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# Repetitive administration of Shaoyao-Gancao-tang to rats restores the bioavailability of glycyrrhizin reduced by antibiotic treatment

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## Abstract

Shaoyao-Gancao-tang (SGT), a traditional Chinese formulation, is often used together with antibiotics such as amoxicillin and metronidazole (AMPC-MET) for the treatment of peptic ulcers in Japan. However, the bioavailability of glycyrrhizin (GL) in SGT is severely reduced by a single administration of AMPC-MET, and the reducing effect continues for 12 days. GL is one of the major pharmacologically important glycosides in SGT and is transformed into the active metabolite 18$\beta$-glycyrrhetic acid (GA) by intestinal bacteria in the gut, followed by absorption of the latter into the blood. In order to reduce the negative effect of AMPC-MET on the bioavailability of GL, the optimum scheduling of the medications was examined. We found that the reduction in the plasma GA concentration and the GL-metabolizing activity in faeces caused by a single dose of AMPC-MET could be sharply attenuated by the repetitive administration of SGT for 4 days. The GA concentration and the GL-metabolizing activity were strongly enhanced by further continuous administration of SGT. These findings suggest that repetitive administration of SGT starting 1 or 2 days after the administration of AMPC-MET speeds the recovery of the bioavailability of GL in SGT. Similar strategies for administering medications may also be useful for combination therapy of antibiotics with other traditional Chinese formulations containing bioactive glycosides.

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## Introduction

Concerns about drug–drug and drug–food interactions occurring during medicinal treatments have recently received increased attention around the world (Kuhlmann & Muck 2001; Tatro 2002). Drug–drug interactions are attributed to a number of factors (Lebsack et al 1992; Holtbecker et al 1996). For traditional Chinese formulations, the glycoside-metabolizing (hydrolyzing) activity of intestinal bacteria plays a key role in the bioavailability of the active glycoside ingredients (Kobashi et al 1992). Since the administration of some antibiotics may affect the flora and metabolizing activity of intestinal bacteria, we have studied the influence of co-administered antibiotics on the bioavailability of glycyrrhizin (GL) in Shaoyao-Gancao-tang (SGT) (He et al 2001).

SGT (Shakuyaku-Kanzo-To in Japanese), composed of Shaoyao (peony root) and Gancao (liquorice), is one of the most frequently prescribed traditional Chinese formulations and is widely used for the treatment of abdominal (Katsura 1995) and colic pain (Yamaguchi et al 1982) in Japan. This formulation is often prescribed together with some antibiotics such as amoxicillin (AMPC) and metronidazole (MET) to eradicate *Helicobacter pylori* in the treatment of peptic ulcers, or ofloxacin for the treatment of urinary tract infections.

GL is one of the active glycosides in SGT and Gancao, and is transformed into glycyrrhetic acid (GA) by intestinal bacteria in the gut after oral administration (Akao et al 1994). Our previous report showed that the oral co-administration of AMPC-MET with SGT in rats significantly decreases the plasma GA concentration (He et al 2001).

The present study aimed to determine some pharmacological parameters that would make it possible to reduce the influence of antibiotics on the bioavailability of GL in SGT. For this purpose, after a single administration of AMPC-MET or ofloxacin, the effects of repetitive administration of SGT for a 1- or 2-week period on the recovery of

the GL-metabolizing activity reduced by the antibiotics were examined. Furthermore, the correlation between the GL-metabolizing activity of intestinal bacteria in faeces and the plasma GA concentration was also examined.

## Materials and Methods

### Materials

The Shaoyao and Gancao used conformed to the Japanese Pharmacopoeia XIV standard, and have been previously described (He et al 2001). The freeze-dried extract of SGT (6 g each of Shaoyao and Gancao; yield: $4.02 \pm 0.05$ g) was prepared and its HPLC fingerprint (not shown in the present report) was analyzed as described previously (He et al 2001). Freeze-dried extracts of Shaoyao ($2.12 \pm 0.03$ g, containing paeoniflorin (PF) at $86.0 \pm 2.6$ mg (g extract)$^{-1}$) and Gancao ($1.95 \pm 0.02$ g, containing GL at $85.4 \pm 0.3$ mg (g extract)$^{-1}$) were also used.

AMPC and ofloxacin were obtained from Sigma Chemical Co., and MET was obtained from Aldrich Chemical Co. All of the other chemicals and solvents used were of analytical or HPLC grade.

### Animals

Male Wistar rats (8 weeks old, approx. 250 g, n = 6 for each group) were purchased from Japan SLC Inc. (Hamamatsu, Japan) and maintained on a 12-h light–dark cycle at 21–24 °C in the Laboratory for Animal Experiments, Toyama Medical and Pharmaceutical University. The rats were given free access to water and standard laboratory chow throughout the study. All animal experiments were carried out in accordance with the Guidelines of the Animal Care and Use Committee of Toyama Medical and Pharmaceutical University approved by the Japanese Association of Laboratory Animal Care.

### Administration of antibiotics and SGT, Gancao and Shaoyao extracts

Antibiotics were administered orally to rats in a single dose of 10 times the common human daily dose on day 0. The three extracts SGT, Gancao and Shaoyao were each administered orally twice a day (morning and evening) at total daily doses of 10 times the common human daily doses or singly at doses of 5 times the common human daily doses according to a specific schedule as shown in Figures 1, 2 and 4.

### Determination of GL-metabolizing activity in rat faeces and plasma GA concentration

Faeces samples (for determination of GL-metabolizing activity) were collected according to the specific schedule described in the legend to Figure 1. The rate of metabolism of GL into GA in fresh rat faeces was estimated by

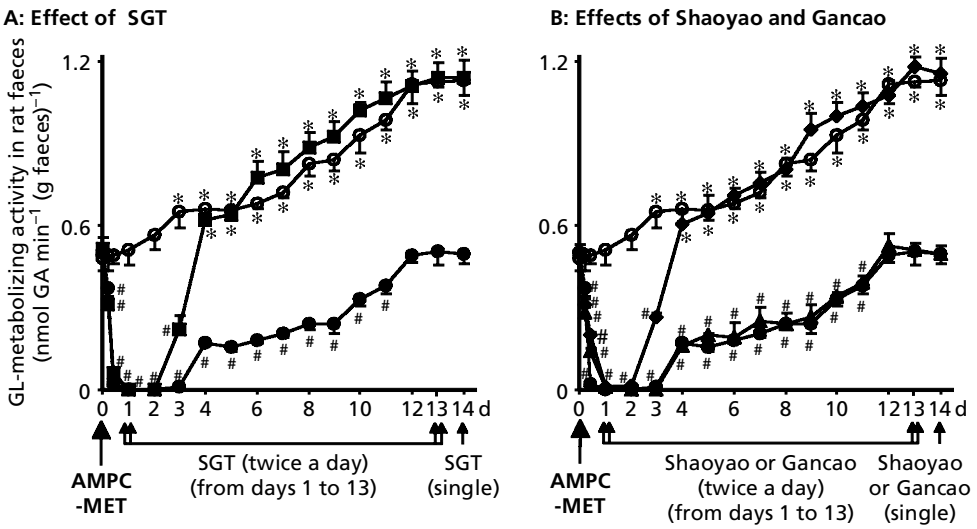


**Figure 1** Restorative effects of repetitive administration of (A) SGT and (B) Gancao and Shaoyao on GL-metabolizing activity in rat faeces reduced by a single administration of AMPC-MET. AMPC-MET, a mixture of AMPC (83.3 mg kg$^{-1}$) and MET (41.7 mg kg$^{-1}$), was administered orally to rats in a single dose on day 0. The three extracts were each administered orally twice a day (morning and evening) at total daily doses of 645 mg kg$^{-1}$ (equivalent to 25 mg kg$^{-1}$ PF and 41 mg kg$^{-1}$ GL) for SGT extract, 480 mg kg$^{-1}$ (equivalent to 41 mg kg$^{-1}$ GL) for Gancao extract and 290 mg kg$^{-1}$ (equivalent to 25 mg kg$^{-1}$ PF) for Shaoyao extract from days 1 (24 h after treatment with AMPC-MET) to 13, and singly at 322, 240 and 145 mg kg$^{-1}$ for SGT, Gancao and Shaoyao, respectively, in the morning on day 14. Control groups were given tap water instead of antibiotics. Faeces samples (about 0.5 g each) were collected before (predose) and at 5, 10 and 24 h, and every 24 h onwards after administration of the antibiotics. ●, AMPC-MET alone; ○, $H_2O$ with SGT (control); ■, AMPC-MET with SGT; ◆, AMPC-MET with Gancao; ▲, AMPC-MET with Shaoyao. Each point represents the mean ± s.e. (n = 6). $^{\#}P < 0.01$, significantly decreased vs the predose value (mean $0.50 \pm 0.01$) (paired two-tailed Student's *t*-test); $^{*}P < 0.01$, significantly increased vs the predose value (paired two-tailed Student's *t*-test).

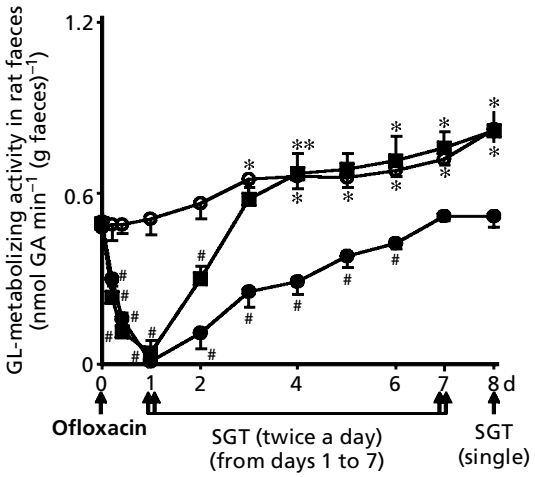


**Figure 2** Restorative effect of SGT on GL-metabolizing activity in rat faeces reduced by a single administration of ofloxacin. Ofloxacin (50 mg kg$^{-1}$) was administered orally to rats in a single dose on day 0. SGT was administered orally twice a day (morning and evening) at total daily doses of 645 mg kg$^{-1}$ from days 1 to 7 and singly at 322 mg kg$^{-1}$ in the morning on day 8. ●, Ofloxacin alone; ○, $H_2O$ with SGT (control); ■, ofloxacin with SGT. Each point represents the mean ± s.e. (n = 6). $^{\#}P < 0.01$, significantly decreased vs the predose value (mean 0.50 ± 0.02) (paired two-tailed Student's *t*-test); $^{*}P < 0.01$, significantly increased vs the predose value (paired two-tailed Student's *t*-test).

determination of the GA formed in a reaction mixture containing rat faecal suspension and 0.5 mM GL using HPLC with a YMC-Pack ODS-A-303 column and spectrophotometric detection at 251 nm as previously reported (He et al 2001). The HPLC conditions are able to clearly separate the two isomers, 18$\alpha$-GA and 18$\beta$-GA.

The recovery time (days) was defined as the average number of days from the time when the activity was reduced to 70% or less of the initial level to when it recovered to 90% or more (Abe et al 2001). The high-level-staying time (days) was defined as the average number of days when the activity was maintained at 130% or more of the initial value (Wu et al 1997).

Blood samples (for the determination of plasma GA concentration) were collected according to the specific schedule described in the legends to Figures 3 and 4. The collected blood samples were immediately centrifuged at 1100 *g* for 10 min and the plasma thus obtained was stored at −20 °C until analysis. The plasma GA concentration was measured using the same HPLC conditions as described in the determination of GL-metabolizing activity. The elimination rate constant (K) was estimated by linear regression analysis of the terminal portion of the semi-logarithmic plot of plasma concentration vs time. The half-life of elimination ($t_{1/2K}$) was calculated from $\ln 2/t_{1/2K}$. The maximum plasma concentration ($C_{max}$) and the time to reach $C_{max}$ ($t_{max}$) were determined directly from the actual drug levels in the plasma. The area under the mean concentration vs time curve from zero to 24 h ($AUC_{0-24\,h}$) was calculated using the trapezoidal rule.

## Statistical analysis

The difference between values before and after treatment was statistically analyzed using the paired two-tailed Student's *t*-test. Comparisons between two groups and among more than two groups were performed using the unpaired two-tailed Student's *t*-test and one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test, respectively. Differences were considered statistically significant at $P < 0.05$.

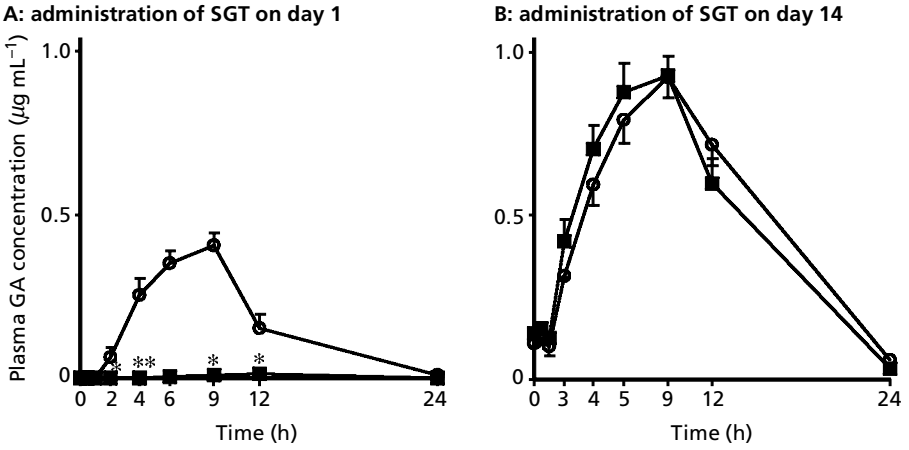


**Figure 3** Time-course of plasma GA concentration after the first and final administrations of SGT. (A) The time-course of the plasma GA concentration after the first dose of SGT (322 mg kg$^{-1}$) on day 1 (24 h after treatment with AMPC-MET). (B) The time-course of the plasma GA concentration after the final dose of SGT (322 mg kg$^{-1}$) on day 14. Blood samples (about 0.24 mL each) were collected from the tail vein using heparinized microcapillary tubes at 0.5, 1, 2, 4, 6, 9, 12 and 24 h after the first and the last morning administrations of SGT on days 1 and 14. ■, SGT administered 24 h after treatment with AMPC-MET; ○, SGT administered 24 h after treatment with $H_2O$ (control). Each point represents the mean ± s.e. (n = 6) determined by HPLC (He et al 2001). $^{*}P < 0.01$ vs the control values (unpaired two-tailed Student's *t*-test).

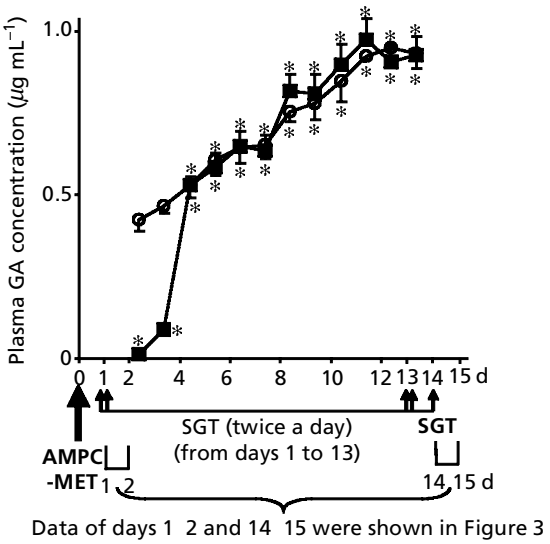


**Figure 4** Restorative effect of repetitive administration of SGT on plasma GA concentration reduced by a single administration of AMPC-MET. Blood samples (about 0.12 mL each) were collected 9 h after each morning dose of SGT (322 mg kg$^{-1}$) on days 2 to 13. The peak concentration of GA occurs at this time after SGT treatment (He et al 2001), and therefore the amount of blood sample required at this time for the determination of the plasma GA concentration by HPLC (with a detection limit of 16 ng mL$^{-1}$) was relatively small. ■, SGT administered repetitively 24 h after treatment with AMPC-MET; ○, SGT administered repetitively 24 h after treatment with $H_2O$ (control). Each point represents the mean ± s.e. (n = 6) determined by HPLC (He et al 2001). *$P < 0.01$ vs the control value after the first dose of SGT (0.40 ± 0.03 μg mL$^{-1}$, see control 1 in Table 2) (unpaired two-tailed Student's *t*-test).

## Results

### Recovery of GL-metabolizing activity of rat faeces reduced by antibiotics (Figures 1 and 2, and Table 1)

In both the plasma of rats administered orally with SGT and the reaction mixture of rat faecal suspension and GL, 18β-GA but no 18α-GA was detected, thus GA hereafter stands for 18β-GA. As shown in Figure 1A, the GL-metabolizing activity of faeces was markedly reduced by a single treatment with AMPC-MET to an undetectable level from days 1 to 3. It slowly increased from day 4 (to approx. 34% of the day 0 level of 0.50 ± 0.02 nmol GA min$^{-1}$ (g faeces)$^{-1}$) but took 12 days to recover from the reduction. However, in response to the repetitive administration of SGT from 1 day after the AMPC-MET treatment, the activity was distinctly elevated on day 3 (to 42 ± 4% of the day 0 level, $P < 0.01$). It rapidly recovered by day 4 to a similar value to that of the control group, which was greater than the day 0 value. Thereafter, the activity increased continuously in parallel with that of the control group and reached a level as high as 2.2 times the day 0 level on day 13.

As shown in Figure 1B, repetitive administration of Gancao after AMPC-MET caused an accelerating effect quite similar to that of SGT; however, Shaoyao did not accelerate the recovery of the reduced GL-metabolizing activity at all. As shown in Table 1, the recovery time of the GL-metabolizing activity reduced by the treatment with AMPC-MET was 11.83 ± 0.40 days, which was considerably shortened by the repetitive administration of SGT (3.67 ± 0.21 days, $P < 0.01$) or Gancao (4.17 ± 0.17 days, $P < 0.01$). The recovery time was not shortened by treatment with Shaoyao (11.50 ± 0.34 days).

A similar accelerating effect of SGT on the recovery of the GL-metabolizing activity was observed in experiments using another antibiotic, ofloxacin (Figure 2, Table 1). In comparison with AMPC-MET, ofloxacin showed a similar but weaker reducing effect on GL-metabolizing activity.

### Recovery of plasma GA concentration reduced by AMPC-MET (Figures 3 and 4, and Table 2)

The plasma GA concentration from 0.5 to 24 h after the first administration of SGT on day 1 in the AMPC-MET-pretreated group decreased almost to zero (Figure 3A). After the final administration of SGT on day 14, however, the plasma GA concentration in the AMPC-MET-pretreated group showed no difference to that in the control group (Figure 3B).

The pharmacokinetic parameters of GA are shown in Table 2. After the first administration of SGT on day 1, the $C_{max}$ and $AUC_{0-24\,h}$ for GA in the group pretreated with AMPC-MET were significantly ($P < 0.01$) smaller than those in the group without pretreatment (control 1). On the other hand, after the final administration of SGT on day 14 these parameters did not show any significant differences between the AMPC-MET-pretreated group and the non-pretreated group (control 14).

The plasma GA concentrations on days 2 to 13, which were determined using the blood samples collected 9 h after each morning administration of SGT, are shown in Figure 4. The mean concentration in the group receiving SGT alone (control) was gradually elevated until day 11 and reached a steady state on day 12, attaining a value (0.91 ± 0.04 μg mL$^{-1}$) as high as 2.3 times the control value after the first dose (0.40 ± 0.03 μg mL$^{-1}$, $P < 0.01$), and the increases were significant after day 4. In the group that received the repetitive administration of SGT after being pretreated with AMPC-MET, the plasma GA concentration rapidly recovered to the control level by day 4 and thereafter gradually increased in the same manner as in the control group, although the recovery was not complete on days 2 and 3.

## Discussion

In the Japanese medical care system, traditional Chinese formulations are frequently used together with some synthetic drugs (Akase et al 2002). It is therefore important to characterize the drug–drug interactions to prevent adverse effects and ensure the effectiveness of combination therapy. A number of reports about the influence of traditional Chinese formulations on the pharmacokinetics of synthetic

**Table 1** Recovery time and high-level-staying time of glycyrrhizin (GL)-metabolizing activity of rat faeces.

| Parameters | AMPC-MET | | | | Ofloxacin | |
|---|---|---|---|---|---|---|
| | AMPC-MET alone | AMPC-MET with SGT | AMPC-MET with Shaoyao | AMPC-MET with Gancao | Ofloxacin alone | Ofloxacin with SGT |
| Recovery time (days)[g] | $11.83 \pm 0.40$ | $3.67 \pm 0.21^{a}$ | $11.50 \pm 0.34^{b}$ | $4.17 \pm 0.17^{a,c}$ | $6.50 \pm 0.22^{e}$ | $2.50 \pm 0.22^{d,f}$ |
| High-level-staying time (days)[h] | $0.33 \pm 0.21$ | $10.17 \pm 0.40^{a}$ | $0.33 \pm 0.21^{b}$ | $9.83 \pm 0.48^{a,c}$ | $0.50 \pm 0.34$ | $5.17 \pm 0.75^{d}$ |

Each value represents the mean ± s.e. (n = 6). [a] $P < 0.01$ vs AMPC-MET alone; [b] $P < 0.01$ vs AMPC-MET with SGT; [c] $P < 0.01$ vs AMPC-MET with Shaoyao; [d] $P < 0.01$ vs ofloxacin alone; [e] $P < 0.01$ vs AMPC-MET alone; [f] $P < 0.01$ vs AMPC-MET with SGT (one-way ANOVA followed by Tukey's post-hoc test). [g]Recovery time for individual rats = [(day of reaching 90% or more of the initial level) – (day of reaching 70% or less of the initial level)]. [h]High-level-staying time for individual rats was the average number of days when the activity was maintained at 130% or more of the initial value. The criterion of 130% was chosen based on the ratio of the mean value on day 4 vs the mean predose value in the groups receiving AMPC-MET (or ofloxacin) and SGT.

**Table 2** Pharmacokinetic parameters of 18$\beta$-glycyrrhetic acid (GA) after the first and final oral doses of SGT in rats pretreated with AMPC-MET.

| Parameters | After the first dose (day 1) | | After the final dose (day 14) | |
|---|---|---|---|---|
| | SGT with AMPC-MET pretreated[a] | SGT alone (control 1) | SGT with AMPC-MET pretreated[b] | SGT alone (control 14) |
| K ($h^{-1}$) | $0.24 \pm 0.04$ | $0.24 \pm 0.03$ | $0.22 \pm 0.03$ | $0.21 \pm 0.05$ |
| $t_{1/2\ K}$ (h) | $2.89 \pm 0.50$ | $2.92 \pm 0.37$ | $3.12 \pm 0.44$ | $3.30 \pm 0.83$ |
| $t_{max}$ (h) | $11.00 \pm 0.55$* | $8.00 \pm 0.71$ | $6.67 \pm 0.80$ | $7.50 \pm 0.77$ |
| $C_{max}$ ($\mu g\,mL^{-1}$) | $0.01 \pm 0.01$* | $0.40 \pm 0.03$ | $0.93 \pm 0.06$* | $0.92 \pm 0.08$* |
| ($C_{max}$%)[c] | ($2.5 \pm 0.4$) | 100% | ($232.5 \pm 2.5$) | ($230.0 \pm 2.8$) |
| $AUC_{0-24\,h}$ ($\mu g\,h\,mL^{-1}$) | $0.13 \pm 0.05$* | $3.89 \pm 0.38$ | $11.90 \pm 0.59$* | $12.45 \pm 0.74$* |
| ($AUC_{0-24\,h}$%)[c] | ($3.3 \pm 0.6$) | 100% | ($305.9 \pm 14.9$) | ($320.1 \pm 12.4$) |

Each value represents the mean ± s.e. (n = 6). The plasma GA concentration was determined using HPLC (He et al 2001). *$P < 0.01$ vs the value of control 1 (unpaired two-tailed Student's $t$-test). [a]SGT was initially administered 24 h after the treatment with AMPC-MET. [b]SGT was finally administered 14 days after the treatment with AMPC-MET. [c]Percentage relative to the value of control 1.

drugs during combination therapy have been published (Hasegawa et al 1995; Nishimura et al 1998; Ohnishi et al 2002). However, little is known about the influence of co-administered synthetic drugs on the pharmacokinetics of the active ingredients in traditional Chinese formulations. Thus, our biopharmaceutical research has been focusing on this field.

In a previous study, we demonstrated that the antibiotic mixture AMPC-MET reduced the GL-metabolizing activity of rat faeces and the plasma GA concentration when co-administered with SGT (He et al 2001). SGT is a famous pain-relieving traditional Chinese formulation and sometimes is administered concomitantly with antibiotics in clinical situations. GL is a major bioactive glycoside in SGT and is metabolized by intestinal bacteria into the bioactive metabolite 18$\beta$-GA, which is absorbed and appears in the blood after oral administration of GL (Akao et al 1994). In this study, we also found that there was only 18$\beta$-GA detected in the faeces and plasma of rats that were administered orally with SGT.

The present study was conducted to examine the restorative effects of the repetitive administration of SGT on the GL-metabolizing activity and bioavailability of GL that had been reduced by the administration of antibiotics. Regarding the drug dose used in animal studies, it has been reported that smaller animals need to be administered at relatively high doses to achieve the same pharmacokinetic values as in humans, since the former eliminate drugs more rapidly than the latter (Boxenbaum 1982). When rats are administered orally with SGT in a single dose of 10 times the human dose, the values of $C_{max}$ and AUC of GA (He et al 2001) are similar to those for humans (Bando et al 2000). A similar correlation is also shown between the data for rats (Sakamoto et al 1985) and humans (Welling et al 1977) when antibiotics such as amoxicillin are orally administered. In the present study therefore both the extracts and the

antibiotics were administered orally to rats at a total daily dose of 10 times the common human daily dose.

As shown in Figure 1, the GL-metabolizing activity of rat faeces reduced by a single treatment with AMPC-MET on day 0 was still undetectable at days 1 to 3 and took a long time (12 days) to return to the normal level. The marked reduction in the GL-metabolizing activity might be related to the eradication of the intestinal bacteria capable of converting GL to GA as a result of the antibiotic treatment. It has been reported that in human faeces the intestinal bacterium that is capable of transforming GL into GA is rare and grows very slowly (Akao et al 1987, 1988). This may also be the case in rats, since the reduced GL-metabolizing activity in rat faeces took such a long time to recover. The long recovery time also suggests that the intestinal bacteria possessing GL-metabolizing activity in the rat faeces had difficulty in recovering once they were interfered with by the treatment with AMPC-MET.

Our findings here proved that the repetitive administration of SGT following treatment with AMPC-MET considerably accelerated the recovery of the reduced GL-metabolizing activity. Similar effects were also observed with repetitive administration of Gancao, but not with administration of Shaoyao. These results indicate that it is Gancao that contributes the restorative effect of SGT on the reduced GL-metabolizing activity. A previous study reported that GL enhances the GL-metabolizing activity of human intestinal bacteria, the mechanism of which is that GL induces the synthesis of GL $\beta$-D-glucuronidase and in turn allows that enzyme-producing bacteria to grow (Akao et al 1988). There may be a similar effect on the intestinal bacteria of rats. Accordingly, the enhancing effect of Gancao and SGT on the GL-metabolizing activity in rats may be due to the GL contained in these extracts.

The accelerating effect of repetitive administration of SGT on the recovery of the GL-metabolizing activity was further confirmed by a similar study using ofloxacin (Figure 2), another antibiotic used for the treatment of urinary tract infections (Drew & Gallis 1988). The differences in the degree and duration of the reducing effects of the two antibiotics on the GL-metabolizing activity might result from differences in their antibacterial activities. The minimum inhibitory concentration of AMPC (Oguri & Kosakai 1979) or MET (Aldridge et al 1983) against many anaerobic bacteria is less than 0.39 $\mu g\,mL^{-1}$, which is lower than that of ofloxacin (Drew & Gallis 1988).

The acceleration of recovery and the continuous increase caused by the repetitive administration of SGT in the plasma GA concentration reduced by pretreatment with AMPC-MET were closely related to the increase in the GL-metabolizing activity of faeces (Figure 4). These results were consistent with the previously reported observation that the AUC for GA was positively correlated with the corresponding GL-metabolizing activity of rat faeces (He et al 2001). Since GA possesses an anti-ulcer effect (Takagi et al 1969), the elevation in the plasma GA concentration may be beneficial for the treatment of peptic ulcers by combination therapy of SGT with AMPC-MET.

In addition, the plasma GA concentration was similarly increased in control rats that were treated repetitively with SGT alone. This observation provides evidence that may in part account for why a relatively long dosing period is usually required for treatment with traditional Chinese formulations. Moreover, recently we have also demonstrated that the bioavailability of paeoniflorin, another bioactive glucoside in SGT, was considerably reduced by a single administration of antibiotics (He et al 2003). Further studies investigating the restorative effect of the repetitive administration of SGT on the reduced bioavailability of paeoniflorin, another bioactive glucoside in SGT and Shaoyao, are in progress in our laboratory.

In summary, in the present study we investigated how to restore the bioavailability of GL in SGT reduced by a single treatment with AMPC-MET or ofloxacin, which are antibiotics often used concomitantly with SGT in clinical situations. Repetitive treatment with an extract of SGT or Gancao starting 1 day after administration of the antibiotics significantly accelerated the recovery of the reduced plasma GA concentration and the GL-metabolizing activity of rat faeces. The present results suggest that it may be clinically useful to administer SGT repetitively starting 1 or 2 days after antibiotic treatment during combination therapy to accelerate the recovery of the reduced bioavailability of GL in SGT.

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