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Effects of Sho-saiko-to on the Pharmacokinetics and Pharmacodynamics of Tolbutamide in Rats

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Abstract

Although Sho-saiko-to (Xiao Chai Hu Tang), a major Chinese traditional medicine, is frequently prescribed with other synthetic or biotechnological drugs for the treatment of various chronic diseases, there is a dearth of information about interactions between sho-saiko-to and co-administered drugs. This paper reports the effects of Sho-saiko-to on the pharmacokinetics and glucose responses of a sulphonylurea hypoglycaemic agent, tolbutamide, after their oral administration in rats.

After oral administration of tolbutamide (50 mg kg^{-1}) with or without Sho-saiko-to extract powder (300 mg kg^{-1}) to male Sprague–Dawley rats cannulated in the jugular vein, plasma tolbutamide and glucose levels were periodically measured. Co-administration of Sho-saiko-to tended to elevate the plasma tolbutamide concentration in the absorption phase. A two-compartment lag-time model was found to describe the plasma tolbutamide concentration–time data. The maximum concentration of tolbutamide was significantly increased and time to reach the maximum concentration was reduced to about 70% by co-administration with Sho-saiko-to. There was no significant change in area under the curve or in the elimination half-life of tolbutamide. The extent of the lowering effect of tolbutamide on plasma glucose levels was increased up to 0·75 h and decreased after 5 h after co-administration of Sho-saiko-to.

In conclusion, these studies suggest that sho-saiko-to slightly hastens the gastrointestinal absorption of tolbutamide. Furthermore, it is considered that elevation of the gastrointestinal absorption rate by Sho-saiko-to might potentiate the hypoglycaemic effect of this sulphonylurea in the early period after oral administration.

Traditional Chinese medicine has recently been used on a large scale for the treatment of many chronic diseases in Japan, because it seems to combine mild, wide therapeutic efficacy with relatively low incidence of adverse reactions in comparison with synthetic drugs.

Sho-saiko-to (Xiao Chai Hu Tang), a widely used traditional Chinese medicine prepared from seven herbs (Table 1), is one of the 'Kampo' formulations prescribed most frequently in Japan. Sho-saiko-to is often used for the treatment of chronic diseases such as hepatitis, bronchitis and gastroenteropathy. Principal synthetic or biotechnological drugs are commonly prescribed for these chronic diseases with traditional Chinese medicine being used for supplementary purposes, so it is important to obtain information about pharmacokinetic and pharmacodynamic interactions between sho-saiko-to and the co-administered drugs. The effects of Chinese medicines, including sho-saiko-to, on the pharmacokinetics and bioavailability of co-administered synthetic drugs have been discussed (Lin et al 1991; Hosoya et al 1993; Hasegawa et al 1994; Homma et al 1995).

Tolbutamide, 1-butyl-3(*p*-tolylsulphonyl)urea, a prototype of the sulphonylurea derivatives that act by increasing pancreatic insulin, is still used as an oral hypoglycaemic agent for the treatment of diabetes mellitus despite serious toxic effects, of which hypoglycaemia caused by overdose or possible drug interaction are probably the most frequent. The compound also has a fairly low therapeutic index, so pharmacokinetic changes of tolbutamide could lead to serious pharmacodynamic reactions (Hansen & Christensen 1977;

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Table 1. Herbal composition of Sho-saiko-to.

Plant name	Family	Composition (%, w/w)
Bupleurum falcatum L.	Umbelliferae	29·2
Pinellia ternata Breitenbach	Araceae	20·8
Scutellaria baicalensis Georgi	Labiatae	12·5
Zizyphus vulgaris Lam.	Rhamnaceae	12·5
Panax ginseng C. A. Meyer	Araliaceae	12·5
Glycyrrhiza glabra L.	Leguminosae	8·3
Zingiber officinale Roscoe	Zingiberaceae	4·2

Jackson & Bressler 1981). Therefore, it is necessary to pay full attention to the interaction of tolbutamide when it is prescribed with other drugs. Although tolbutamide is used with Sho-saiko-to in many cases of non-insulin-dependent diabetes mellitus, neither pharmacokinetic nor pharmacodynamic interaction between them has yet been reported.

In this study we have conducted fundamental investigations on the effect of Sho-saiko-to on the pharmacokinetics and glucose responses of tolbutamide after oral co-administration to rats. To elucidate the net effect of Sho-saiko-to, its extract powder was used rather than the commercially available product.

Materials and Methods

Materials

Tolbutamide was obtained from Sigma (St Louis, MO). Sho-saiko-to extract powder was kindly supplied by Tsumura (Tokyo, Japan). Other chemicals were of analytical grade and purchased from Wako Pure Chemicals Industries (Osaka, Japan) or Nacalai Tesque (Kyoto, Japan).

Animals

Experiments were performed on 10-week-old male Sprague–Dawley rats (Japan SLC, Hamamatsu, Japan), 285 to 337 g. Approximately 18 h before drug administration each rat was anaesthetized with ether and the right external jugular vein was cannulated (Upton 1975). Animals were then fasted with free access to water in individual cages.

Drug administration

Tolbutamide was uniformly dispersed in a solution of 1% potato-starch in 0·9% NaCl (potato starch saline), with or without Sho-saiko-to extract powder, by use of a teflon homogenizer. The suspension was administered orally to the rats under light ether anaesthesia. The doses of tolbutamide and Sho-saiko-to extract powder were 50 and 300 mg kg^{-1}, respectively, and the volume of suspension administered was 4 mL kg^{-1}. Blood samples (300 μL) were collected 0, 0·25, 0·5, 0·75, 1, 2, 3, 5, 8, 16 and 24 h after dosing and the plasma was immediately separated, by centrifugation, for determination of tolbutamide and glucose.

Analytical procedures

Tolbutamide. Plasma tolbutamide concentrations were determined by high-performance liquid chromatography (HPLC), the method being similar to several methods reported previously (Hill & Crechiolo 1978; Wählin-Boll & Melander 1979; Kivistö & Neuvonen 1991) but with minor modifications. Hydrochloric acid (0·5 mol L^{-1}; 0·5 mL) and internal standard solution (100 μL of a solution of chlorpropamide (20 μg mL^{-1}) in a 1 : 1 (v/v) mixture of acetonitrile and water) were added to plasma (100 μL). The mixture was then added to a 1 : 1 (v/v) mixture of dichloromethane and hexane (5 mL) and vigorously shaken for 10 min. After centrifugation for 5 min at 3000 rev min^{-1} the organic phase was evaporated to dryness under a gentle stream of nitrogen at 40°C. The residue was reconstituted in acetonitrile–water (1 : 1 v/v; 200 μL) and 10 μL was injected into the chromatograph. The mobile phase was a 40 : 60 (v/v) mixture of acetonitrile and 0·01 mol L^{-1} phosphate buffer, the pH of which was adjusted to 3·5 with phosphoric acid, and the flow rate was 1·0 mL min^{-1}. Reversed-phase HPLC was performed on a 4·6 mm i.d. × 150 mm Wakosil-II C18 ODS column (Wako Pure Chemicals Industries, Osaka, Japan). Ultraviolet spectrophotometric detection (Shimadzu, Kyoto, Japan; SPD-10A) was performed at 230 nm. Under these conditions, the calibration plot for plasma tolbutamide was linear over the concentration range 0·5–150 μg mL^{-1}. The regression equation was $y = 0{\cdot}210x + 0{\cdot}014$, $r = 1{\cdot}000$, where y is the peak area ratio of the drug to the internal standard, x is plasma concentration (μg mL^{-1}) of the drug and r is the correlation coefficient. The coefficients of variation for the assay were within 3·3% over the range.

Glucose. Immediately after plasma separation, 30 μL of plasma was analysed for glucose by the glucose oxidase method using a Reflotron (Boehringer Mannheim, Mannheim, Germany) biochemical assay system.

Data analysis

After single oral administration of tolbutamide, plasma tolbutamide concentration (C_t)–time (t) data

were analysed by means of two-compartment lag-time model (Wagner 1975) represented by the equation:

$$C_t = A \cdot e^{-\alpha(t-t_{lag})} + B \cdot e^{-\beta(t-t_{lag})} - (A+B) \cdot e^{-K_a(t-t_{lag})} \quad (1)$$

where A, B, α and β are hybrid parameters, K_a is the absorption rate constant and t_{lag} is the time delay of drug absorption. These kinetic parameters were estimated by use of the non-linear least-squares regression software WinNonlin (Scientific Consulting, Cary, USA). The elimination rate constant (K_e), the elimination half-life ($t_{1/2\beta}$), the maximum concentration (C_{max}), the time to reach the maximum concentration (t_{max}), the area under the plasma concentration–time curve (AUC), the total body clearance (CL_{tot}) and the distribution volume (V_d) were calculated by use of conventional equations.

To evaluate the pharmacological effect of tolbutamide, decremental levels of plasma glucose (C_{dec}) were calculated by use of the equation:

$$C_{dec} = (C_{g0} - C_{gt}) - (C_{g0} \text{ of the control} - C_{gt} \text{ of the control}) \quad (2)$$

where C_{gt} is the plasma glucose level at time t and C_{g0} is the plasma glucose level before drug administration. Control data were obtained from rats administered potato starch saline or Sho-saiko-to extract powder without tolbutamide.

Statistics

Student's *t*-test was used to estimate the statistical significance of differences between the means of two groups of results. A *P* value of 0·05 or less was considered to be indicative of statistical significance.

Results

Pharmacokinetics of tolbutamide

Plots of plasma tolbutamide concentration against time after single oral administration to rats, with or without Sho-saiko-to extract powder, are presented in Figure 1. The plasma tolbutamide concentration increased rapidly after drug administration and then declined biexponentially with time for both groups. It was observed that plasma tolbutamide concentrations in the absorption phase were elevated in the group of rats receiving co-administered Sho-saiko-to; there was a significant difference between plasma tolbutamide concentrations in these groups 1 h after drug administration (Figure 1). In the elimination-phase the plasma tolbutamide concentration tended to be reduced by co-administration with sho-saiko-to.

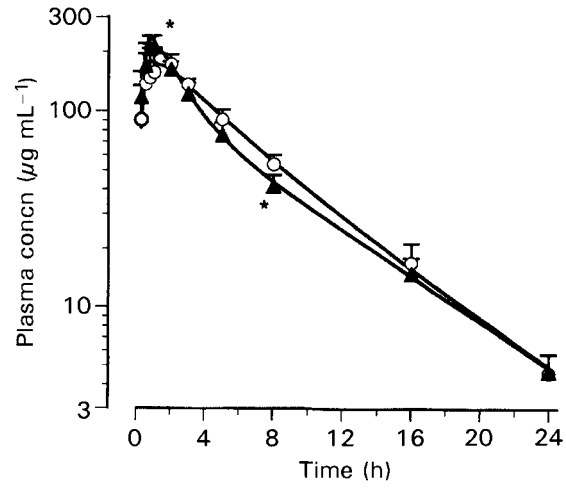

Figure 1. Time-courses of plasma tolbutamide levels after oral administration of tolbutamide (50 mg kg^{-1}) without (○) or with (▲) Sho-saiko-to extract powder (300 mg kg^{-1}) to rats. Each value is the mean and s.d. of results from 5 or 6 rats. *$P < 0.05$, significantly different from result for tolbutamide alone. Each line indicates the simulation curve obtained from the mean data by use of the computer program WinNonlin.

The plasma concentration–time curves for both groups were more adequately described by a two-compartment lag-time model (Wagner 1975; Figure 1). The corresponding pharmacokinetic parameters for tolbutamide, estimated by analysis of the observed data, are given in Table 2. C_{max} for tolbutamide was significantly increased from 176 to 213 $\mu g\ mL^{-1}$ by co-administration with Sho-saiko-to. For rats receiving co-administered Sho-saiko-to the t_{max} for tolbutamide was reduced to approximately 70% that of the control. However, co-administration with Sho-saiko-to had no significant effect on $t_{1/2\beta}$, AUC, CL_{tot} and V_d.

Glucose responses

To evaluate the effect of tolbutamide on plasma glucose levels, rats administered potato starch saline or Sho-saiko-to alone were used as respective control groups against rats given tolbutamide alone or tolbutamide plus Sho-saiko-to. The profiles of plasma glucose level against time after single oral administration of tolbutamide with or without Sho-saiko-to are shown, with the profiles from the respective control groups, in Figure 2. Plasma glucose levels of rats given tolbutamide alone decreased instantaneously after administration and reached a trough after approximately 2 h. Plasma glucose levels for this group then gradually increased and returned to initial values 8 h after dosage. Although the time-courses of plasma glucose levels were similar for rats given tolbutamide

Table 2. Tolbutamide pharmacokinetic parameters estimated from plasma concentration–time data after oral administration of tolbutamide (50 mg kg^{-1}) with or without sho-saiko-to extract powder (300 mg kg^{-1}).

Parameter	Tolbutamide alone	With Sho-saiko-to
Hybrid Parameter A ($\mu g\ mL^{-1}$)	1126 ± 1115	1368 ± 1307
Hybrid Parameter B ($\mu g\ mL^{-1}$)	149·0 ± 81·0	113·0 ± 36·2
Hybrid Parameter α ($10^{-2}\ h^{-1}$)	80·2 ± 58·2	81·6 ± 41·5
Hybrid Parameter β ($10^{-2}\ h^{-1}$)	13·8 ± 3·5	12·9 ± 1·8
Time delay of drug absorption (min)	0·92 ± 1·42	2·54 ± 2·64
Absorption rate constant (h^{-1})	2·13 ± 1·15	2·28 ± 1·40
Elimination rate constant (h^{-1})	0·19 ± 0·07	0·32 ± 0·10*
Elimination half-life (h)	5·35 ± 1·64	5·46 ± 0·86
Time to reach the maximum concentration (h)	1·42 ± 0·56	0·99 ± 0·30
Maximum concentration ($\mu g\ mL^{-1}$)	176·0 ± 37·2	213·0 ± 27·9*
Area under the plasma concentration–time curve ($\mu g\ h\ mL^{-1}$)	1228 ± 153	1164 ± 121
Total body clearance (mL $h^{-1}\ kg^{-1}$)	41·2 ± 4·4	43·4 ± 5·2
Distribution volume (mL kg^{-1})	255·0 ± 134·0	144·0 ± 42·5

Parameters were estimated by use of the computer program, WinNonlin. Estimates are expressed as means ± s.d. of results from 5 or 6 rats. *$P < 0.05$, significantly different from result for tolbutamide alone.

and Sho-saiko-to simultaneously, the minimum glucose level for these rats tended to be lower than that for rats administered tolbutamide alone. In the control groups, plasma glucose levels increased temporarily shortly after administration and this temporary elevation was larger after administration of sho-saiko-to than after administration of potato starch saline alone.

Differences between the plasma glucose levels of tolbutamide-administered groups and the respective control groups were calculated to clarify the effect of Sho-saiko-to on the hypoglycaemic activity of tolbutamide. Decreases in glucose levels after single oral doses of tolbutamide with or without Sho-saiko-to are shown in Table 3. The extent of the effect of tolbutamide on the reduction of plasma glucose levels tended to be enhanced in the early period after the dosing with co-administration of Sho-saiko-to. A significant difference was observed 0·75 h after administration. On the other hand, 3 h after dosage Sho-saiko-to tended to reduce the decrease in plasma glucose levels induced by tolbutamide, significant differences being observed 5 and 8 h after drug administration.

Discussion

There have been a few reports of Sho-saiko-to affecting the pharmacokinetics of co-administered drugs. For example, co-administration of Sho-

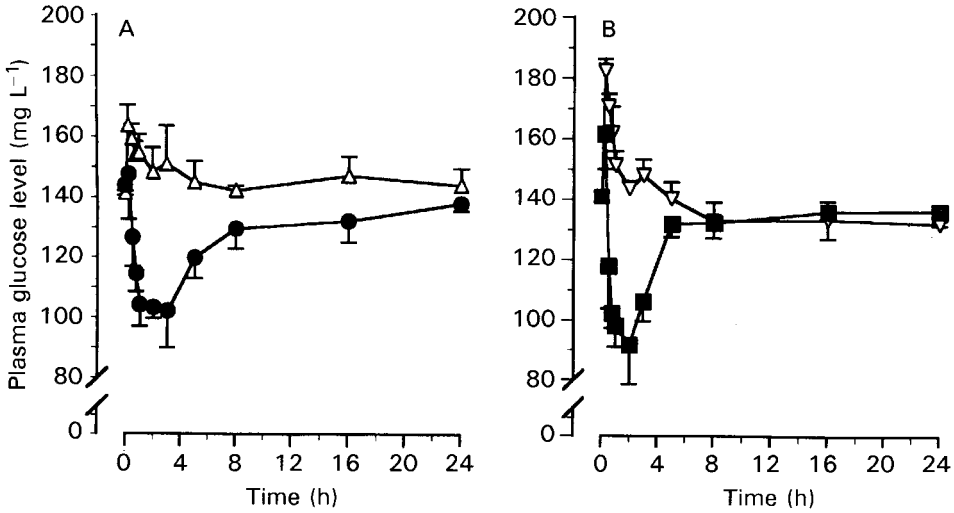

Figure 2. Time-courses of plasma glucose levels after oral administration of tolbutamide (50 mg kg^{-1}) without (●, panel A) or with (■, panel B) Sho-saiko-to extract powder (300 mg kg^{-1}), and the respective controls (potato starch saline alone (△) or Sho-saiko-to alone (▽)) in rats. Each point represents the mean ± s.d. of results from 3 rats.

Table 3. Decrease in plasma glucose levels after oral administration of tolbutamide (50 mg kg^{-1}) with or without Sho-saiko-to extract powder (300 mg kg^{-1}).

Time (h)	Tolbutamide alone	With Sho-saiko-to
0·25	18·7 ± 11·7	20·7 ± 11·5
0·5	35·3 ± 7·5	52·7 ± 15·7
0·75	42·0 ± 3·2	59·7 ± 5·5**
1	53·0 ± 7·1	53·1 ± 8·3
2	47·5 ± 4·8	51·9 ± 12·5
3	51·3 ± 10·9	41·7 ± 5·9
5	27·7 ± 5·6	8·3 ± 2·7**
8	15·3 ± 6·0	2·0 ± 2·7*
16	17·7 ± 10·0	2·8 ± 4·8
24	8·7 ± 5·7	0·0 ± 0·0

Each value is the mean ± s.d. of results from three rats. *$P < 0.05$, **$P < 0.01$, significantly different from result for tolbutamide alone.

saiko-to reduced the AUC for prednisolone after oral administration in man (Homma et al 1995) and pre-administration of Sho-saiko-to reduced the serum concentration of phenytoin given intravenously to the rabbit (Hosoya et al 1993). In contrast, it has been reported that Sho-saiko-to has no effect on the bioavailability of ofloxacin after oral administration to man (Hasegawa et al 1994). Although these reports were not sufficient to clarify the influences of Sho-saiko-to on the pharmacokinetics or pharmacodynamics of the co-administered drugs, it has been suggested that in total the information available on interactions between Chinese medicines and co-administered drugs is relatively important. On the other hand, it is known that interactions between tolbutamide and other drugs are based on displacement of plasma-protein binding or inhibition of hepatic oxidation of tolbutamide by the combined drugs. Various interactions between tolbutamide and co-administered drugs have been reported to be related to its hypoglycaemic reaction (Hansen & Christensen 1977; Jackson & Bressler 1981). These interactions have occasionally induced serious hypoglycaemia. The current studies were performed to elucidate the effect of co-administered Sho-saiko-to on the pharmacokinetics and pharmacodynamics of tolbutamide.

Sho-saiko-to slightly but significantly raised plasma tolbutamide concentrations up to 1 h after drug administration. Co-administration of Sho-saiko-to significantly increased C_{max} for tolbutamide and reduced t_{max} for this sulphonylurea to about 70%; there was no change in other pharmacokinetic parameters for tolbutamide. These changes in both the peak plasma concentration and the time to the peak during an early period after the administration of tolbutamide suggest that Sho-saiko-to facilitates the gastrointestinal absorption of this sulphonylurea.

Although the mechanism of this apparent facilitation of absorption of tolbutamide by Sho-saiko-to is unclear, a few possibilities can be suggested. It has been reported that absorption of tolbutamide, a weakly acidic compound, was accelerated by elevation of gastric pH (Kivistö & Neuvonen 1992). Possible elevation of gastric pH by co-administered Sho-saiko-to might alter the initial rate of absorption of tolbutamide. It has been reported that *Zingibraceae* crude drugs might effect the small-intestinal absorption of sulphaguanidine in various ways (Sakai et al 1986), and also that crude saponin fractions isolated from pericarps of Enmei-hi (*Sapindus mukurossi*) enhance the small-intestinal absorption of β-lactam antibiotics in rats (Yata et al 1986). Because Sho-saiko-to contains *Zingiberis Rhizoma* and various saponins, it is considered likely that crude drugs such as Sho-saiko-to might affect the gastrointestinal absorption of co-administered drugs such as tolbutamide. Alternatively, gastric emptying rate might be modified by co-administration of Sho-saiko-to. Sho-saiko-to is a mixture of several kinds of crude drug such as *Zingiberis Rhizoma* and *Ginseng Radix*. It is known that, owing to enhancement of gastrointestinal motility, these crude drugs have a variety of pharmacological effects on gastrointestinal function. Therefore, it is likely that Sho-saiko-to could increase the gastric emptying rate. As a result of facilitated gastric emptying, tolbutamide could rapidly reach the small intestine, the predominant site of drug absorption.

Hosoya et al (1993) suggested that the decrease in serum phenytoin concentration induced by treatment with Sho-saiko-to might be mainly a result of the stimulation of hepatic phenytoin-oxidizing metabolic enzyme activity by Sho-saiko-to. Because tolbutamide is eliminated mainly by hepatic oxidation (Shibasaki et al 1973), the rate of elimination of this drug might also be expected to be altered by co-administration of Sho-saiko-to. However, as shown in Table 2, Sho-saiko-to had no effect on $t_{1/2\beta}$ and CL_{tot} of tolbutamide, indicating that hepatic metabolism of tolbutamide was not affected by co-administered Sho-saiko-to.

With regard to the pharmacological effects of tolbutamide, it was found that trough levels of plasma glucose after administration of tolbutamide tended to be reduced when the drug was co-administered with Sho-saiko-to. These results suggest that Sho-saiko-to could enhance the hypoglycaemic effect of tolbutamide. In contrast, as is shown in Figure 2B administration of Sho-saiko-to alone induced temporary but remarkable elevation of

plasma glucose levels in the control rats, presumably owing to the glucides contained in Sho-saiko-to. Therefore, the net hypoglycaemic effect of tolbutamide was evaluated in terms of the decrease in plasma glucose levels. The decrease in glucose levels after oral administration of tolbutamide was increased up to 0·75 h and then reduced 5 h after dosage by co-administration with Sho-saiko-to (Table 3). Thus, pharmacokinetic changes in plasma tolbutamide concentrations induced by Sho-saiko-to seem to be strongly reflected by these changes in the plasma glucose response to tolbutamide. Possible pharmacodynamic interactions should also be considered. *Ginseng Radix*, one of the components of Sho-saiko-to, is known to have a mild hypoglycaemic effect. In addition, Sho-saiko-to contains many crude drugs, e.g., saponins, glucides, lipids, alkaloids and aliphatic compounds. One or more of these constituents might affect pancreatic insulin secretion.

In conclusion, these studies suggest that Sho-saiko-to might hasten the gastrointestinal absorption of tolbutamide during an early period after oral administration. Furthermore, it is considered that the elevation of the rate of gastrointestinal absorption of tolbutamide by Sho-saiko-to might potentiate the hypoglycaemic effect of this sulphonylurea after oral administration.

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