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Comparison of Pharmacokinetics between Glycyrrhizin and Glycyrrhetic Acid in Rabbits

HUI CHING[1], SU-LAN HSIU[2], YU-CHI HOU[1], CHUNG-CHUAN CHEN[1] AND PEI-DAWN LEE CHAO[2]*

[1] Institute of Chinese Pharmaceutical Sciences, [2] Department of Pharmacy, China Medical College, 91 Hsueh Shih Road, Taichung 404, Taiwan, R.O.C.

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ABSTRACT

Glycyrrhizin is a bioactive natural glycoside. Glycyrrhetic acid is an aglycone and an active metabolite of glycyrrhizin. The anti-inflammatory activity of glycyrrhetic acid is even stronger than that of glycyrrhizin and glycyrrhetic acid is responsible for the adverse effect of aldosteronism. This study attempted to compare the pharmacokinetics of glycyrrhetic acid after oral administration of equal molar doses of glycyrrhizin and glycyrrhetic acid to rabbits.

Six New Zealand White rabbits were orally given glycyrrhizin or glycyrrhetic acid at a dose of 178.5 μmol kg^{-1} in a randomized crossover design. HPLC methods were used to determine the serum concentrations of glycyrrhizin and glycyrrhetic acid. A noncompartment model was used to calculate the pharmacokinetic parameters and a paired Student's t-test was used for statistical comparison.

The results indicated that in addition to the absorption of glycyrrhizin per se at small intestine, oral dosing of glycyrrhizin resulted in higher AUC_{0-t} and MRT of glycyrrhetic acid by 443 % and 354 %, respectively, than those after oral dosing of glycyrrhetic acid. It can be concluded that glycyrrhizin is a good prodrug of glycyrrhetic acid.

Key words: glycyrrhizin, glycyrrhetic acid, pharmacokinetics

INTRODUCTION

Glycyrrhizin is a major and active constituent of the root of *Glycyrriza uralensis* Fisch (licorice) which is the most common herb used in traditional Chinese medicine. Glycyrrhizin possesses various pharmacological effects and has been used for the treatment of chronic hepatitis, inflammation, gastric ulcers and immunodeficiency virus infection[1-4]. Overconsumption of glycyrrhizin can produce the adverse effect of aldosteronism[5]. Glycyrrhetic acid is an aglycone and an active metabolite of glycyrrhizin. Glycyrrhetic acid was reported to be responsible for the toxic effect of aldosteronism[6]. The oral pharmacokinetics of glycyrrhetic acid and the comparison with the pharmacokinetics of glycyrrhizin have not been reported in the literature. Therefore, in the present study we attempted to characterize the oral pharmacokinetics of glycyrrhetic acid and furthermore, to compare the pharmacokinetics of glycyrrhetic acid after oral administrations of equal molar doses of glycyrrhizin and glycyrrhetic acid to rabbits.

MATERIALS AND METHODS

I. *Chemicals and Reagents*

Glycyrrhizin, propylparaben and glycofurol were purchased from Sigma Chemical Company (St Louis, MO, USA). Glycyrrhetic acid and 2-methylanthraquinone were products of Aldrich Chemical Company Inc.. All other chemicals and solvents used were of analytical grade or HPLC quality. Milli-Q plus water (Millipore, Bedford, MA, USA) was used for all preparations.

II. *Animals*

Six male New Zealand white rabbits, weighing 2.1 ~ 3.2 kg, were used throughout this study. Animals were housed in a 12-hr light-dark, constant temperature environment prior to study. All rabbits were fasted for 1 day before the experiment. Water was supplied *ad libitum*.

III. *Pharmacokinetic Analysis*

The pharmacokinetic experiments were performed with six rabbits in a randomized crossover design. Glycyrrhizin was given orally as an aqueous solution at a dose of 150 mg kg^{-1} (178.5 μmol kg^{-1}) and glycyrrhetic acid was given orally as a solution in glycofurol at a dose of 84 mg kg^{-1} (178.5 μmol kg^{-1}). Drug administration was carried out via gastric gavage throughout the study. One week was allowed for wash-out.

Blood samples (1.2 mL) were withdrawn via the right ear vein at 0, 1, 2, 4, 6, 8, 10, 12, 24, 36 and 48 hr after glycyrrhizin administration and at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 hr after glycyrrhetic acid administration. All blood samples were centrifuged for 15 min at 9860 x g and the serum samples obtained were stored at -30°C until analysis.

VI. *Quantitation of Glycyrrhizin and Glycyrrhetic Acid in Serum*

* Author for correspondence. Tel: 04-22053366 ext. 1905; Fax: 04-22031028; E-mail: pdlee@mail.cmc.edu.tw

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Twenty μL of glycyrrhizin solution of appropriate concentrations was spiked into 180 μL serum to afford serum standards with concentrations of 1.2, 2.5, 5.0, 10.0, 20.0, and 50.0 μg mL^{-1}. To 200 μL of serum standards, 800 μL of methanol containing 0.12 μg mL^{-1} of propylparaben as the internal standard was added for deproteinization. The mixture was vortexed for 30 sec and centrifuged at 9860 x g for 15 min, the supernatant was removed and evaporated to dryness by blowing nitrogen. The residue was reconstituted with 50 μL of mobile phase (acetonitrile: 1% acetic acid = 36: 64), of which 20 μL was subjected to HPLC analysis. The peak ratios (glycyrrhizin to propylparaben) of serum standard were determined in duplicate. The calibration curve was calculated by linear regression of the peak-area ratios against concentrations of glycyrrhizin.

Thirty μL of glycyrrhetic acid solution of appropriate concentrations was spiked into 270 μL serum to afford serum standards with concentrations of 0.1, 0.2, 0.5, 1.0, 2.0, 4.0 and 8.0 μg mL^{-1}. To 300 μL of serum, 100 μL of 0.1N HCl was added, then partitioned with 400 μL of ethyl acetate containing 0.1 μg mL^{-1} of 2-methylanthraquinone as the internal standard. The later process followed that for glycyrrhizin. The peak ratios (glycyrrhetic acid to 2-methylanthraquinone) of serum standards were determined in duplicate. The calibration curve was calculated by linear regression of the peak-area ratios against concentrations of glycyrrhetic acid.

V. *Quantitation of Glycyrrhetic Acid Mono-β-D-glucuronide*

Three hundred μL of each serum sample after oral dosing of glycyrrhetic acid was subjected to glycyrrhetic acid quantitation before and after hydrolysis by β-glucuronidase at 37˚C shaking water bath. For the detection of glycyrrhetic acid mono-β-D-glucuronide, glycyrrhetic acid concentrations in the serum before and after enzymatic hydrolysis were compared.

VI. *HPLC Conditions*

The HPLC apparatus included one pump (LC-10AS, Shimadzu, Japan) and an UV-VIS detector (SPD-10A, Shimadzu, Japan). The assay employed a LiChrospher 100 RP-18e column (4.0 × 250 mm, 5 μm, Merck). The UV detector was set at 248 nm and the flow rate was 1.0 mL min^{-1}. Chromatographic separation was achieved by using a mobile phase consisting of acetonitrile and 1% acetic acid (36:64, v/v) for glycyrrhizin determination. As for the assay of glycyrrhetic acid and 3-dehydroglycyrrhetic acid, a mobile phase consisting of acetonitrile and 1% acetic acid (67:33, v/v) was used.

VII. *Validation of Assay Methods*

The precision and accuracy of those assay methods were evaluated by intra-day and inter-day analysis of triplicate serum standards over a period of three days. The accuracy of this method was further assessed with recovery studies by spiking glycyrrhizin and glycyrrhetic acid into blank serum and water in triplicates to afford 5.0, 10.0, 50.0 and 0.5, 1.0, 4.0 μg mL^{-1}, respectively, and the concentrations obtained in blank serum to the corresponding ones in water were compared. LOQ (Limit of Quantitation) represents the lowest concentration of analyte in a sample that can be determined with acceptable precision and accuracy, whereas LOD (Limit of Detection) represents the lowest concentration of analyte in a sample that can be detected (with S/N > 3).

VIII. *Data Analysis*

The glycyrrhizin and glycyrrhetic acid serum concentration-time data were analyzed by noncompartment method with the aid of the program WINNONLIN (version 1.1, SCI software, Statistical Consulting, Inc., Apex, NC). The peak plasma concentration (C_{max}) and the time to peak concentration (T_{max}) were obtained from experimental observations. The paired Student's t-test was used for statistical comparison of pharmacokinetic parameters.

RESULTS AND DISCUSSION

Typical chromatograms of glycyrrhizin and glycyrrhetic acid are shown in Figure 1. Good linear relationships were obtained for glycyrrhizin and glycyrrhetic acid over the concentration ranges of 1.2 - 50.0 μg mL^{-1} (Y = 0.194 X - 0.025, r = 0.999) and 0.1 - 8.0 μg mL^{-1} (Y = 1.016 X + 0.008, r = 0.999), respectively. The precision and accuracy of these methods are shown in Table 1 and Table 2. The LOQ (limit of quantitation) of glycyrrhizin and glycyrrhetic acid were 1.2 μg mL^{-1} and 0.1 μg mL^{-1}, respectively. The LOD (limit of detection) of glycyrrhizin and glycyrrhetic acid were 0.30 μg mL^{-1} and 0.04 μg mL^{-1}, respectively. The LOQ and LOD of glycyrrhizin were about 10 times of glycyrrhetic acid. This is due to the higher molar extinction coefficient and lower molecular weight of glycyrrhetic acid than those of glycyrrhizin. The recoveries of glycyrrhizin and glycyrrhetic acid were

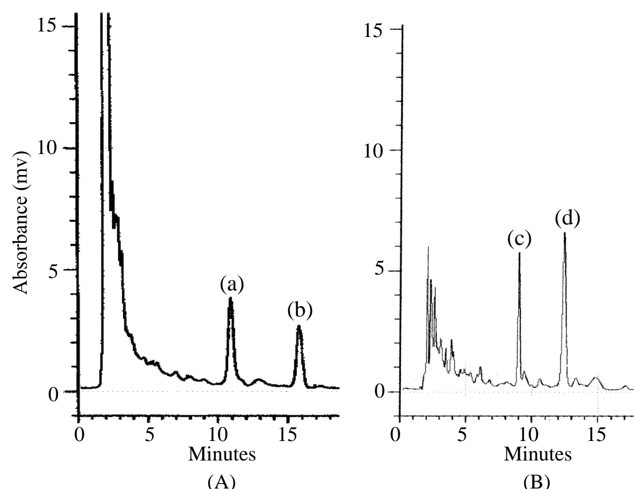

Figure 1. HPLC chromatograms of (A): glycyrrhizin (a, 6.4 μg mL^{-1}) with propylparaben (b) and (B): glycyrrhetic acid (d, 1.5 μg mL^{-1}) with 2-methylanthraquinone (c) in serum sample.

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Table 1. Intraday and interday analytical precision and accuracy of glycyrrhizin determination in rabbit serum

Concentration (μg mL^{-1})	Intraday (n=3)		Interday (n=3)	
	Precision Mean ± S.D. (C.V.%)	Accuracy R. E.(%)	Precision Mean ± S.D. (C.V.%)	Accuracy R. E. (%)
50.0	50.6 ± 0.4 (0.8)	1.2	50.7 ± 1.7 (3.3)	1.3
20.0	19.5 ± 0.4 (2.2)	-2.6	19.9 ± 0.6 (2.9)	-0.3
10.0	9.8 ± 0.0_2 (0.2)	-2.3	10.0 ± 0.2 (1.8)	0.4
5.0	5.0 ± 0.0_1 (0.3)	-0.1	5.1 ± 0.1 (1.5)	1.4
2.5	2.6 ± 0.0_3 (1.1)	4.2	2.6 ± 0.0_5 (2.0)	2.0
1.2	1.3 ± 0.0_1 (0.8)	4.4	1.3 ± 0.0_4 (3.0)	3.7

Table 2. Intraday and interday analytical precision and accuracy of glycyrrhetic acid assay in serum

Concentration (μg mL^{-1})	Intraday (n=3)		Interday (n=3)	
	Precision Mean ± S.D. (C.V.%)	Accuracy R. E. (%)	Precision Mean ± S.D. (C.V.%)	Accuracy R. E. (%)
8.0	7.2 ± 0.0_1 (0.1)	-9.3	7.7 ± 0.4 (4.8)	-4.3
4.0	4.0 ± 0.0_1 (0.3)	-0.1	4.3 ± 0.2 (5.3)	6.7
2.0	2.0 ± 0.0_2 (1.0)	1.6	2.2 ± 0.1 (6.2)	7.4
1.0	1.0 ± 0.0_4 (3.6)	-2.2	1.0 ± 0.0_4 (3.8)	-1.6
0.5	0.5 ± 0.0_0 (0.2)	-0.1	0.5 ± 0.0_1 (1.2)	-1.3
0.2	0.2 ± 0.0_0 (0.5)	-1.3	0.3 ± 0.0_1 (4.8)	4.8
0.1	0.1 ± 0.0_0 (3.9)	2.1	0.1 ± 0.0_1 (6.1)	12.1

Table 3. Recoveries (%) of glycyrrhizin and glycyrrhetic acid from serum (n=3)

Constituents spiked	Concentration (μg mL^{-1})	Recoveries (Mean ± S.E.) (%)
	5.0	108.0 ± 4.6
Glycyrrhizin	10.0	100.7 ± 0.4
	50.0	112.9 ± 4.9
	0.5	100.2 ± 5.2
Glycyrrhetic acid	1.0	97.9 ± 2.7
	4.0	112.8 ± 3.1

100.7 - 112.9% and 97.9 - 112.8%, respectively, as listed in Table 3.

The profiles of mean serum concentrations of glycyrrhizin and glycyrrhetic acid after glycyrrhizin administration are shown in Figure 2 and the pharmacokinetic parameters of glycyrrhizin and glycyrrhetic acid are listed in Table 4. The mean T_{max} of glycyrrhizin and glycyrrhetic acid after glycyrrhizin administration were 2.8 and 7.0 hr, respectively. Because the elimination rate constants of some rabbits could not be estimated, therefore, AUC_{0-t} was calculated instead of $AUC_{0-\infty}$. The AUC_{0-t} of glycyrrhizin and glycyrrhetic acid after glycyrrhizin administration were 47.9 and 16.3 μg mL^{-1} hr (57.0 and 34.6 nmol mL^{-1} hr), respectively. The mean MRT of glycyrrhizin and glycyrrhetic acid after glycyrrhizin administration were about 4.8 and 12.7 hr, respectively.

After glycyrrhizin administration, glycyrrhetic acid, glycyrrhetic acid mono-β-D-glucuronide, 3-dehydroglycyrrhetic acid and 3α-glycyrrhetic acid appearing in the plasma of rats and humans were metabolized from glycyrrhizin by both the intestinal bacteria and various organs[7]. In this study, only glycyrrhizin and glycyrrhetic acid were determined in rabbit serum, whereas glycyrrhetic acid mono-β-D-glucuronide, 3-dehydroglycyrrhetic acid and 3α-glycyrrhetic acid were not detected. However, 3-dehydroglycyrrhetic acid

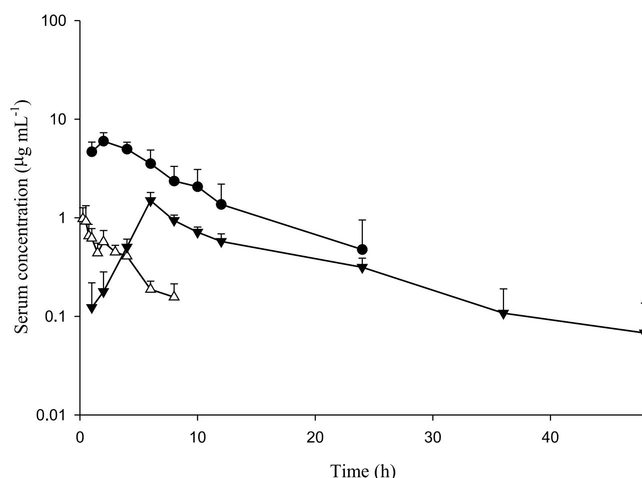

Figure 2. Mean serum concentration-time profiles (± S.E.) of glycyrrhizin (closed circles) and glycyrrhetic acid (closed triangles) after oral administration of glycyrrhizin (150 mg kg^{-1}) and glycyrrhetic acid (open triangles) after oral administration of glycyrrhetic acid (84 mg kg^{-1}) to six rabbits.

has been detected as a metabolite of glycyrrhizin when glycyrrhizin was incubated in fresh rabbit feces in an *in vitro* study in our laboratory (data not shown). The serum level of 3-dehydroglycyrrhetic acid may be too low to be detected. Imai *et al.*[8] reported that the hydrolysis of glycyrrhizin to glycyrrhetic acid mono-β-D-glucuronide was extremely slow and glycyrrhetic acid mono-β-D-glucuronide was rapidly transformed to glycyrrhetic acid. Therefore, a blood profile of glycyrrhetic acid mono-β-D-glucuronide was never reported by any pharmacokinetic studies of glycyrrhizin. Our results indicated that glycyrrhizin could be absorbed per se and in its main metabolite form - glycyrrhetic acid from gut in rabbits, which was similar to the fates of glycyrrhizin upon oral administration to rats and humans[9,10]. Our results

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Table 4. Pharmacokinetic parameters of glycyrrhizin or glycyrrhetic acid after oral administration of glycyrrhizin (150 mg kg^{-1}) and glycyrrhetic acid (84 mg kg^{-1}), respectively, to six rabbits

Drug administered	Glycyrrhizin		Glycyrrhetic acid
Parameters	Glycyrrhizin	Glycyrrhetic acid	Glycyrrhetic acid
T_{max}[a] (hr)	2.8 ± 0.7	7.0 ± 1.0	1.7 ± 0.7**
C_{max}[b] (μg mL^{-1})	6.7 ± 1.4	1.6 ± 0.3	1.3 ± 0.3
AUC[c] (μg mL^{-1} hr)	47.9 ± 17.9	16.3 ± 2.7	3.0 ± 0.5**
MRT[d] (hr)	4.8 ± 1.1	12.7 ± 2.1	2.8 ± 0.3**

Data is expressed as mean ± S.E. [a] time of peak plasma level. [b] concentration of peak plasma level.
[c] area under plasma concentration - time curve to the last point. [d] mean residence time. ** p<0.01.

showed that T_{max} and MRT of glycyrrhizin were 2.8 hr and 4.8 hr, whereas those of glycyrrhetic acid were 7.0 hr and 12.7 hr, respectively, indicating glycyrrhetic acid was absorbed at a later phase and stayed longer in the body than glycyrrhizin. This is consistent with the previous finding in rats by Wang *et al*.[11] who stated that glycyrrhizin was absorbed through the small intestine and the unabsorbed glycyrrhizin was hydrolyzed by bacteria in the large intestine. Thus, most of the glycyrrhetic acid metabolized from glycyrrhizin was absorbed from the large intestine. The C_{max} and AUC_{0-t} of glycyrrhizin (6.7 μg mL^{-1}, 47.9 μg mL^{-1} hr) were much higher than those of glycyrrhetic acid (1.6 μg mL^{-1}, 16.3 μg mL^{-1} hr). However, the *in vivo* anti-inflammatory activity of glycyrrhetic acid was shown to be 10 to 50 times higher than that of glycyrrhizin[12], therefore, in terms of therapeutic consequence, glycyrrhetic acid might be more important than glycyrrhizin although the serum levels were much lower for glycyrrhetic acid.

The profile of mean serum glycyrrhetic acid concentration after glycyrrhetic acid administration is also shown in Figure 2 and the pharmacokinetic parameters of glycyrrhetic acid are listed in Table 4. The mean T_{max} of glycyrrhetic acid after glycyrrhetic acid administration was about 1.7 hr. The AUC_{0-t} of glycyrrhetic acid after glycyrrhetic acid administration was 3.0 μg mL^{-1} hr (6.4 nmol mL^{-1} hr). The mean MRT of glycyrrhetic acid was 2.8 hr.

After glycyrrhetic acid administration, the presence of its conjugate metabolite - glycyrrhetic acid mono-β-D-glucuronide in serum has been investigated by comparing the concentrations of glycyrrhetic acid in serum samples before and after hydrolysis with β-D-glucuronidase. No significant increase of glycyrrhetic acid concentration was found upon hydrolysis. Therefore, it is proposed that a negligible amount of glycyrrhetic acid mono-β-D-glucuronide was circulating in plasma after oral dosing of glycyrrhetic acid. It revealed that the metabolic fate of the alcohol group was quite different from that of the phenolic group.

In order to compare the pharmacokinetic behavior between glycoside and its aglycone, this study carried out a comparison of glycyrrhizin and glycyrrhetic acid based on giving equal molar doses to six rabbits in a crossover design. The results showed that the AUC_{0-t} of glycyrrhetic acid after oral dosing of glycyrrhizin were significantly greater than those after oral dosing of glycyrrhetic acid by 443%. The smaller exposure of glycyrrhetic acid after oral dosing of glycyrrhetic acid compared to that after oral dosing of equal molar glycyrrhizin can be explained by the less water solubility of glycyrrhetic acid in the gastrointestinal tract. The T_{max} of glycyrrhetic acid after oral dosing of glycyrrhizin occurred at 7.0 hr, which was about 5.3 hr later than that after oral dosing of glycyrrhetic acid. This was in good agreement with the fact that glycyrrhizin was metabolized gradually into glycyrrhetic acid by various organs and by enterobacteria in the large intestine where most glycyrrhetic acid was absorbed when glycyrrhizin was orally administered, whereas glycyrrhetic acid was mainly absorbed in the small intestine when glycyrrhetic acid was orally administered[7]. In contrast to the MRT of glycyrrhetic acid (2.8 hr) after oral dosing of glycyrrhetic acid, the MRT of glycyrrhetic acid (12.7 hr) after oral administration of glycyrrhizin was 354 % longer, indicating that glycyrrhizin was serving like a sustained - release dosage form of glycyrrhetic acid. The metabolite glycyrrhetic acid was formed from glycyrrhizin gradually and then absorbed thereafter. It can be concluded that in addition to the absorption of its parent form, glycyrrhizin is an even better prodrug of glycyrrhetic acid than glycyrrhetic acid itself, because it revealed higher exposure of glycyrrhetic acid and lasted for longer residence time.

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甘草酸與甘草次酸於兔體內之動力學比較

經　緦[1]　徐素蘭[2]　侯鈺琪[1]　陳忠川[1]　李珮端[2]*

中國醫藥學院　1. 中國藥學研究所　2. 藥學系
台中市學士路91號

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摘　要

甘草酸為一具生物活性之天然配醣體，甘草次酸為其非醣體及活性代謝物。甘草次酸之抗炎活性較甘草酸為強，亦為副作用醛類脂醇過多症之主因，本研究之目的為比較家兔口服等莫耳之甘草酸與甘草次酸後，其甘草次酸藥物動力學之差異。

六隻紐西蘭大白兔以隨機交叉設計，口服給予178.5 μmol kg^{-1}之甘草酸或甘草次酸後，以高效液相層析法測定血中甘草酸與甘草次酸之濃度；採用非室性模式計算動力學參數並用paired Student’s t-test比較其統計上之差異。

結果顯示口服甘草酸時，除了先有甘草酸原形於小腸吸收外，其代謝物甘草次酸的曲線下面積及平均滯留時間與口服甘草次酸相比較，顯著增加了443%及354%。因此，甘草酸可視為甘草次酸之極佳前驅藥。

關鍵詞：甘草酸，甘草次酸，藥物動力學