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Different Effects of Traditional Chinese Medicines Containing Similar Herbal Constituents on Prednisolone Pharmacokinetics

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Abstract

Three major traditional Chinese medicines (TCM), Sho-saiko-To, Saiboku-To, and Sairei-To, consist of similar herbal prescriptions containing glycyrrhizin, which is a strong inhibitor of 11 β-hydroxysteroid dehydrogenase. We performed cross-over open trials in healthy subjects to clarify prednisolone pharmacokinetics on co-administration of these preparations.

All subjects received a single oral dose of 10 mg prednisolone before oral treatment with one of the test preparations. After a 2-week wash-out interval, they received one of the test preparations for three days at daily doses of 7·5 or 9·0 g. On the third study day, 10 mg prednisolone was administered orally in combination with the test preparation. Area under the curves (AUC) of prednisolone before and after the treatment decreased from 0·94 to 0·78 mg h L^{-1} ($P < 0·05$) in the Sho-saiko-To group, increased from 0·92 to 1·06 mg h L^{-1} ($P < 0·01$) in the Saiboku-To group, and did not change in the Sairei-To group. AUC ratios of prednisone and prednisolone, which reflect the 11β-hydroxysteroid dehydrogenase activity, increased in the Sho-saiko-To group ($P < 0·01$), decreased in the Saiboku-To group ($P < 0·01$), and did not change in the Sairei-To group after the treatments. Similar results were observed in ratios of endogenous cortisone to cortisol.

Because of the equal glycyrrhizin content in all three preparations, it was unexpected that the 11β-hydroxysteroid dehydrogenase effect was different amongst the three groups. These observations suggest that some unknown metabolic enzyme modifiers, promoters or inhibitors, may be involved in these traditional treatments.

Glucocorticoids comprise the most potent class of anti-inflammatory and immunosuppressive agents for treatment of acute and chronic disease states. However, long-term use of glucocorticoids has been restricted owing to side-effects (Fauci et al 1976). To use minimal doses of glucocorticoid without loss of symptom control, non-steroidal agents with different mechanisms of action have been co-administered with reduced doses of glucocorticoid. An alternative approach has recently been reported using a glucocorticoid metabolic enzyme inhibitor. Mackenzie et al (1990) showed that glycyrrhetinic acid decreased blood concentration ratios of cortisone to cortisol in healthy volunteers. A therapeutic application can be found in the topical use of cortisol ester (Teelucksingh et al 1990). Glycyrrhetinic acid inhibits 11β-hydroxysteroid dehydrogenase which mediates dehydrogenation of the 11β-hydroxyl substituent (Monder et al 1989). Also, glycyrrhetinic acid is an active form of glycyrrhizin, which is a liquorice glycoside contained in *Glycyrrhiza glabra*.

Three major traditional Chinese medicines, Sho-saiko-To, Saiboku-To, and Sairei-To, contain *G. glabra* and have been occasionally prescribed for collagen diseases, severe asthma, and nephrotic syndrome in conjunction with prednisolone (Senaga & Kawashima 1986; Tani et al 1986; Nagano et al 1988). The herbal constituents of these preparations are listed in Table 1. However, it is not known whether steroid dose-sparing effects of such a complex matrix as mixed herbal medicines are attributable simply to enzyme inhibition. In the present paper, we investigated the effects of the three preparations on prednisolone pharmacokinetics, focusing our attention on the major metabolic pathway via 11β-hydroxy-dehydrogenation.

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Materials and Methods

Preparations

The traditional Chinese medicine preparations used in this study were mixtures of dry aqueous extracts of constituent herbs as indicated in Table 1. Sho-saiko-To, Saiboku-To and Sairei-To were obtained from Tsumura Co. (Tokyo, Japan). They are fine granular formations for ethical use. The prescription guidelines described in the Japanese Pharmacopoeia recommended daily doses of 7·5, 7·5 and 9·0 g for Sho-saiko-To, Saiboku-To and Sairei-To, respectively.

Determination of glycyrrhizin

Amounts of glycyrrhizin contained in the preparations were

Table 1. Herbal compositions of Sho-saiko-To, Saiboku-To and Sairei-To.

Plant name	Family	Composition (%; w/w)		
		Sho-saiko-To	Saiboku-To	Sairei-To
Bupleurum falcatum L.	Umbelliferae	29·2	20·6	17·5
Pinellia ternata Breitenbach	Araceae	20·8	14·7	12·5
Scutellaria baicalensis Georgi	Labiatae	12·5	8·8	7·5
Zizyphus vulgaris Lam.	Rhamnaceae	12·5	8·8	7·5
Panax ginseng C. A. Meyer	Araliaceae	12·5	8·8	7·5
Glycyrrhiza glabra L.	Leguminosae	8·3	5·9	5·0
Zingiber officinale Roscoe	Zingiberaceae	4·2	3·0	2·5
Poria cocos Wolf.	Polyporaceae	–	14·7	7·5
Magnolia officinalis	Magnoliaceae	–	8·8	–
Perillae frutescens Britton var. *acuta* Kudo	Labiatae	–	5·9	–
Alisma orientale Juzepczuk	Alismaceae	–	–	12·5
Atractylodes lancea D. C.	Compositae	–	–	7·5
Polyporus umbellatus Fries	Polyporaceae	–	–	7·5
Cinnamomum cassia Blume	Lauraceae	–	–	5·0

determined by reversed-phase high-performance liquid chromatography (HPLC) (Ogawa et al 1976). Specimens of 100 mg granules were added to 10 mL 50% aqueous ethanol and stirred for 20 min at 65°C. After cooling to room temperature (21°C), the mixtures were centrifuged at 2000 g for 10 min. Ten microlitres of the supernatant was analysed by HPLC. Our HPLC apparatus was a U-880 series obtained from Jasco (Tokyo, Japan), equipped with a conventional ODS-column (Finepack STL, 125 × 4 mm i.d., Jasco). The solvent system was 0·05 M phosphate/methanol (5 : 2, v/v) with a flow rate of 1·0 mL min^{-1}. Direct peak height calibration of glycyrrhizin was conducted at a wavelength of 254 nm and sensitivity of 0·04 aufs. The detection limit of glycyrrhizin was 20 ng injected and coefficients of variation were less than 3% (Ogawa et al 1976).

Subjects and study design

Two-period cross-over open trials were completed by healthy male volunteers. Mean age and body weight of the subjects were 21·8 ± 1·2 years and 63·3 ± 6·8 kg in the Sho-saiko-To group (n = 6), 23·5 ● 1·5 years and 61·3 ± 4·5 kg in the Saiboku-To group (n = 9) and 22·4 ± 1·9 years and 62·0 ± 7·1 kg in the Sairei-To group (n = 7). All subjects were non-smokers and were not taking any medication known to influence glucocorticoid hepatic metabolism or pharmacokinetics.

The subjects in each group were further divided randomly into two groups and participated in both control and test studies in different test periods two weeks apart. The control studies were carried out by administering single 10 mg doses prednisolone orally at 10 00 h. In the test studies, the subjects were given an assigned preparation three times a day, 2 h after meals for three days. Daily doses of Sho-saiko-To and Saiboku-To were 7·5 g (2·5 g × 3) and that of Sairei-To, 9·0 g (3·0 g × 3). On the third day, preparations were co-administered with 10 mg prednisolone at 10 00 h. Blood samples for determination of prednisolone and prednisone were drawn before and 1, 2, 4, 6, and 8 h after prednisolone administration. Blood samples for cortisol and cortisone determination were taken at around 10 00 h on the first and third day before the administration of the preparations. Serum specimens were separated by centrifugation at 1500 *g* for 10 min and stored at −20°C until analysis.

Our study protocol was approved by the ethics committee of our hospital and all subjects gave their informed consent.

Determination of serum glucocorticoids

Serum concentrations of prednisolone, prednisone, cortisol, and cortisone were determined simultaneously by HPLC in combination with rapid-flow fractionation (Oka et al 1984, 1987). Glucocorticoids including dexamethasone as an internal standard were fractionated into small amounts of dichloromethane solution. We used 0·5 mL serum and 50 ng internal standard. Our HPLC system was a U-880 series (Jasco, Tokyo, Japan) equipped with a conventional silica-gel column LiChrosorb Si 60, 5 μm, 250 × 4 mm i.d. (Cica-Merck, Tokyo, Japan). The solvent system was water/methanol/dichloromethane/*n*-hexane (0·1 : 6·0 : 30·0 : 63·9) at a flow rate of 1·5 mL min^{-1}. Detection wave-length was set at 245 nm and sensitivities, 0·0025–0·005 aufs. The analytical detection limit for each glucocorticoid was 1 ng mL^{-1} and the coefficient of variations were less than 5%. Other analytical accuracies were similar to those previously described (Oka et al 1984, 1987).

Calculations

Areas under the serum drug concentrations (AUC) were calculated for prednisolone and prednisone according to the linear trapezoidal rule, extrapolated to 10 h after administration. The elimination rate constant (k_e) was calculated by fitting individual data from the terminal portion of the serum prednisolone concentration–time profile with a log-linear regression equation using the least-squares method. The corresponding elimination half-life ($t_{\frac{1}{2}}$) was calculated by dividing ln 2 by k_e. Individual systemic availability of

Table 2. Glycyrrhizin content of Sho-saiko-To, Saiboku-To and Sairei-To.

Herbal remedy	Daily dose (g)	Glycyrrhizin (mg) in	
		1 g of preparation	Daily dose
Sho-saiko-To	7·5	8·8	66·0
Saiboku-To	7·5	8·5	63·5
Sairei-To	9·0	6·7	60·3

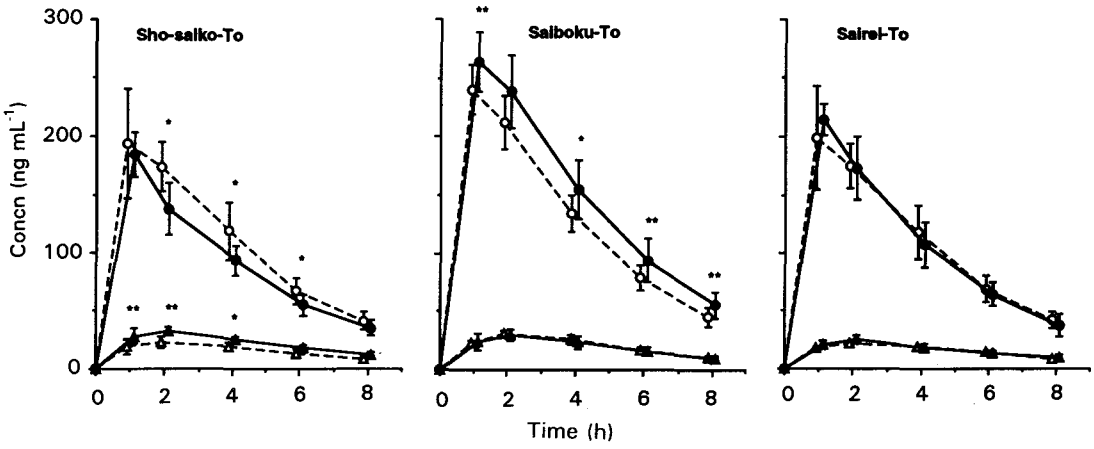

FIG. 1. Plot of serum concentrations of prednisolone (●, ○) and prednisone (▲, △) or after administration of 10 mg prednisolone alone (control, ---) and with the test preparation (—) . $^{*}P < 0.05$, $^{**}P < 0.01$ compared with control values.

prednisolone was not determined in this study; therefore, we used the dosage amount to calculate total body clearance on the assumption that the availability of prednisolone equals 1. Thus, total body prednisolone clearance (CL) was determined by dividing the dose (10 mg) by the AUC. The apparent distribution volume (Vd) was calculated by dividing CL by k_e.

The pharmacokinetic parameters of prednisolone were compared statistically between the control and the test studies, using Student's *t*-test for paired observations. Differences were considered to be significant for $P < 0.05$.

Results

Glycyrrhizin content

The three preparations contain *G. glabra* as a common constituent herb as shown in Table 1. This herb has been known to contain the strong 11β-hydroxysteroid dehydrogenase inhibitors, glycyrrhizin and glycyrrhetinic acid (Ogawa et al 1976; Ojima et al 1990). In our experiments, amounts of glycyrrhetinic acid in the preparations were less than the assay detection limit. However, we found considerable amounts of glycyrrhizin in the three preparations as shown in Table 2. Glycyrrhizin contained in the daily doses of the preparations varied from 60 to 66 mg, but there was not a considerable difference between the remedies.

Effects on prednisolone pharmacokinetics

Mean serum concentrations vs time profiles of prednisolone and prednisone following administration of prednisolone alone (control study) and in combination with the individual preparations (test study) are shown in Fig. 1. Prednisolone concentrations in the test study as compared with the control study decreased in the Sho-saiko-To group ($P < 0.05$), increased in the Saiboku-To group ($P < 0.05$), and remained unchanged in the Sairei-To group. Prednisone concentrations changed significantly only in the Sho-saiko-To group ($P < 0.05$), while they remained unchanged in the other groups.

Different effects of the three preparations on pharmacokinetic parameters of prednisolone are given in Table 3. The control parameters were comparable with those reported by Schrier & Gambertoglio (1991). Sho-saiko-To and Saiboku-To treatment affected the parameters inversely and significantly, whereas Sairei-To treatment showed no considerable changes.

In the Sho-saiko-To group, prednisolone AUC decreased by 16·6% ($P < 0.05$) and the prednisone AUC increased by

Table 3. Comparison of prednisolone pharmacokinetics in subjects receiving Sho-saiko-To, Saiboku-To and Sairei-To.

Group		AUC_{0-10} (μg h mL^{-1})		AUC_{0-10} ratio Prednisone/ prednisolone	CL (L h^{-1})	$t_{\frac{1}{2}}$ (h)	Vd (L)
		Prednisolone	Prednisone				
Sho-saiko-To							
(n = 6)	Control	0·94 ± 0·13	0·14 ± 0·03	0·15 ± 0·03	10·9 ± 1·6	2·84 ± 0·20	43·4 ± 7·1
	Test	0·78 ± 0·10*	0·19 ± 0·01	0·25 ± 0·03**	13·0 ± 1·6*	2·74 ± 0·27	55·4 ± 6·4*
Saiboku-To							
(n = 9)	Control	0·92 ± 0·08	0·15 ± 0·02	0·16 ± 0·02	10·9 ± 0·9	2·69 ± 0·29	42·2 ± 4·6
	Test	1·06 ± 0·12**	0·14 ± 0·02	0·14 ± 0·02**	9·6 ± 1·1**	2·82 ± 0·23	38·7 ± 2·7
Sairei-To							
(n = 7)	Control	0·95 ± 0·12	0·14 ± 0·02	0·15 ± 0·03	10·7 ± 1·5	2·80 ± 0·21	43·6 ± 6·5
	Test	0·91 ± 0·13	0·15 ± 0·02	0·16 ± 0·02	11·1 ± 1·5	2·73 ± 0·22	43·6 ± 3·9

$^{*}P < 0.05$, $^{**}P < 0.01$ compared with control.

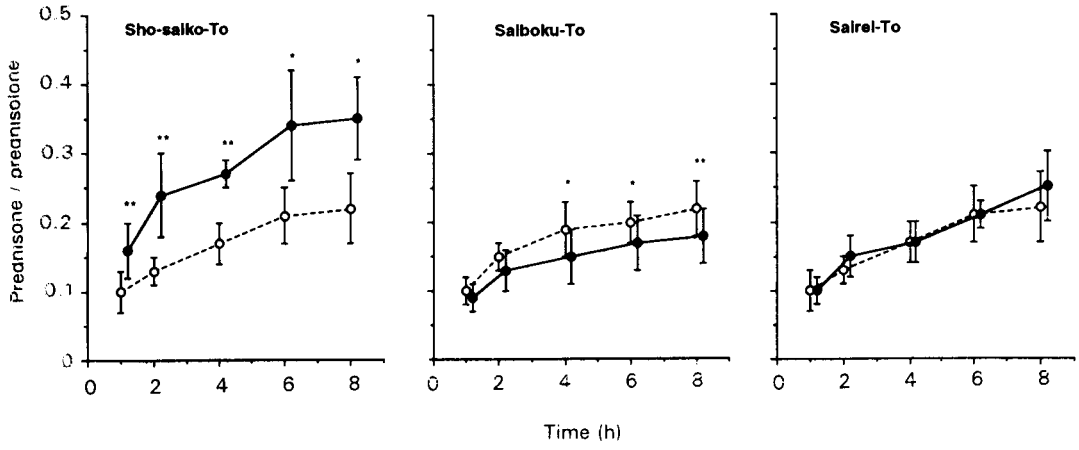

FIG. 2. Plot of concentration ratios of prednisone/prednisolone after oral administration of 10 mg prednisolone alone (control - - -) and with the test preparation (—). $*P < 0.05$ $**P < 0.001$ compared with control values.

19·4% ($P < 0.05$). The elimination half-life ($t_{\frac{1}{2}}$) of prednisolone in this group tended to shorten but the change was not statistically significant.

In the Saiboku-To group, parameters changed in the opposite direction. Prednisolone AUC increased significantly by 14% ($P < 0.01$), while prednisone AUC tended to decrease. Also, $t_{\frac{1}{2}}$ tended to lengthen, but not significantly.

Changes in ratio of prednisone/prednisolone

Time profiles of mean serum concentration ratios of prednisone to prednisolone with and without co-administration of the preparations were compared between the treatment groups (Fig. 2). Concentration ratios after the treatment increased in the Sho-saiko-To group, decreased in the Saiboku-To group, and remained unchanged in the Sairei-To group. This suggested that interconversion of prednisolone to prednisone is promoted by Sho-saiko-To and inhibited by Saiboku-To. The magnitude of these modifications was deduced from AUC ratios of prednisone/prednisolone as described in Table 3. Observed AUC ratios in the Sho-saiko-To group showed a 67% increase after the treatment ($P < 0.01$), whereas those in the Saiboku-To group showed a 13% decrease. These data strongly suggested that the converting enzyme activity was modified differently in the two groups.

Effects on endogenous cortisol and cortisone

Effects of the preparations on endogenous cortisol and cortisone concentrations, and their ratio (cortisone/cortisol) were compared (Table 4). Mean cortisol concentration in the Sho-saiko-To and Sairei-To groups decreased after the treatment ($P < 0.05$), but tended to increase in the Saiboku-To group. Although effects of the treatment on cortisone concentrations were not statistically significant, changes in the concentration ratios, cortisone/cortisol, were comparable with those of prednisone/prednisolone. The mean concentration ratios increased by 72% in the Sho-saiko-To group ($P < 0.05$), decreased by 15·4% in the Saiboku-To group ($P < 0.05$), and remained unchanged in the Sairei-To group (Table 4).

Discussion

G. glabra (liquorice) derivatives such as glycyrrhizin and glycyrrhetinic acid have been known to inhibit 11β-hydroxysteroid dehydrogenase (Monder et al 1989). Intravenous administration of glycyrrhizin at a dose of 40 mg

Table 4. Comparison of serum cortisol and cortisone concentrations in subjects receiving Sho-saiko-To, Saiboku-To and Sairei-To.

Group		Serum concentration (ng mL^{-1})		Concentration ratio cortisone/cortisol
		Cortisol	Cortisone	
Sho-saiko-To				
(n = 6)	Control	101·1 ± 27·3	24·1 ± 6·7	0·25 ± 0·10
	Test	75·3 ± 30·0*	27·1 ± 5·6	0·43 ± 0·21*
Saiboku-To				
(n = 9)	Control	119·1 ± 45·4	27·7 ± 7·1	0·26 ± 0·08
	Test	131·9 ± 63·1	25·1 ± 4·6	0·22 ± 0·08*
Sairei-To				
(n = 7)	Control	97·9 ± 23·6	20·9 ± 3·2	0·23 ± 0·09
	Test	88·2 ± 26·6*	18·5 ± 1·8	0·23 ± 0·06

*$P < 0.05$ compared with control.

revealed no effect on the diurnal rhythm of endogenous cortisol, while it increased AUC and the half-life of prednisolone (Ojima et al 1990). Oral administration of glycyrrhetinic acid for one week at daily doses of 500 mg decreased the cortisone/cortisol ratio (Mackenzie et al 1990). These results suggest that oral administration of mixed herbal remedies containing liquorice might also alter prednisolone pharmacokinetics.

The three herbal remedies tested in this study contained considerable amounts of glycyrrhizin, 60–66 mg, in their daily doses. Reported bioavailability of glycyrrhizin when administered orally is very low (Groot et al 1988) unless the glycoside is converted to its aglycone, glycyrrhetinic acid. If this occurs in the intestinal tract, then glycyrrhetinic acid may contribute to steroid metabolism via its potent inhibition of 11 β-hydroxysteroid dehydrogenase. We considered that this predictable effect of glycyrrhetinic acid may be equally displayed by the three preparations in this study because they contained similar amounts of the glycoside in their daily doses.

Our most important finding is that the effects of the three preparations on prednisolone pharmacokinetics were significantly different.

Our results support the idea that unknown modifiers of the hydrogenase including promoters and inhibitors will affect the pharmacokinetics of prednisolone. Sho-saiko-To is characterized by promotion of 11β-hydroxysteroid dehydrogenase, resulting in transformation of prednisolone into inactive prednisone whereas Saiboku-To is characterized by inhibition of the enzyme. A similar situation may occur for Sairei-To, even though this medicine had no effect on apparent prednisolone pharmacokinetics.

The lack of statistical differences observed for endogenous hormones cortisol and cortisone may depend on differences in major metabolic enzymes between cortisol and prednisolone; the former is subjected primarily to A-ring hydrogenase and the latter to 11β-hydroxysteroid dehydrogenase (Rodchenkov et al 1991). Another reason may be the negative feedback controls that hold cortisol concentrations at intrinsic physiological levels.

We ruled out the possibility of other pathways to regulate prednisolone pharmacokinetics as follows. Prednisolone pharmacokinetics are influenced by agents which modify microsomal liver enzymes such as 6β-hydroxylase, or protein binding (Frey & Frey 1990). Although ketoconazol and oral contraceptive steroids increase plasma prednisolone concentration by 6β-hydroxylase inhibition and plasma transcortin induction, respectively, these pharmacological changes do affect prednisolone interconversion as assessed by the prednisone/prednisolone ratio (Frey & Frey 1990). On the contrary, 6β-hydroxylase inducers such as phenytoin, barbiturates, carbamazepin, and rifampicin decrease the plasma prednisolone concentration and modify the interconversion. In this case, however, the concentration ratio prednisone/prednisolone decreased despite declining plasma prednisolone concentration (Frey & Frey 1990). Although the reason for this is still unclear, the contribution of 11β-hydroxysteroid dehydrogenase is unlikely. Thus, the relationships between the plasma prednisolone concentration and prednisone/prednisolone ratio in these inducers could not explain the situation for the traditional Chinese medicine.

Multiple chemical components in addition to glycyrrhizin could play a role in the modifications. Saiboku-To contains at least three additional herbal extracts in addition to the seven constituents of Sho-saiko-To, and suggests the existence of additional inhibitory candidates in the form, such as magnolol. Magnolol has been detected in urine at considerable concentrations in subjects receiving Saiboku-To (Homma et al 1992). Higher urinary excretion of magnolol was characteristic of the responsive asthmatic patients rather than non-responsive ones in this treatment (Homma et al 1993a, b), and inhibition of 11β-hydroxysteroid dehydrogenase in-vitro has recently been demonstrated by us using rat liver homogenates (Homma et al 1994). We suggest that the clinical effect of this preparation on steroid dehydrogenase may also be attributable to magnolol.

The three preparations used in this study are recommended for use in steroid dose-sparing, and are thought to act by inhibition of glucocorticoid metabolism by liquorice triterpenoids such as glycyrrhizin and glycyrrhetinic acid (Monder et al 1989; Teelucksingh et al 1990), activation of ACTH secretion and thus elevation of endogenous serum cortisol (Hiai et al 1981; Yokoyama et al 1983), or by replacing endogenous steroids (Abe et al 1981; Nagano et al 1988). The first mechanism was partly confirmed in the case of Saiboku-To, with magnolol as the inhibitor, but this mechanism does not operate for Sho-saiko-To or Sairei-To. The second mechanism is unlikely as we could not detect any elevation of endogenous cortisol. The third mechanism may take place to a certain extent, because the remedies contain some anti-inflammatory (Toda et al 1988) or anti-allergic (Koda et al 1982; Nishiyori et al 1983) components which we have shown to be absorbed into the body after administration of these preparations (Homma et al 1992, 1993a).

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