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Basic Study

Optimal timing for the oral administration of Da-Cheng-Qi decoction based on the pharmacokinetic and pharmacodynamic targeting of the pancreas in rats with acute pancreatitis

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Abstract

AIM

To identify the optimal oral dosing time of Da-Cheng-Qi decoction (DCQD) in rats with acute pancreatitis (AP) based on the pharmacokinetic and pharmacodynamic parameters.

METHODS

First, 24 male Sprague-Dawley rats were divided into a sham-operated group [NG(a)] and three model groups [4hG(a), 12hG(a) and 24hG(a)]. The NG(a) and model groups were administered DCQD (10 g/kg.BW) intragastrically at 4 h, 4 h, 12 h and 24 h, respectively, after AP models induced by 3% sodium taurocholate. Plasma samples were collected from the tails at 10 min, 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, 12 h and 24 h after a single dosing with DCQD. Plasma and pancreatic tissue concentrations of the major components of DCQD were determined by high-performance liquid chromatography tandem mass spectroscopy. The pharmacokinetic parameters and serum amylase were detected and compared. Second, rats were divided into a sham-operated group [NG(b)] and three treatment groups [4hG(b), 12hG(b) and 24hG(b)] with three corresponding control groups [MG(b)s]. Blood and pancreatic tissues were collected 24 h after a single dosing with DCQD. Serum amylase, inflammatory cytokines and pathological scores of pancreatic tissues were detected and compared.

RESULTS

The concentrations of emodin, naringin, honokiol, naringenin, aloe-emodin, chrysophanol and rheochrysidin in the 12hG(a) group were higher than those in the 4hG(a) group in the pancreatic tissues ($P < 0.05$). The area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration values ($AUC_{0 \rightarrow t}$) for rhein, chrysophanol, magnolol and naringin in the 12hG(a) group were larger than those in the 4hG(a) or 24hG(a) groups. The 12hG(a) group had a higher C_{max} than the other two model groups. The IL-10 levels in the 12hG(b) and 24hG(b) groups were higher than in the MG(b)s (96.55 ± 7.84 vs 77.46 ± 7.42 , 251.22 ± 16.15 vs 99.72 ± 4.7 respectively, $P < 0.05$), while in the 24hG(b) group, the IL-10 level was higher than in the other two treatment groups (251.22 ± 16.15 vs 154.41 ± 12.09 / 96.55 ± 7.84 , $P < 0.05$). The IL-6 levels displayed a decrease in the 4hG(b) and 12hG(b) groups compared to the

MG(b)s (89.99 ± 4.61 vs 147.91 ± 4.36 , 90.82 ± 5.34 vs 171.44 ± 13.43 , $P < 0.05$).

CONCLUSION

Late-time dosing may have higher concentrations of the most major components of DCQD, with better pharmacokinetics and pharmacodynamics of anti-inflammation than early-time dosing, which showed the late time to be the optimal dosing time of DCQD for AP.

Key words: Da-Cheng-Qi decoction; Acute pancreatitis; Pharmacokinetics; Oral dosing time; Pharmacodynamics

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Core tip: Our study group had raised the hypothesis of tissue pharmacology of an herbal recipe, which assumed the effect of an herb formula is related to its target tissue distribution or concentration of effective components in target tissues. This study was then designed to screen the optimal oral dosing time of Da-Cheng-Qi decoction (DCQD) in rats with acute pancreatitis based on the pharmacokinetics of the main absorbed components and the pharmacodynamics of DCQD targeting of the pancreas.

Zhang YM, Zhu L, Zhao XL, Chen H, Kang HX, Zhao JL, Wan MH, Li J, Zhu L, Tang WF. Optimal timing for the oral administration of Da-Cheng-Qi decoction based on the pharmacokinetic and pharmacodynamic targeting of the pancreas in rats with acute pancreatitis. *World J Gastroenterol* 2017; 23(39): 7098-7109 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i39/7098.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i39.7098>

INTRODUCTION

Da-Cheng-Qi decoction (DCQD) was first described in Shang-Han-Lun, a classical work of Traditional Chinese Medicine (TCM). DCQD consists of four Chinese herbs: dahuang (*Rheum palmatum* L.), mangxiao (*Mirabilite*, $Na_2SO_4 \cdot 10H_2O$), houpu (*Magnolia officinalis* Rehd. et Wils.), and zhishi (*Citrus aurantium* L.). It has been widely used as a purgative to treat diseases with constipation and to clear away internal heat^[1], such as in acute pancreatitis (AP), which has a consensus in the relative treatment guidelines in China. The efficacy of DCQD, administered orally or by colocolyster to patients with AP, is obvious. According to clinical observation, it can reduce intra-abdominal hypertension^[2] and decrease the risk of developing acute respiratory distress syndrome in severe AP (SAP) patients with systemic inflammatory response syndrome, and shorten their length of hospitalization^[3].

In animal experiments, it can ameliorate acute pancreatic, intestinal, lung and liver injury complicated with SAP^[4,5]. It can also reduce the generation of reactive oxygen species in AR42J cells and regulate the apoptosis/necrosis switch, to ameliorate the pancreatic inflammation and pathological damage^[6]. Other therapeutic activities of DCQD for AP, such as its antioxidant, anti-inflammatory and anti-ulcer properties^[7] are important. Its numerous roles indicate the wide applicability of DCQD in AP.

However, early oral dosing with DCQD is contradictory to the conventional therapy that considers fasting and water deprivation are necessary for pancreatic rest in the early stage of AP. Conventionally, any stimulation of the exocrine function of the pancreas by fluid or solid nutrients would promote the release of proteolytic enzymes and affect the disease course negatively^[8]. Early oral dosing with DCQD may increase gastric contents, worsen stomachache and abdominal distension, and even aggravate the disease severity. However, it is not clear whether early oral administration of DCQD increases pancreatic secretion and worsens the disease severity. One clinical observation revealed that the best time for gastrointestinal unblocking by herbs was within 48 h after the onset of AP^[9]. At the same time, releasing excessive turbidity should be done sooner rather than later to prevent intestinal function failure and disease deterioration^[9]. Some studies have indicated that AP patients must pass feces within 24 h after the onset of AP, as one method to support intestinal function to control systemic inflammatory response syndrome and protect organ functions^[9]. It is still unclear if the optimal oral dosing time of DCQD should be earlier or later. Therefore, it is important to find the optimal dosing time of DCQD at which DCQD will not worsen the disease severity.

The necrosis of pancreatic acinar cells would worsen the disease, and the induction of apoptosis would decrease the disease severity^[6]. Thus, based on the effect of DCQD on regulation of the apoptosis/necrosis switch of pancreatic acinar cells to ameliorate pancreatic inflammation and pathological damage^[6], the study aimed to identify the optimal oral dosing time of DCQD in rats with AP according to the pharmacokinetics of the absorbed components and the pharmacodynamics of DCQD targeting of the pancreas.

MATERIALS AND METHODS

Animals

Sprague-Dawley male rats ($n = 66$) aged 90 ± 5 d, with body weights of 280–300 g, were purchased from Chengdu Dashuo Bio-Technique Co. Ltd. (Chengdu, China). The animals were maintained as previously described^[10]. Before AP induction, rats were fasted for 12 h. This study was performed according to the Guide

for the Care and Use of Laboratory Animals of Sichuan University (Chengdu, China) and the Animal Ethics Committee Guidelines of the Animal Facility of the West China Hospital (Chengdu, China).

Preparation of drugs

Sodium taurocholate was supplied by Sigma (St. Louis, MO, United States). Spray dried particles of dahuang, mangxiao, houpu, and zhishi were purchased from Chengdu Green Herbal Pharmaceutical Co. Ltd. (Chengdu, China). Chloral hydrate (10%), paraformaldehyde (4%) and methanol were obtained from Tedia Co. Ltd. (Nos. 509221 and 609144; Fairfield, OH, United States). Glacial acetic acid (No. 20030911) and ethyl acetate (No. 20070116) were purchased from Chengdu Kelon Chemical Reagent Factory (Chengdu, China). Reference standards of the 10 components of DCQD were purchased from the same companies. According to the proportion of crude drugs (dahuang 12 g, houpu 24 g, zhishi 12 g, and mangxiao 9 g), the granules of the four drugs were stirred with ultra-pure water by magnetic stirrers with a speed setting of grade 5 for 1 h in a water bath at a temperature of 37 °C for 30 min. According to the Method of Pharmacology, the least dosage of DCQD is 0.6 g/100 g.BW for rats. In this study, the dosage was 1 g/100 g.BW (10 g/kg.BW) with the concentration of 1 g/mL.

Equipment and conditions

The magnetic stirrer (C-MAG, MS 7) was provided by the IKA Company (Breisgau, Germany). The analytical balance (BSA-224S-CW) was provided by the Sartorius Company (Goettingen, Germany). The micro-infusion pump was obtained from KD Scientific (Holliston, MA, United States). Conventional operation instruments, fixation-machines for rats, and the 1.5 mL and 10 mL centrifuge tubes were purchased from Shimadzu (Kyoto, Japan). The high-performance liquid chromatography tandem mass spectroscopy (HPLC-MS/MS) system consisted of a SIL-HTc autosampler (Shimadzu), a LC-10ADvp pump (Shimadzu), and an API3000 triple-quadrupole LC-MS system (Applied Biosystems, Foster City, CA, United States). This system was controlled by Analyst 1.4. Software (Chinese Pharmacological Society, Beijing, China). The chromatographic column was an Ultimate XB-C₁₈ (5 μ m, 50 mm \times 4.6 mm). The mobile phase consisted of methanol-water (92:8, v/v) delivered at a flow rate of 0.3 mL/min. The column was maintained at ambient temperature, and the injection volume was 80 μ L. The Anke centrifuge TGL-16B was supplied by Shanghai An-Ting Science Technology Instrument Factory (Shanghai, China). All aqueous solutions and buffers were prepared with ultra-pure water from a Millipore RiosTM-16 water purifier (Millipore, Billerica, MA, United States). Standard stock solutions were prepared

by dissolving the reference standards (100 µg/mL for emodin, aloe-emodin, chrysophanol, naringin, naringenin, hesperidin, magnolol and honokiol; 20 µg/mL for rhein and rheochrysidin) and internal standard (40 µg/mL for ibuprofen) in methanol^[1]. Stock solutions were stored at -20 °C. Working standard solutions were prepared freshly by diluting stock solutions in sodium hydroxide solution (0.1 mol/L). Internal standard working solution (200 ng/mL) was prepared by diluting the stock solution in methanol-water (1:1, v/v)^[1].

Induction of AP and dosing of DCQD

First part: Rats were randomly allocated into the following four groups ($n = 6$ each): a sham-operated group [NG(a)] and three model groups [4hG(a), 12hG(a) and 24hG(a)]. AP models were induced by retrograde perfusion of 3% sodium taurocholate (1 mL/kg.BW) into the biliopancreatic duct^[11] at a rate of 6 mL/h with a micro-infusion pump after anesthetization with 10% chloral hydrate (3 mL/kg.BW) injected into the abdominal cavity. The NG(a) group was established by the same procedure, but with use of saline instead of sodium taurocholate. The dosing time of DCQD for the NG(a) and model groups were 4 h, 4 h, 12 h and 24 h after operation.

Second part: Forty-two rats were divided into a sham-operated group [NG(b)], and 4h-, 12h- and 24h-dosing treatment groups [4hG(b), 12hG(b) and 24hG(b), respectively] with three corresponding control groups [MG(b)s]. Only the three treatment groups were administered the same dosage of DCQD at 4 h, 12 h and 24 h, respectively, after AP induction. The three corresponding control groups were given saline instead of DCQD at the same time. Rats were euthanized at 24 h after drug dosing.

Collection and measurement of samples

First part: Plasma samples (0.5 mL) were collected from the tails at 10 min, 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, 12 h and 24 h after a single dosing of DCQD. Serum samples for amylase (AMS) and pancreatic tissues for the tissue concentrations of the absorbed components of DCQD were collected 24 h after drug dosing. A total of 0.05 mL of internal standard working solution and 0.1 mL of hydrochloric acid buffer solution were added into 0.2 mL of the plasma or tissue homogenate samples, followed by 3.0 mL of ethyl acetate. Then, the mixtures were extracted by vortex mixing for 7 min and centrifuged at 3000 rpm for 7 min at a low temperature. After that, 2.4 mL supernatants were evaporated at 45 °C, followed by incubation with 0.1 mL of double-solvents (methanol-water: 92:8, v/v). Thereafter, 20 µL of supernatant was injected automatically into the HPLC-MS/MS

system for analysis. The 10 major components of DCQD (aloe-emodin, rhein, emodin, chrysophanol, honokiol, rheochrysochanol, magnolol, hesperidin, naringenin and naringin) were detected. The mean contents of the components were detected three times, as in our previous study^[12]. The detected DCQD samples were stored in the Public Experiment Platform at West China Hospital (Chengdu, China).

Second part: Serum for AMS and inflammatory cytokines measurement and pancreatic tissues for pathological scoring were collected 24 h after drug dosing. Pancreatic samples were fixed in 10% neutral formalin for paraffin sections and stained with hematoxylin and eosin (HE). All the histopathology specimens were scored in a blinded fashion by two independent pathologists using a scoring system for the extent and severity of tissue injury (0-4, edema, neutrophil infiltration, necrosis and hemorrhage, respectively), as previously described^[4,13]. The IL-10 and IL-6 levels were detected by enzyme-linked immunosorbent assay kits. The following formula was used to calculate the value of AMS: AMS (U/dL) = (blankOD - measurementOD)/blankOD \times 0.4 \times 0.5/10 \times 30 min/7.5 min \times 100/0.1 \times 10

Statistical analysis

The pharmacokinetic parameters were processed by pharmacokinetic statistical software DAS2.0.1 programmed by the Chinese Pharmacological Society. The data were obtained by statistical moment calculation. The following pharmacokinetic parameters were calculated: the maximum plasma concentration (C_{max}), the time to reach maximum concentration (T_{max}), the mean residence time ($MRT_0 \rightarrow t$), the elimination half-life ($T_{1/2}$) and the area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration ($AUC_{0 \rightarrow t}$). The data were processed with statistical software PEMS3.1. All values were expressed as the mean \pm SD. A one-way repeated-measure ANOVA, followed by multiple pairwise comparisons using the Student-Newman-Keuls procedure, was used to detect differences among the groups. $P < 0.05$ was considered a statistically significant difference.

RESULTS

Ten major components of DCQD distributed in pancreatic tissues

In this study, all 10 major components of DCQD in pancreatic tissues could be detected by HPLC-MS/MS. The concentrations of naringin, hesperidin, naringenin, aloe-emodin and chrysophanol in pancreatic tissues were relatively high. Compared to the NG(a) group, the concentrations of emodin,

Table 1 Concentrations of the 10 components of DCQD distributed in pancreatic tissues

	NG(a)	4hG(a)	12hG(a)	24hG(a)
Rhein	12.65 ± 3.7	179.15 ± 77.6 ^a	199.89 ± 34.8	50.08 ± 17.6 ^e
Emodin	18.68 ± 8.7	1.33 ± 0.8 ^a	34.46 ± 10.3 ^c	39.75 ± 12.4
Naringin	415.30 ± 17.8	19.47 ± 1.4 ^a	32.10 ± 2.7 ^c	269.16 ± 12.9 ^e
Honokiol	2.38 ± 1.2	1.98 ± 0.1	19.79 ± 2.2 ^c	4.26 ± 1.0
Magnolol	1.34 ± 0.9	0.97 ± 0.2	0.97 ± 0.2	7.51 ± 0.8 ^e
Hesperidin	162.01 ± 34.3	34.94 ± 12.6 ^a	24.31 ± 10.3	113.26 ± 13.8 ^e
Naringenin	847.98 ± 76.9	858.58 ± 19.6	1077.06 ± 26.8 ^c	262.30 ± 100.6 ^e
Aloe-emodin	439.05 ± 179.8	89.53 ± 14.8 ^a	502.74 ± 70.7 ^c	501.45 ± 143.4
Chrysophanol	60.99 ± 16.4	5.16 ± 2.1 ^a	197.29 ± 17.9 ^c	113.43 ± 23.7 ^e
Rheochrysidin	6.79 ± 1.2	0.55 ± 0.2 ^a	17.92 ± 1.9 ^c	11.67 ± 0.9 ^e

Rats were orally administered with DCQD (10 mL/kg.BW). Pancreatic tissues were collected 24 h after a single dosage of DCQD. The concentrations of the 10 components of DCQD were determined by HPLC-MS/MS. The results are presented as the mean ± SD of µg/mg (*n* = 6). NG(a): the sham-operated group with the dosing time at 4 h after operation. 4hG(a), 12hG(a) and 24hG(a): rats were dosed orally with DCQD at 4 h, 12 h and 24 h, respectively, after AP induction. 4hG(a) *vs* NG(a): ^a*P* < 0.05, 12hG(a) *vs* 4hG(a): ^c*P* < 0.05, 24hG(a) *vs* 12hG(a): ^e*P* < 0.05. AP: Acute pancreatitis; DCQD: Da-Cheng-Qi decoction; HPLC-MS/MS: High-performance liquid chromatography tandem mass spectroscopy.

naringin, hesperidin, aloe-emodin, chrysophanol and rheochrysidin were lower in the 4hG(a) group (*P* < 0.05), while the rhein concentration was higher (*P* < 0.05). The concentrations of emodin, naringin, honokiol, naringenin, aloe-emodin, chrysophanol and rheochrysidin in the 12hG(a) group were higher than in the 4hG(a) group (*P* < 0.05). The concentrations of rhein, naringenin, chrysophanol and rheochrysidin in the 24hG(a) group were lower than in the 12hG(a) group (*P* < 0.05), while the concentrations of naringin, magnolol and hesperidin in the 24hG(a) group were higher (*P* < 0.05) (Table 1).

Eight major components of DCQD detected in plasma

Only eight of the ten components were successfully fitted to the concentration-time curves according to the testing data (Figure 1). The *T*_{max} values were all at 40 min (0.67 h) after a single dosage of DCQD in the NG(a) group. The *T*_{max} of six components (aloe-emodin, rhein, emodin, chrysophanol, naringenin and naringin) in the 4hG(a) group, all components in the 12hG(a) group and that of five components (aloe-emodin, rhein, rheochrysidin, magnolol and naringin) in the 24hG(a) were delayed (Figure 1).

In the NG(a) group, the *C*_{max} values of the components were as follows: aloe-emodin, 3218.33 ng/mL; rhein, 8638.42 ng/mL; emodin, 510.97 ng/mL; naringin, 204.56 ng/mL; chrysophanol, 5419.89 ng/mL; rheochrysidin, 146.75 ng/mL; naringenin, 419.94 ng/mL; and magnolol, 19.58 ng/mL. Compared to the NG(a) group, the *C*_{max} values of aloe-emodin, rhein, emodin, chrysophanol and magnolol were reduced in the 4hG(a) group (Figure 1). Compared to the 4hG(a) or 12hG(a) groups, the *C*_{max} values of aloe-emodin, rhein, emodin, naringenin and magnolol were higher in the 24hG(a) group, and they were as follows: 5885.13 ng/mL, 8245.18 ng/mL, 88.65 ng/mL, 606.41 ng/mL and 11.018 ng/mL, respectively. Among the three

model groups, the *C*_{max} values of chrysophanol and naringin were highest in the 12hG(a) group, and for rheochrysidin the *C*_{max} was in the 4hG(a) group; the concentrations were 4054.73 ng/mL, 519.53 ng/mL and 557.06 ng/mL, respectively (Figure 1).

The pharmacokinetic parameters were analyzed by statistical moment calculation, and those in model groups were different from those in the NG(a) group (Table 2). Compared to the NG(a) group, the *AUC*_{0→∞} values of aloe-emodin, chrysophanol, emodin and magnolol were smaller in the 4hG(a) group (*P* < 0.05), while those of rheochrysidin, naringin and naringenin were larger (*P* < 0.05). The *AUC*_{0→∞} of aloe-emodin in the 24hG(a) group was larger than in the 4hG(a) or 12hG(a) groups, and those of rhein, chrysophanol, magnolol and naringin in the 12hG(a) group were larger than in the 4hG(a) or 24hG(a) groups. The *T*_{1/2} values of rhein, emodin, aloe-emodin, rheochrysidin, naringin and magnolol in the 24hG(a) group were longer than in the 4hG(a) or 12hG(a) groups.

DCQD elevated the IL-10 levels and lowered the IL-6 levels in serum

In serum, the IL-10 and IL-6 levels in the three corresponding control groups were all higher than in the NG(b) group (IL-10: 152.8 ± 18.58/77.46 ± 7.42/99.72 ± 4.7 *vs* 48 ± 12, *P* < 0.05; IL-6: 147.91 ± 4.36/171.44 ± 13.43/98.48 ± 2.7 *vs* 68 ± 20, *P* < 0.05). Compared to the corresponding control groups, the IL-10 levels in the 12hG(b) and 24hG(b) groups were increased (96.55 ± 7.84 *vs* 77.46 ± 7.42, 251.22 ± 16.15 *vs* 99.72 ± 4.7, *P* < 0.05), and the IL-10 level in the 24hG(b) group was higher than in the 4h(b) and 12hG(b) groups (251.22 ± 16.15 *vs* 154.41 ± 12.09/96.55 ± 7.84, *P* < 0.05) (Figure 2A). The IL-6 levels displayed a decrease in the 4hG(b) and 12hG(b) groups compared to their corresponding control groups (89.99 ± 4.61 *vs* 147.4.36, 90.82 ± 5.34 *vs* 171.44 ±

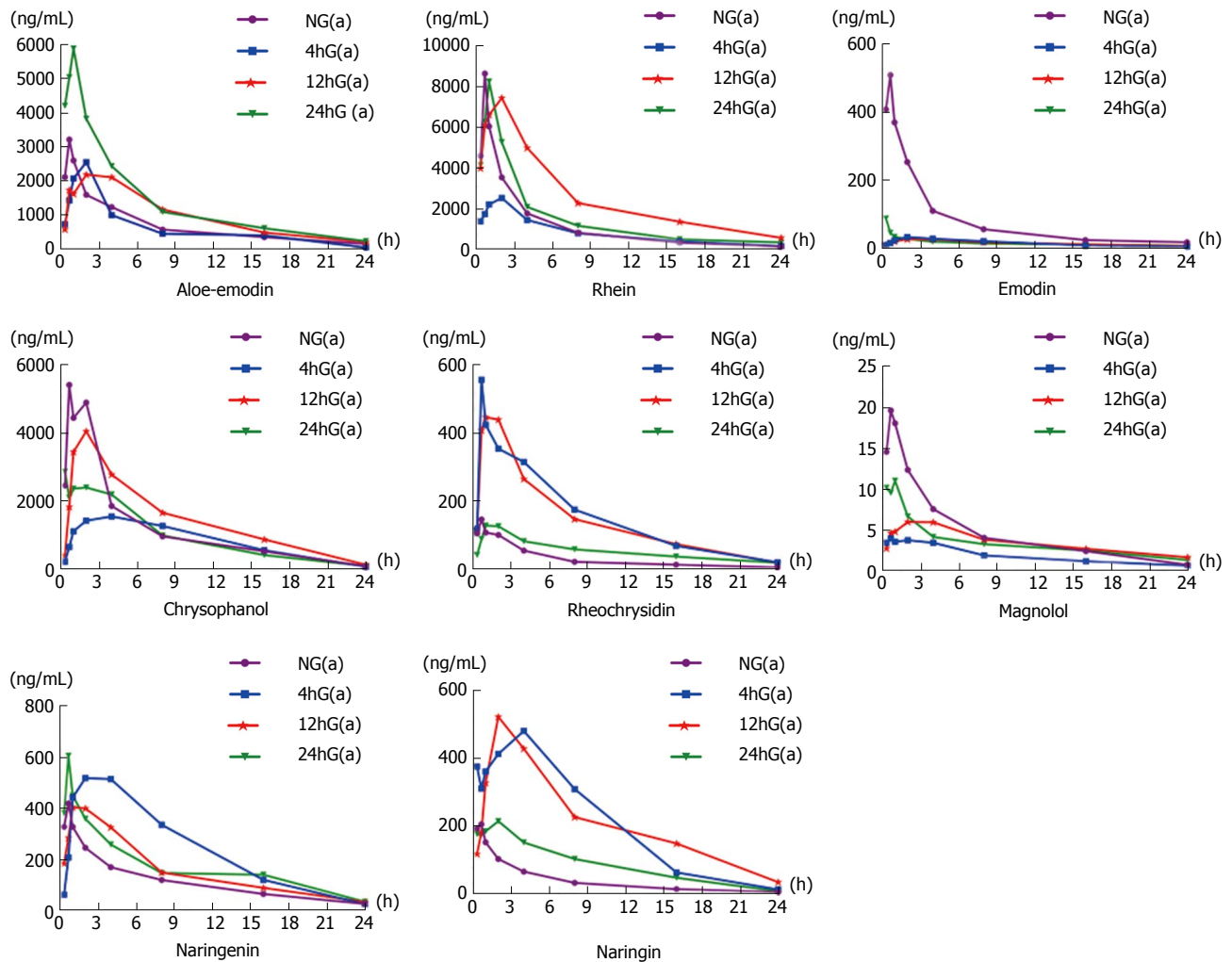


Figure 1 Concentration-time curves of the eight components of Da-Cheng-Qi decoction in plasma of the rats with acute pancreatitis. Rats ($n = 6$ per group) were orally dosed with DCQD (10 mL/kg.BW). Plasma samples were collected from the tails at 10 min, 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, 12 h and 24 h after a single dosage of DCQD. Plasma concentrations of the components of DCQD were determined by HPLC-MS/MS. The results are presented as the mean \pm SD. NG(a): the sham-operated group with the dosing time 4 h after operation; 4hG(a), 12hG(a) and 24hG(a): the dosing times were 4 h, 12 h and 24 h, respectively, after AP induction. AP: Acute pancreatitis; DCQD: Da-Cheng-Qi decoction; HPLC-MS/MS: High-performance liquid chromatography tandem mass spectroscopy.

13.43, $P < 0.05$) (Figure 2B).

Pathological damages in the pancreatic tissues and serum AMS levels

In the NG(b) group, the pancreatic tissues were edematous with a few neutrophils but without obvious hemorrhage and necrotic acinar tissues. In the MG(b) groups, edema, hemorrhage and neutrophils with some necrotic acinar tissues were obvious. In the 12hG(b) group, the pathological damages were improved, while those in the 4hG(b) or 24hG(b) groups had no obvious improvement (Figure 3A). Compared to the NG(b) group, the pathological scores in the MG(b) groups were increased ($1.79 \pm 0.3/2.2 \pm 0.2/2.67 \pm 0.67$ vs 0.7 ± 0.26 , $P < 0.05$). Those in the 12hG(b) group were evidently reduced compared to its control group (1.3 ± 0.4 vs 2.2 ± 0.2 , $P < 0.05$) or the 4hG(b) and 24hG(b) groups (1.3 ± 0.4 vs 2.63

$\pm 0.4/2.5 \pm 0.3$, $P < 0.05$) (Figure 3B).

The AMS levels in the 4hG(a), 12hG(a) and 24hG(a) groups were all higher than in the NG(a) group ($724.17 \pm 42.8/673.67 \pm 26.64/659.65 \pm 41.38$ vs 273.67 ± 93.23 , $P < 0.05$) (Figure 3C). Compared to the NG(b) group, that in the MG(b) groups were higher ($718.65 \pm 51.04/711.68 \pm 55.37/666.4 \pm 73.4$ vs 389 ± 98 , $P < 0.05$). The AP model was successful. That in the 12hG(b) group was reduced compared to its control group (649 ± 131.69 vs 711.68 ± 55.37 , $P < 0.05$) (Figure 3D).

DISCUSSION

According to the present study, AP reduced the concentrations of the major components of DCQD to the target pancreas, and the oral administration time also played an important role; their absorption

Table 2 Pharmacokinetic parameters of the 8 detected components of Da-Cheng-Qi decoction in plasma

Parameter	NG(a)	4hG(a)	12hG(a)	24hG(a)
Aloe-emodin				
T _{1/2} (h)	7.5 ± 3.4	4.8 ± 1.9	7.3 ± 2.7	7.5 ± 4.3
AUC _{0→t} (μg/mL·h)	16582.3 ± 523.7	15180.5 ± 245.3 ^a	23266.6 ± 2848.4 ^b	32517.8 ± 3109.6 ^{dc}
MRT _{0→t} (h)	7.0 ± 1.8	6.5 ± 1.6	7.7 ± 0.9	6.2 ± 1.3
T _{max} (h)	1.22 ± 1.38	1.45 ± 0.62	2.28 ± 1.44	0.67 ± 0.30 ^{dc}
C _{max} (μg/mL)	4080.9 ± 2491.6	2890.5 ± 955.0	2948.2 ± 997.6	7706.6 ± 2366.7 ^{dc}
Rhein				
T _{1/2} (h)	4.7 ± 1.5	6.3 ± 1.8	6.2 ± 1.2	16.6 ± 2.1 ^{dc}
AUC _{0→t} (μg/mL·h)	27164.9 ± 1686.9	19164.9 ± 1680.3	60705.9 ± 2870.4 ^b	35470.0 ± 1910.1 ^{dc}
MRT _{0→t} (h)	4.7 ± 1.0	6.3 ± 1.5 ^a	7.4 ± 1.3	5.9 ± 3.2
T _{max} (h)	0.7 ± 0.3	1.4 ± 0.9 ^a	1.3 ± 0.7	1.3 ± 0.4
C _{max} (μg/mL)	11033.4 ± 3248.9	3037.9 ± 1040.5 ^a	9439.4 ± 3191.6 ^b	9938.6 ± 3349.6 ^d
Chrysophanol				
T _{1/2} (h)	5.2 ± 1.7	6.8 ± 3.6	4.5 ± 0.8	6.2 ± 3.8
AUC _{0→t} (μg/mL·h)	28925.5 ± 7837.2	20214.5 ± 1460.6 ^a	34977.3 ± 1927.7 ^b	23102.4 ± 1614.8 ^c
MRT _{0→t} (h)	5.7 ± 0.8	7.2 ± 1.7 ^a	7.3 ± 1.0	6.2 ± 1.2
T _{max} (h)	1.2 ± 0.6	3.5 ± 2.5 ^a	1.7 ± 0.5	1.3 ± 0.5 ^d
C _{max} (μg/mL)	7708.1 ± 2234.3	2296.1 ± 7643.8 ^a	4521.8 ± 1127.1 ^b	4772.6 ± 1078.4 ^d
Emodin				
T _{1/2} (h)	8.2 ± 6.6	14.7 ± 11.7	11.7 ± 6.0	20.8 ± 19.6
AUC _{0→t} (μg/mL·h)	1891.5 ± 1692.8	395.3 ± 159.0 ^a	395.4 ± 82.4	391.2 ± 135.8
MRT _{0→t} (h)	5.2 ± 1.9	8.4 ± 1.7 ^a	9.4 ± 0.8	8.6 ± 1.9
T _{max} (h)	0.6 ± 0.3	3.8 ± 3.3 ^a	3.2 ± 2.6	0.7 ± 0.7 ^{dc}
C _{max} (μg/mL)	546.2 ± 496.8	37.9 ± 18.4 ^a	34.1 ± 9.6	91.8 ± 37.4
Rheochrysidin				
T _{1/2} (h)	6.4 ± 0.9	4.6 ± 1.9	5.4 ± 2.1	8.3 ± 2.3 ^{dc}
AUC _{0→t} (μg/mL·h)	740.2 ± 623.3	3680.6 ± 1903.0 ^a	3489.2 ± 1354.1	1301.8 ± 420.9 ^{dc}
MRT _{0→t} (h)	5.7 ± 1.4	6.4 ± 0.9	6.3 ± 1.5	8.2 ± 1.1 ^{dc}
T _{max} (h)	0.9 ± 0.6	2.1 ± 1.6	1.7 ± 1.3	1.5 ± 0.6
C _{max} (μg/mL)	184.7 ± 92.4	713.8 ± 201.6 ^a	642.3 ± 211.5	155.5 ± 56.4 ^{dc}
Magnolol				
T _{1/2} (h)	8.5 ± 4.9	9.4 ± 2.8	12.2 ± 3.3	22.8 ± 7.6 ^{dc}
AUC _{0→t} (μg/mL·h)	111.4 ± 37.2	44.4 ± 14.3 ^a	83.9 ± 27.2 ^b	81.5 ± 25.0 ^d
MRT _{0→t} (h)	7.2 ± 0.9	7.9 ± 1.2	9.4 ± 1.1	8.9 ± 1.2
T _{max} (h)	0.7 ± 0.3	1.3 ± 0.5Δ	2.8 ± 1.4	0.6 ± 0.3 ^{dc}
C _{max} (μg/mL)	24.2 ± 8.6	5.8 ± 2.3Δ	7.7 ± 3.6	15.3 ± 13.1 ^{dc}
Naringin				
T _{1/2} (h)	5.8 ± 1.2	4.9 ± 1.8	5.3 ± 1.4	5.5 ± 1.4
AUC _{0→t} (μg/mL·h)	918.1 ± 106.8	4920.6 ± 310.7 ^a	5054.4 ± 435.1	2044.1 ± 26.9 ^{dc}
MRT _{0→t} (h)	5.9 ± 1.1	6.6 ± 0.8	7.9 ± 0.6	6.9 ± 1.0
T _{max} (h)	0.7 ± 0.2	1.4 ± 1.4	2.5 ± 1.2	1.8 ± 1.3
C _{max} (μg/mL)	229.3 ± 195.6	724.4 ± 584.7	595.1 ± 338.9	322.9 ± 148.4
Naringenin				
T _{1/2} (h)	7.2 ± 1.7	4.9 ± 1.1a	9.3 ± 3.6 ^b	7.7 ± 1.3 ^d
AUC _{0→t} (μg/mL·h)	2705.2 ± 164.6	5795.1 ± 291.4 ^a	3758.1 ± 250.1 ^b	4099.2 ± 148.8 ^{dc}
MRT _{0→t} (h)	6.4 ± 1.7	7.3 ± 0.4	7.7 ± 1.2	7.9 ± 1.8
T _{max} (h)	0.8 ± 0.6	2.3 ± 1.4	1.6 ± 1.3	0.6 ± 0.3 ^d
C _{max} (μg/mL)	552.9 ± 226.7	720.4 ± 165.9	543.3 ± 110.4	624.9 ± 143.7

Rats were orally dosed with DCQD (10 mL/kg.BW). Plasma samples were collected from the tails at 10 min, 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, 12 h and 24 h after a single dosage of DCQD. The samples were assessed by HPLC-MS/MS. The pharmacokinetic parameters were processed by pharmacokinetic statistic software DAS2.0.1 and the data were obtained by statistical moment calculation. The results are presented as the mean ± SD. NG(a): the sham-operated group with the dosing time at 4 h after operation. 4hG(a), 12hG(a) and 24hG(a): rats were dosed orally with DCQD at 4 h, 12 h and 24 h, respectively, after AP induction. Compared with NG(a): ^a*P* < 0.05, 12hG(a) vs 4hG(a); ^b*P* < 0.05, 24hG(a) vs 12hG(a); ^c*P* < 0.05, 24hG(a) vs 4hG(a); ^d*P* < 0.05. AP: Acute pancreatitis; DCQD: Da-Cheng-Qi decoction; HPLC-MS/MS: High-performance liquid chromatography tandem mass spectroscopy.

may be better if the oral administration time of DCQD is approximately 12 h after the onset of AP (Table 1). AP delayed the T_{max} and reduced the C_{max} of the components of DCQD in the circulation of rats (Figure 1). The components of DCQD displayed a higher C_{max} and a longer T_{1/2} when the oral administration time of DCQD was approximately 24 h after the onset of AP

(Figure 1 and Table 2). The AUC_{0→t} was larger when that time was approximately 12 h after the onset of AP (Table 2). DCQD increased the IL-10 levels and lowered the IL-6 levels (Figure 2A and B), and the later administration of the DCQD dose corresponded to higher IL-10 levels (Figure 2A). Therefore, administering the DCQD dose too early may not be

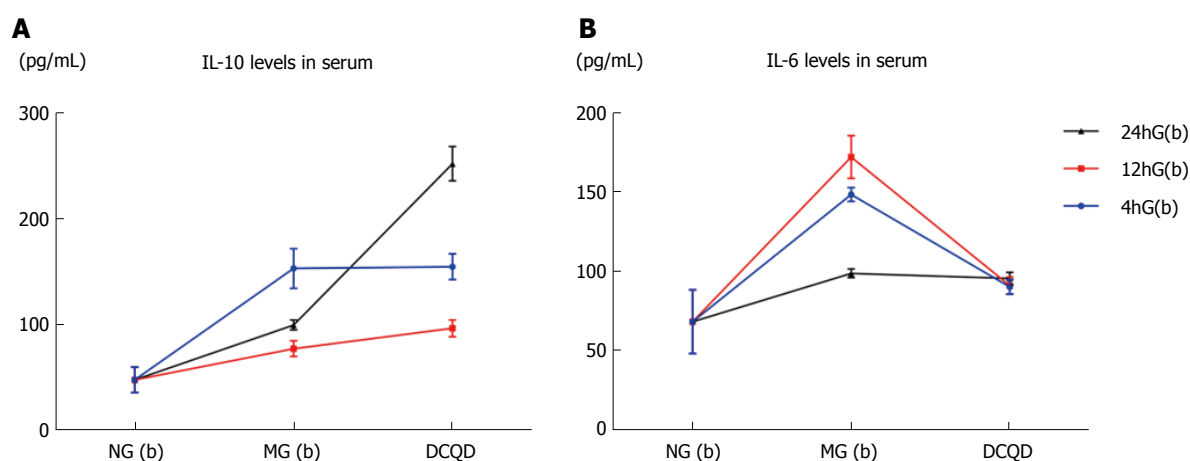


Figure 2 Da-Cheng-Qi decoction elevated IL-10 levels and lowered IL-6 levels in serum of the rats with acute pancreatitis. Rats ($n = 6$ per group) in the three treatment groups were orally dosed with DCQD (10 mL/kg.BW) 4 h, 12 h and 24 h after AP induction. Serum samples were collected at 24 h after a single dosage of DCQD. The results are presented as the mean \pm SD. NG(b): the sham-operated group; MG(b): the model group or the control group; 4hG(b), 12hG(b) and 24hG(b): rats were orally dosed with DCQD 4 h, 12 h and 24 h, respectively, after AP induction. AP: Acute pancreatitis; DCQD: Da-Cheng-Qi decoction.

appropriate for AP, and administration should at least be 12 h after the onset of AP.

Pathological circumstances may affect the absorption of the components of DCQD and affect the pharmacokinetics in AP. Pancreatic ischemia, reduced pancreatic blood flow and increased capillary permeability are usually common in AP^[14]. The systemic hemodynamic disturbances lead to ischemia of the intestine^[15]. In addition, one retrospective analysis (197 patients) showed that 65% of patients with AP had acute gastrointestinal mucosal lesions detected by upper gastrointestinal endoscopy^[16]. As well, 59% of patients with AP showed gut barrier dysfunction with increased intestinal permeability in a meta-analysis of 18 studies^[17]. Both propulsion and contractility were reduced in necrotizing pancreatitis of rats^[18]. It was reported that permeability of the ileum was significantly increased at 6 h, the blood endotoxin level was elevated and bacterial translocation occurred 18 h after induction of SAP-induced by injection of 3% sodium deoxycholate^[19].

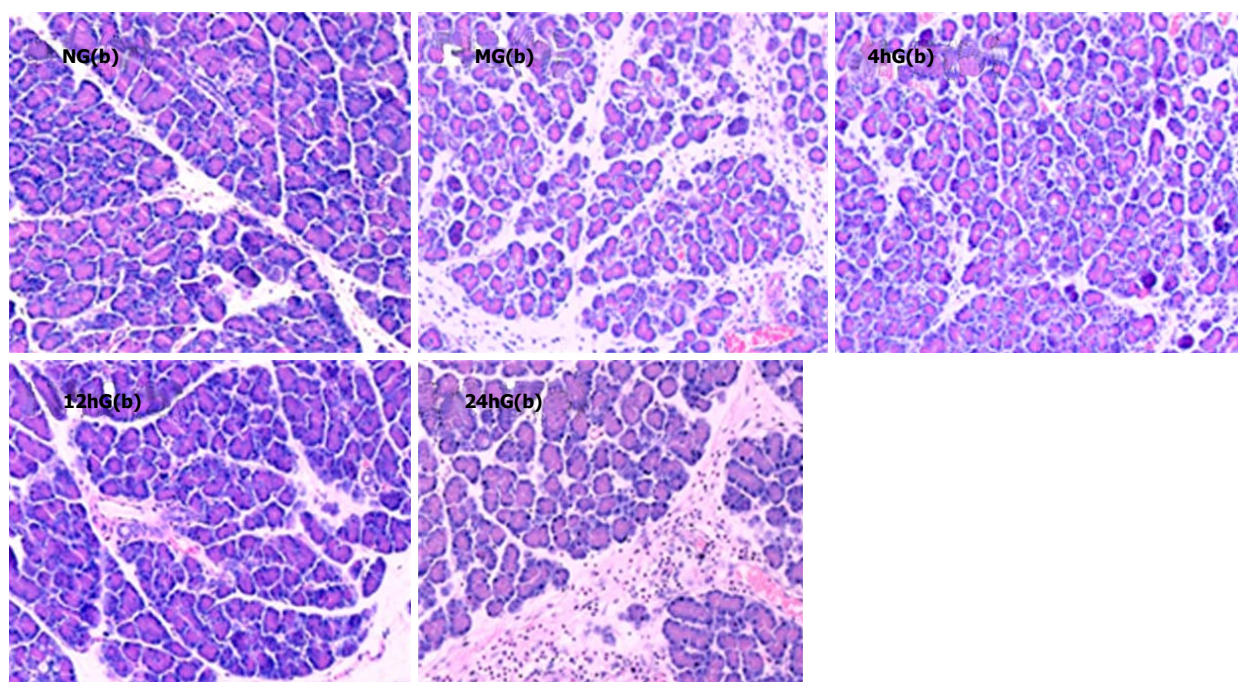
As we know, oral medicines, including herbs, are generally absorbed by the gastrointestinal mucosa. The process of drug absorption into the blood circulation from the plasma membrane barrier proceeds as follows: drug molecule encounters the gastrointestinal mucous layer, brush border, epithelial cell membrane, intracellular fluid, basal lamina, lamina propria, externa of vessels, cytoplasm of vessels, intima of vessels and then the blood. Therefore, these aforementioned factors may play an important role in the delay of the T_{max} of the components of DCQD in reaching the circulation and establishing their concentrations in pancreatic tissues.

Another factor may be the physicochemical properties of these components. Chrysophanol belongs to the Class II poorly water soluble drugs in the Biopharmaceutics Classification System (BCS), with

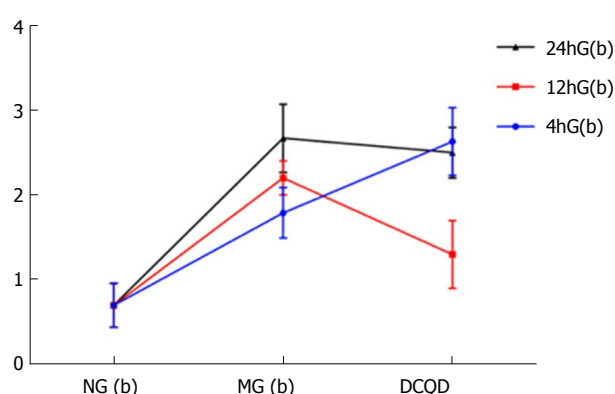
low solubility but high permeability^[20,21]. Magnolol, a small-molecule neolignan^[22], has an extensive first-pass metabolism and low absorption^[23]. Naringin is moderately soluble in water, and it is broken into its aglycon naringenin in the intestine by the gut microflora and then absorbed from the gut^[24]. These different characteristics may influence the absorption of these components. Furthermore, the pharmacokinetics of phytochemicals have substantial variation^[25] and circulating concentrations of phytochemicals, which could vary widely among individuals, even in the context of controlled feeding studies^[26]. In brief, the internal environments of rats and the characteristics of the components of DCQD may be the major factors affecting the absorption of these components.

It is well known that the avoidance of gastric and intestinal secretion has been the cornerstone of management of patients with AP for nearly a century^[27]. To espouse the "pancreatic rest" concept, fasting and water deprivation have become the fundamental treating rules. However, the benefits of oral dosing with DCQD in the early stage of AP have been demonstrated, especially in gastrointestinal internal environments. This approach could improve intestinal propulsive function, relieve abdominal distension and abdominal pressure^[28], and protect the intestinal immune barrier, with amelioration of the levels of high mobility group box-1 protein (HMGB1) RNA and cyclooxygenase 2 (COX-2) RNA expression^[29]. One meta-analysis showed that purgative therapy could shorten the time of first defecation and the hospitalization time^[30]. Thus, the advantages of DCQD are obvious. Future studies should be done to determine whether the oral dose of DCQD could increase gastrointestinal and pancreatic secretion.

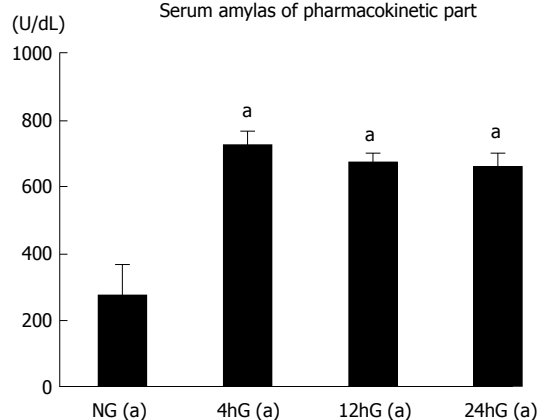
The finding of DCQD regulating the balance of pro-inflammation and anti-inflammation was consistent with our previous studies^[4]. However, the current

A

B

Histopathologic scores of pancreatic tissues


C

Serum amylase of pharmacokinetic part


D

Serum amylase of pharmacodynamic part

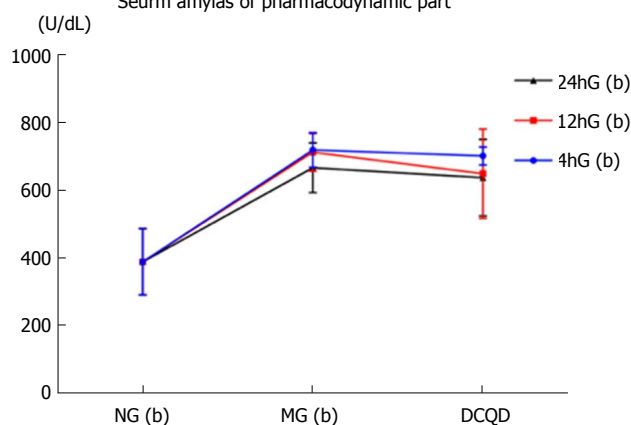


Figure 3 Pathological damages in the pancreatic tissues and changes in the serum amylase concentration. Rats ($n = 6$ per group) were orally administered DCQD (10 mL/kg.BW) 4 h, 12 h and 24 h after AP induction. Pancreatic tissues were collected for staining with hematoxylin-eosin (A, $\times 200$) 24 h after a single dosage of DCQD; B: Pathological scores of the pancreatic tissues. Serum amylase was detected by enzyme-linked immunosorbent assay (C and D). The results are presented as the mean \pm SD. $^aP < 0.05$ vs NG(a). NG(a/b): the sham-operated group; MG(b): the model group or the control group; 4hG(a/b) 12hG(a/b), and 24hG(a/b): rats were orally dosed with DCQD 4 h, 12 h and 24 h, respectively, after AP induction. AP: Acute pancreatitis; DCQD: Da-Cheng-Qi decoction.

study showed that its oral dosing time might affect the inflammatory cytokines and pharmacokinetics of the effective components of DCQD targeting of pancreatic tissues and plasma. The chronomedicine of TCM, with thousands of years of history and in which the midnight-noon ebb-flow theory is typical, is similar to modern chronobiology. Theoretically, the function of Chinese medicine will be most effective at driving out pathogenic factors when the function of some meridian is at its peak^[31]. For example, erythrocyte C3b receptor rosette and erythrocyte immune complex rosette can reach peak value when the kidney meridian has its most active function^[32].

Along with the improvement of modern technology, the research on the relationship between the dosing time of Chinese medicine and plasma concentration or curative effect has been performed. Nishioka *et al.*^[33] demonstrated that the dosing time of Sho-Saiko-To could affect the plasma concentrations of the effective components (glycyrrhizin and baicalein). Additionally, the pharmacokinetic processes of emodin and aloe-emodin of DCQD presented a circadian rhythm phenomenon^[34]. According to our study, the oral dosing time also affects the drug tissue concentrations. Therefore, the oral dosing time of DCQD is closely related to its pharmacokinetics and pharmacodynamics.

In this study, the pathological damages of pancreatic tissues had been improved only in the 12hG(b) group, and was not improved in the 4hG(b) or 24hG(b) groups. However, this finding was not consistent with those of a previous study showing that a similar dose of DCQD 2 h after AP induction confers some protection against pancreatic tissue damage. Although the weight of rats showed no difference, this finding may be related to the different experimenters, which may have resulted in large differences among the various groups. We should ensure the consistency of experimenters. In clinical practice, orally dosing or coloclysis of DCQD are performed immediately when patients with AP are admitted to hospital. Whether these approaches could increase secretion of the gastrointestinal tract remains unclear. Recently, little research on the optimal administration time of Chinese herbs has been reported, and there are no definite opinions on this topic in the Chinese guidelines, although the guidelines are generally used in clinical practice in China. Therefore, our conjecture needs further clinical studies to be confirmed.

In conclusion, AP and the oral administration time of DCQD could affect the pharmacokinetics of the absorbed components of DCQD in the pancreatic tissues and plasma of rats. Late-time dosing may result in higher concentrations of the major components of DCQD with better pharmacokinetics and pharmacodynamics of anti-inflammation than seen

with early-time dosing, thereby showing the late time to be the optimal dosing time of DCQD for AP.

ARTICLE HIGHLIGHTS

Research background

Oral administration with Da-Cheng-Qi decoction (DCQD) is the conventional therapy at the early phase of acute pancreatitis (AP) patients in China. But oral dosing with DCQD is contrary to the idea of pancreatic rest at the early stage of AP, which may inhibit the absorption of the components of DCQD, influence its pharmacokinetics or pharmacodynamics and even worsen the disease severity.

Research motivation

The necrosis of pancreatic acinar cells would worsen the disease and the induction of apoptosis would relieve the disease severity. In clinical practice, oral dosing or coloclysis of DCQD are performed immediately when patients with AP are admitted to hospital. Whether these approaches could increase secretion of gastrointestinal tract remain unclear. What's more, little research on the optimal administration time of Chinese herbs has been reported, and there are no definite opinions on this topic in the Chinese guidelines. Thus, based on effect of DCQD regulating the apoptosis/necrosis switch of pancreatic acinar cells to ameliorate the pancreatic inflammation and pathological damage, the study aimed to screen the optional oral dosing time of DCQD in rats with AP according to the pharmacokinetics of the absorbed components and the pharmacodynamics of DCQD targeting of pancreas.

Research objectives

This objective was to screen the optional oral dosing time of DCQD in rats with AP based on the pharmacokinetic and pharmacodynamic parameters. We hoped to find an optimal dosing time of DCQD without increasing the severity of AP.

Research methods

This animal experiment was divided into pharmacokinetic and pharmacodynamic parts. AP models were induced by 3% sodium taurocholate. Rats were dosed at three different times. Plasma samples were collected from the tails at nine different times. The main components' concentrations of plasma and pancreatic tissues were detected by high-performance liquid chromatography tandem mass spectroscopy, confirmed as a specific, sensitive, accurate and reproducible method. The pharmacokinetic parameters [the maximum plasma concentration (C_{max}), the time to reach maximum concentration (T_{max}), the mean residence time ($MRT_{0 \rightarrow \infty}$), the elimination half-life ($T_{1/2}$) and the area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration ($AUC_{0 \rightarrow \infty}$)] were processed by pharmacokinetic statistical software DAS2.0.1 programmed by the Chinese Pharmacological Society. The IL-10, IL-6 and amylase concentrations in serum and pathological scores of pancreatic tissues were calculated.

Research results

According to the present study, AP reduced the concentrations of the major components of DCQD to the target pancreas, and the oral administration time also played an important role. AP delayed the T_{max} and reduced the C_{max} of the components of DCQD in the circulation of rats. The $AUC_{0 \rightarrow \infty}$ was larger when that time was approximately 12 h after the onset of AP. DCQD increased the IL-10 levels and lowered the IL-6 levels, and the later administration of the DCQD dose corresponded to higher IL-10 levels. Therefore, administering the DCQD dose too early may not be appropriate for AP. However, our results need further clinical studies to be confirmed.

Research conclusions

Late-time dosing may result in higher concentrations of the major components of DCQD with better pharmacokinetics and pharmacodynamics of anti-inflammation than seen with early-time dosing, thereby showing the late time to

be the optimal dosing time of DCQD for AP.

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