboku-To on prednisolone metabolism may be attributable to this simple phenolic compound rather than glycyrrhizin and its active metabolite, glycyrrhetinic acid, which could not be detected in blood or urine after administration of Saiboku-To (Homma et al 1992). An additional pharmacological effect of magnolol on lymphocyte proliferation induced by concanavalin A (Hirano et al 1991) may amplify the corticosteroid-sparing mechanism. Thus, magnolol may contribute to the corticosteroid-sparing effect of Saiboku-To in asthmatic patients treated with prednisolone or similar corticosteroids.

Large individual variation of daily magnolol excretion was observed in both patient groups under the uniform Saiboku-To treatment. Our comparative studies between the responders and the non-responders indicated that the excretion of the free magnolol in the former was higher than that in the latter. This observation seems to be particularly important, suggesting that the higher bioavailability of the total magnolol or the lower conjugation rate of glucuronidation causes the clinical effects of Saiboku-To in the responder group. Therefore, patients with these pharmacokinetic characteristics are considered to be more suitable for Saiboku-To treatment than others. Although some liver or kidney impairments might affect the rate of glucuronidation, our patients' biochemical data such as serum bilirubin, aminotransferase, and creatinine were all in the normal range and did not differ between the responders and non-responders.

One reason that many Japanese doctors use Saiboku-To is its freedom from side-effects. Our results suggest that the pharmacokinetic explanation may be useful in the selection of the responders or in the dosage adjustment for the non-responders to obtain full efficacy of this traditional medicine. More precise pharmacokinetic studies of the relationship between other possible constituents of Saiboku-To and the efficacy of the treatment, however, need to be performed.

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