Pharmacokinetics of Hu-Pi-Cheng-Qi decoction administered via enema to rats with acute pancreatitis

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To the Editor: Acute pancreatitis (AP) is a common digestive system disease without specialized treatment until recently. Gastrointestinal function plays essential role in AP treatment and could be restored with Da-Cheng-Qi decoction (DCQD) as evidenced by our previous clinical study.[1] Based on the formula composing principles and our clinical experience, according to the traditional Chinese medicine theory that the lung and the large intestine are internal and externally related, Huzhang and Gualoupi were added into DCQD to form a new formula named Hu-Pi-Cheng-Qi decoction (HPCQD) which could increase the effects of purging Fu-Organ and ventilating lung. Enema with HPCQD is effective against AP in clinical practice; however, the pharmacokinetic parameters of HPCQD after enema administration in AP is unclear. According to formula tissue pharmacology, prescription compatibility is based on its pharmacokinetics. Furthermore, the active ingredients types absorbed into the body and the metabolic process could be significantly affected by different compatibility.[2] Therefore, our purpose was to elucidate the pharmacokinetic parameters when HPCQD is absorbed into blood circulation through the rectum, the effective components and the distribution of HPCQD via enema administration on AP rats.

The study protocol was approved by Animal Ethics Committee of Animal Facility of the West China Hospital (No. 2018215A). Each herb of HPCQD (Dahuang 12 g, Gualoupi 15 g, Houpu 15 g, Huzhang 15 g, Mangxiao 10 g, and Zhishi 12 g) was prepared in the form of spray-dried drug powders. The granules were dissolved in hot ultrapure water (50–60°C) and stirred by magnetic stirrers with grade 5 speed for 0.5 h. According to the method of pharmacology, the concentration of HPCQD given to rats was calculated as 1.2 g/mL.

In this study, twelve male healthy Sprague-Dawley rats (Animal license No. SCXK [Chuan] 2015–030, Certificate No. 0015783), each with a weight of 200 to 250 g, were adaptively fed for 2 weeks. From the 12 h before experiment to the end, all rats stayed under food-free and water-free states. The rats were randomized into two groups ($n = 6$ per group) by random number table: a normal group (NG) and an experimental group (EG). Rats in EG were AP models.[2] HPCQD was administered by enema to NG and EG at 12 h after operation. After HPCQD enema, serum samples of 0.5 mL from rat caudal veins were collected at the 13 consecutive time points, respectively at 5, 10, 20, 30 min, 1, 2, 3, 4, 5, 6, 8, 12, and 24 h. Each rat was given 5 mL saline by subcutaneous injection as fluid supplements after each blood collection. Furthermore, lungs, pancreas, and colon tissue samples were collected at 24 h after the enema. High performance liquid chromatography-tandem mass spectrometry (HPLC-MS)/MS was applied to quantify concentrations of HPCQD in serums and tissues. All data were described as mean ± standard deviation and analyzed with GraphPad Prism 6.01 by Dunnett test or a one-way repeated-measure analysis of variance. When $P < 0.05$, the difference was considered to be statistically significant.

We observed that some effective components of HPCQD were tested by HPLC-MS/MS, including emodin, hesperidin, magnolol, polydatin, and vanillic acid. On the one hand, each component was differently absorbed and distributed in three tissues (lungs, pancreas, and colon). Interestingly, in the lung tissues of EG, polydatin concentration was lower than that of NG ($P < 0.05$), while magnolol was higher than that in NG ($P < 0.05$). In addition, compared to that of NG, magnolol of EG in colon tissues was higher ($P < 0.05$). On the other hand, based on component concentration of consecutive time points, standard concentration-time curves could be successfully fitted. Tmax of EG was about 30 min (namely, 0.5 h). Furthermore, Tmax of emodin, magnolol, polydatin, and vanillic acid of NG was earlier than EG [Figure 1A and 1B].

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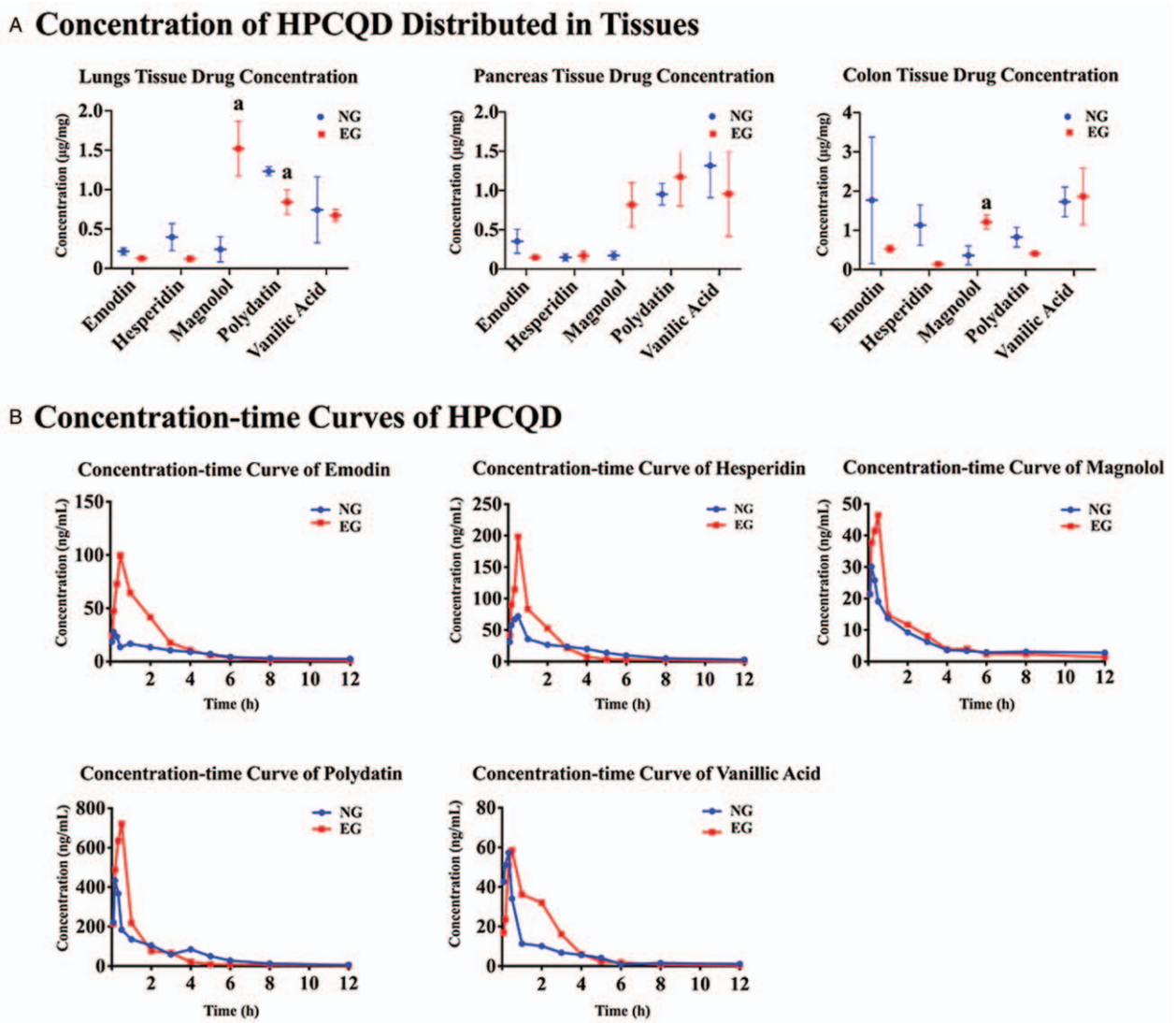

Figure 1: (A) Concentration of HPCQD distributed in lungs, pancreas, and colon tissues; (B) Concentration-time curves of HPCQD in AP rats. *: EG *vs.* NG, $P < 0.05$ ($n = 6$). EG: Experimental group. NG: Normal group. HPCQD: Hu-Pi-Cheng-Qi decoction; AP: Acute pancreatitis.

According to our pharmacokinetic results, after administrating HPCQD via enema, the five effective components, namely emodin, hesperidin, magnolol, polydatin, and vanillic acid, were differently absorbed and distributed in AP rats. In EG, magnolol was significantly increased in lungs and colon tissues and polydatin was significantly decreased in lung tissues. Polydatin was accumulated in lungs tissues, which was consistent with a previous study where tissue distribution were inhibited in AP rats based on the hypothesis about recipe pharmacology of tissue.[2] Due to its physical and chemical properties, magnolol, which features a phenolic structure, has showed strong lipsolubility and good absorption through passive transport. Therefore, we could conclude that magnolol might be a potential active component of HPCQD in AP treatment to target on lungs and colon tissues.

Previous studies have demonstrated that emodin was proven to be a redox-active enzyme which could exhibit anti-viral, anti-inflammatory, anti-cancer, immunosuppressive, and proapoptotic activities.[3] Hesperidin has also been reported to possess immunoregulatory properties in the intestinal immune response by inhibiting effectively inflammatory responses. Furthermore, magnolol has anti-oxidative properties which could modulate inflammatory mediators.[4] Moreover, polydatin could markedly suppress the oxidative stress-related inflammatory cascade. Additionally, vanillic acid could protect biofilms, inhibit lipid peroxidation in cells, and eliminate hydroxyl radicals and lipid peroxide radicals.[5] Therefore, we could infer that these components of HPCQD may promote the reduction and elimination of the inflammatory response.

In conclusion, active components of HPCQD administered via enema could absorbed into blood circulation; and then distributed to pulmonary, pancreatic, and colonic tissues. These components might be effective monomers of HPCQD and potential target organs may involve lungs, pancreas, and colon.

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Conflicts of interest

None.

References

1. Wan MH, Li J, Huang W, Mukherjee R, Gong HL, Xia Q, *et al*. Modified Da-Cheng-Qi decoction reduces intra-abdominal hypertension in severe acute pancreatitis: a pilot study. Chin Med J 2012;125:1941–1944. doi: 10.3760/cma.j.issn.0366-6999.2012.11.019.
2. Zhang YM, Ren HY, Zhao XL, Li J, Li JY, Wu FS, *et al*. Pharmacokinetics and pharmacodynamics of Da-Cheng-Qi decoction in the liver of rats with severe acute pancreatitis. World J Gastroenterol 2017;23:1367–1374. doi: 10.3748/wjg.v23.i8.1367.
3. Xu JD, Liu S, Wang W, Li LS, Li XF, Li Y, *et al*. Emodin induces chloride secretion in rat distal colon through activation of mast cells and enteric neurons. Brit J Pharmacol 2012;165:197–207. doi: 10.1111/j.1476-5381.2011.01573.x.
4. Yang TC, Zhang SW, Sun LN, Wang H, Ren AM. Magnolol attenuates sepsis-induced gastrointestinal dysmotility in rats by modulating inflammatory mediators. World J Gastroenterol 2008; 14:7353–7360. doi: 10.3748/wjg.14.7353.
5. Prince PSM, Rajakumar S, Dhanasekar K. Protective effects of vanillic acid on electrocardiogram, lipid peroxidation, antioxidants, proinflammatory markers and histopathology in isoproterenol induced cardiotoxic rats. Eur J Pharmacol 2011;668:233–240. doi: 10.1016/j.ejphar.2011.06.053.

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