

Short-term effect of *Salvia miltiorrhiza* in treating rat acetic acid chronic gastric ulcer and long-term effect in preventing recurrence

WANG Guo-Zhong¹, RU Xin², DING Li-Hua², LI He-Qun³

Subject headings Danshen; disease models, animal; *Salvia miltiorrhiza*; stomach ulcer; acetic acid; cimetidine; gastric mucosa; recurrence; rats, Wistar; chronic diseases

Abstract

AIM To study the short-term effect of Danshen (*Salvia miltiorrhiza*) on acetic acid induced chronic gastric ulcer in rats and its long-term effect in preventing recurrence.

METHODS Rats with acetic acid-induced gastric ulcer were treated with Danshen and cimetidine for 30 days. Traditional gastric mucosal auto-radiography and ³H-TdR incorporation into gastric mucosa in vitro were employed to study the effects of Danshen in rat acetic acid-induced chronic gastric ulcer, including ulcer index (UI), ulcer inhibitory rate (IR) and label rate (LR).

RESULTS On the day 5, 30 and 126 of ulcer-making, the UI in the Danshen group was obviously lower than that in the cimetidine group and the control group (42.3±3.9, 3.6±1.2, 4.4±2.3; 49.1±3.6, 5.9±1.4, 9.2±1.3; 61.0±3.8, 8.9±2.5, 12.4±2.4, respectively, *P*<0.01), the IR (%) in the Danshen group was obviously higher than that in the cimetidine group (31, 59, 64.8; 19, 33, 26, respectively), and the LR in the Danshen group was obviously higher than that in the cimetidine group and the control group (10.0±0.5, 16.2±0.8, 15.0±0.6; 9.0±0.5, 13.9±0.6, 10.8±0.7; 6.5±0.7, 10.1±0.5, 8.0±0.7, respectively, *P*<0.01). There was no obvious difference in UI in the

Danshen group on day 30 as compared with that on day 126.

CONCLUSION Danshen is effective in promoting ulcer healing and preventing recurrence. The mechanism of action is to strengthen the gastric mucosal barrier and to promote the gastric mucosal cell proliferation along the edge of the ulcer.

INTRODUCTION

Human peptic ulcer is characterized by repeated relapses and difficulty in prevention^[1]. So, the emphasis of treatment of peptic ulcer should be put on preventing relapse. A rat model of acetic acid-induced chronic gastric ulcer has the features of repeated relapses and is similar to that of the human case^[2,3]. This study is to observe the effect of the traditional Chinese medicine Danshen (*Salvia miltiorrhiza*) on the rat chronic gastric ulcer induced by acetic acid and its effect in preventing recurrence, and the relationship between the therapeutic effect and regeneration of gastric mucosal cells on the edge of the ulcer.

MATERIALS AND METHODS

Materials

Danshen water solution: prepared according to the reported method (240 g/L and 120 g/L)^[4]. Cimetidine water solution: with cimetidine for injection (product of the 3rd Pharmaceutical Plant, Harbin), diluted to 2.4g/L and 1.2g/L water solution. ³H-TdR supplied by China Atomic Scientific Institute, with radiation concentration of 18.5GBq/L.

Methods

Rat model-making and grouping. Wistar male rats (*n* = 126), weighing 210g ± 30g, were given 200ml/L acetic acid 0.05ml to create the model of chronic gastric ulcer, and then were divided into 3 groups randomly: Control group: allowed to drink water (pH 6.5) freely, continuing to day 126. Cimetidine group: During day 1-5 after ulcer was made, allowed to drink 2.4g/L cimetidine water solution (pH 6.5) freely; allowed to drink 1.2g/L

¹Department of Pathophysiology, ²Surgical Department, the First Affiliated Hospital, Qiqihaer Medical College, Qiqihaer 161042, Heilongjiang Province, China

³Department of Pathophysiology, China Medical University, Shenyang 110001, Liaoning Province, China

WANG Guo-Zhong, male, born on 1958-02-16 in Qiqihaer City, Heilongjiang Province, Han nationality, graduated from China Medical University as a postgraduate in 1993, lecturer of pathophysiology, majoring gastric ulcer pathophysiology, having 12 papers published.

*Project supported by the Natural Science Foundation of China, No. 39070961.

Correspondence to: Dr. WANG Guo-Zhong, Department of Pathophysiology, the First Affiliated Hospital, Qiqihaer Medical College, Qiqihaer 161042, Heilongjiang Province, China

Tel. +86-452-6713981 ext 2066

Received 1997-09-25 Revised 1997-12-18

cimetidine water solution freely on day 6-30; only water freely on day 31-126. Danshen Group: On day 1-5 after the ulcer is made, allowed to drink 240g/L Danshen water solution (pH 6.5) freely; 120g/L Danshen water solution freely on day 6-30; only water freely on day 31-126. Preliminary tests proved that each rat drank liquid on an average of about 35ml/d, without statistical difference.

Gastric mucosal auto-radiography. A 0.5 cm × 1cm tissue piece taken for the ulcer edge was put into 2ml 1640 culture fluid (pH 7.2-7.2) containing ³H-TdR and 100ml/L beef serum, hatched in 37°C ±0.5°C CO₂ incubator for 1 hour, fixed for 3-6 hours in Carnoy liquid, and then embedded in paraffin, 5 μm slices were made for HE staining, coating H-4 emulsion in emulsion-coating box, and to expose for 14 days in 4°C refrigerator, and to develop, fix and take the nucleus over 5 silver granules as label cells.

Index and calculation. Ulcer index (UI)-ulcer maximum length × maximum width; ulcer inhibitory rate (IR) (%) = (1 - experimental group UI mean/control group UI mean) × 100%; label rate (LR) (%) = (label cells number/300 multiplication area cells) × 100%.

Statistical analysis

All values were given as $\bar{x} \pm s$. Paired Student's *t* test was used. *P* values <0.05 were considered significant.

RESULTS

Effect of Danshen in rat chronic gastric ulcers of different stages, UI and ulcer IR is shown in Table 1.

Table 1 Rat chronic gastric ulcers of different stages, UI and IR ($\bar{x} \pm s$) (%)

Groups	Day 5		Day 30		Day 126			
	<i>n</i>	UI(mm) ²	IR(%)	<i>n</i>	UI(mm) ²	IR(%)		
Control	8	61.0±3.8		8	8.9±2.5 ^f	11	12.4±2.4	
Cimetidine	10	49.1±3.6 ^b	19	10	5.9±1.4 ^{bf}	33	11	9.2±1.3 ^b
Danshen	11	42.3±3.9 ^d	31	10	3.6±1.2 ^d	59	12	4.4±2.3 ^d

^b*P*<0.01, vs control; ^d*P*<0.01, vs Cimetidine; ^f*P*<0.01, vs the same group on day 126.

Table 2 Rat chronic gastric ulcers of different stages, IR of gastric mucosal cells (*n* = 6, $\bar{x} \pm s$) (%)

Groups	Day 5	Day 30	Day 126
Control	6.5±0.6	10.1±0.5	8.0±0.7
Cimetidine	9.0±0.5 ^b	13.9±0.6 ^b	10.8±0.7 ^b
Danshen	10.0±0.5 ^d	16.2±0.8 ^d	15.0±0.6 ^d

^b*P*<0.01, vs control group, ^d*P*<0.01, vs cimetidine group.

Effect of Danshen in rat chronic gastric ulcers of different stages and gastric mucosal cell multiplication is shown in Table 2

DISCUSSION

It is reported in the literature^[5,6] that the natural healing process of acetic acid-induced gastric ulcer in rats is as follows: On day 1-35 UI decreased rapidly which is considered as acute stage; UI decreased steadily and slowly on day 36-80, which is a slow healing stage; UI slightly increased as the recurrence stage; UI increased obviously on day 120-140, the recurrence rate being the highest. In this experiment, we treated the ulcer with Danshen and cimetidine from day 1-30 to observe their therapeutic effects in the acute stage. During the period from day 31 to day 126 without the two drugs, we observed whether Danshen has a long-term effect in preventing ulcer recurrence. From Table 1, we can see the UI in the cimetidine group was obviously lower than in the control group (*P*<0.01), and that in the Danshen group was even lower than that in the cimetidine group (*P*<0.01). As for the ulcer IR Danshen group was definitely superior to the cimetidine group. This indicated that Danshen might promote ulcer healing. In comparison of the UI of each group on day 30 and day 126, significant difference was found in both the control and cimetidine groups (*P*<0.01), but in the Danshen group there was no significant difference on day 30 and day 126. This indicated that Danshen has significant effect in preventing recurrence. From Table 2, one could see a higher LR in the cimetidine group than in the control group (*P*<0.01), and the Danshen group had a higher rate than the cimetidine group (*P*<0.01). So, the mechanism of Danshen in promoting ulcer healing and preventing ulcer recurrence was an enhancement of gastric mucosal cell multiplication along the edge of ulcer and also a fortification of the mucosal barrier.

REFERENCES

- 1 Tao J. On some problems of peptic ulcer. *Jpn Med Introd*, 1992;8(13): 386-387
- 2 Zhang SH, Chen L, Chen DM, Shi AR. A method of making rat acetic acid ulcer model. *Dissectol J*, 1987;10(2):158-159
- 3 Houteng YM, Sangyun KZ. Experiment gastric ulcer model. *Clin Science*, 1990;26(1):87-94
- 4 Li HQ, Chang LG, Ju BQ, Liu RD. The study of the experiment that Danshen resists ulcer action. *J China Med Uni*, 1985;4(2):89-92
- 5 Umeda Y, Nakamura K. Effects of Trimprostol on healing and recurrence of acetic acid-induced gastric ulcer in rats. *Jpn J Pharmacol*, 1986;42(8):457-463
- 6 Baimu ZY, Shanqi SY, Shisan GX, Shenbian MS, Shunei YY, Qiantian XE et al. Recurrence and relapse of acetic acid ulcer as well as effect of strengthening defence factor medicine Proamipide. *Folia Pharmacol Jpn*, 1988;92(6):389-395