

A comparison between Zhishi Xiaopiwan and cisapride in treatment of functional dyspepsia *

LIN Jiang¹, CAI Gan¹ and XU Jia-Yu²

Subject headings Dyspepsia/therapy; Zhishi xiaopi; cisapride; gastric emptying

Abstract

AIM To compare the therapeutic effect of the herbal medicine Zhishi Xiaopi with that of Cisapride in the treatment of functional dyspepsia (FD).

METHODS Fifty-one FD patients were randomized into Herbal group ($n = 27$) and Cisapride group ($n = 24$). Two two groups were given a four-week treatment of *Zhishi Xiaopiwan* 100ml, tid, a.c. and Cisapride 5mg, tid, a.c. respectively. Patients' symptoms were assessed and 39 patients' (22 of Herbal group and 17 of Cisapride group) gastric liquid emptying times were measured with ultrasonography before and after the treatment.

RESULTS The therapeutic effective rates of Herbal group and Cisapride group were 81.49% and 87.50% ($P > 0.05$). The half gastric emptying time (GET₅₀) and gastric emptying time (GET) of healthy controls and FD patients were 36.12min±10.22min vs 52.95min±13.49min and 87.07min±21.11min vs 120.74min±23.08min ($P < 0.001$). The GET₅₀ and GET of Herbal group before and after the treatment were 51.63min±13.15min vs 45.62min±10.82min and 117.34min±23.29min vs 103.26min±22.19min ($P < 0.01$). The results of Cisapride group were 54.66min±14.14min vs 40.95min±11.29min and 125.12min±24.47min vs 95.49min±22.31min ($P < 0.01$). The differences in values (median) of GET₅₀ and GET for Herbal group and Cisapride group before

and after treatment were 5.75min vs 17.18min and 13.22min vs 33.54min ($P < 0.05$).

CONCLUSION Delayed gastric emptying is one of the pathogenesis of FD. Both *Zhishi Xiaopi* pills and *Cisapride* can effectively alleviate the symptoms of FD and accelerate gastric liquid emptying. The effect of *Zhishi Xiaopiwan* on enhancing gastric motility is comparable with but less than that of *Cisapride*.

INTRODUCTION

Dyspepsia is a common syndrome, Outpatients in gastrointestinal clinics complaining of dyspeptic symptoms amount to about 30%-40% of the total visits. Among them, more than half have no organic lesions after examination. So it is called functional dyspepsia (FD). Some of the patients with FD present symptoms suggestive of delayed gastric emptying. So gastrointestinal hypomotility is considered one of the pathogenesis. In this study, we compared the therapeutic effect of *Zhishi Xiaopiwan* made of (herbal medicine) with *Cisapride* in the treatment of FD by assessing symptomatic improvement and measurement of gastric liquid emptying time.

MATERIALS AND METHODS

Diagnosis of functional Dyspepsia

Epigastric pain, discomfort or bloating, postprandial fullness, eructation, nausea and other upper abdominal symptoms lasting at least for 4 weeks; esophagitis, peptic ulcer, upper gastrointestinal erosion and neoplasm were excluded by endoscopy; diseases of liver, gallbladder, pancreas and lower gastrointestinal tract by laboratory, ultrasound and X-ray examinations; and diabetes, hyperthyroidism, connective tissue diseases and history of abdominal surgery were excluded.

Patients and healthy controls

Fifty-one patients meeting the above diagnostic criteria were randomly divided into two groups:

¹Department of Gastroenterology, Shuguang Hospital, Shanghai Traditional Chinese Medicine University, Shanghai 200021, China

²Department of Gastroenterology, Ruijin Hospital, Shanghai Second Medical University, Shanghai 200025, China

LIN Jiang, born on June 21, 1969, graduated from Shanghai Traditional Chinese Medicine University in 1997 with Ph.D., now attending physician, engaged in the study of chronic atrophic gastritis and gastrointestinal motility, having 4 papers published.

Correspondence to: Dr. LIN Jiang, Department of Gastroenterology, Shuguang Hospital, Shanghai Traditional Chinese Medicine University, Shanghai 200021, China.

Tel. +86-21-53821650-291

Received 1998-11-09

Herbal group, 27 patients (average age, 45.1±9.67 year; range, 25-63 years; a ratio of men/women, 10±17) and Cisapride group, 24 patients (average age, 48.5±12.9 years; range, 26-72 year; a ratio of men/women, 13:11). Healthy control group consisted of 10 volunteers without gastrointestinal symptoms (average age, 41.4±11.75 years; range, 25-58 year; a ratio of men/women, 7:3).

Symptom assessment

Five symptoms (epigastric pain or discomfort, bloating, postprandial fullness, eructation and nausea) were assessed for each patient once a week or two weeks. Symptoms were assessed according to Stanghellini criteria^[1]: 0 = absent, 1 = occasionally present and not affecting patients' daily activities; 2 = present moderately often, slightly affecting their activities; 3 = present moderately or more often, affecting considerably patients' activities. The symptom complex index (SCI) was calculated by dividing the summation of all presenting symptoms' scores with the number of symptoms.

Therapeutic efficacy assessment criteria

Noticeable efficiency (NE): SCI was less than pre-treatment value by 2 or more; efficiency: SCI was less than pre-treatment value by 1 or more but less than 2; and inefficiency: SCI was less than pre-treatment value by less than 1.

Measurement of gastric liquid emptying

Gastric liquid emptying was measured in one vertical section of antrum with real time ultrasonography as used by Marizo^[2]. All medication was stopped for 3 days and the patients were fasted for 12 hours before the test. Milk of 250ml with a total caloric value of 597KJ, prewarmed to 37°C, was used as a testing meal.

Treatment

Herbal group was treated with Zhishi Xiaopiwan in the form of decoction (100ml three times a day before meal) for 4 weeks. Zhishi Xiaopiwan consisted for the following ingredients: *Citrus aurantium* L.15g, *Officinal Magnolia Bark* 12g, *Tangshen Asiabell Root* 10g, *Largehead Atractylodes Rhizome* 10g, *Poria* 12g, *Ternate Pinellia Tuber* 10g, *Golden Thread Rhizome* 3g, *Nardostachys Rhizome and Root* 6g, etc. If pain was severe, *Paniclate Swallowwort Root* 10g and *Corydalis yanhusuo* W.T.Wang 15g were added. If bloating was severe, *Finger Citron* 10g, *Akebi Fruit* 10g and *Costus Root* 10g were supplemented. If eructation and nausea were severe, *Inula Flower* 10g and *Bamboo Shavings* 5g were added. If there

was regurgitation, *Ark Shell* 30g and *Cuttle Bone* 30g were used. Cisapride group was treated with Cisapride (5mg three times a day before meals) for 4 weeks.

Statistical analysis

Student's *t* test, χ^2 test, rank sum test and linear regression were used and *P* values less than 0.05 were considered significant.

RESULTS

Therapeutic efficiency of symptoms

Both Zhishi Xiaopiwan and Cisapride could effectively alleviate patients' symptoms (Tables 1-3). There were no significant difference between the efficiencies of the two medications on the symptoms of the FD, and in improvement SCI between two groups after treatment. The total efficacy rates (NE +E) of Herbal group and Cisapride group were 81.49% and 87.5% respectively (*P*>0.05). During treatment, 3 patients of Cisapride group had fewer gastrointestinal symptoms (1 with lower abdominal pain, 2 with loose stool). Patient in Herbal group had no side reactions, but with no statistical significance ($\chi^2 = 3.59, P > 0.05$).

Table 1 Comparison of the therapeutic efficiency for symptoms relief

Symptoms	Group	Cases	NE ^a (n)	E ^a (n)	IE ^a (n)	EF ^a (%)
Epigastric pain	Herbal	16	1	10	5	68.75 ^b
	Cisapride	15	4	7	4	73.33
Bloating	Herbal	22	10	8	4	81.89 ^b
	Cisapride	18	13	3	2	88.89
Postprandial fullness	Herbal	19	9	8	2	89.47 ^b
	Cisapride	16	12	3	1	93.00
Eructation	Herbal	14	5	7	2	85.71 ^b
	Cisapride	17	10	4	3	82.35
Nausea	Herbal	6	3	3	0	100.00 ^b
	Cisapride	8	2	4	2	75.00

^aNE: noticeable efficiency, E: efficiency, IE: inefficiency, ER: efficiency rate; ^b*P*>0.05 v Cisapride group.

Table 2 Comparison of symptoms complex index

Group	Cases	Before treatment	After treatment	Differential values
Herbal	27	2.28±0.32	1.02±0.60 ^a	1.26±0.56 ^b
Cisapride	24	2.19±0.40	0.71±0.55 ^a	1.49±0.56

^a*P*<0.001 v before treatment, ^b*P*>0.05 v Cisapride group.

Table 3 Comparison of the clinical therapeutic efficiency rate

Group	Cases	NE ^a rate %(n)	Ea rate %(n)	IEa rate %(n)
Herbal	27	25.93 (7) ^b	55.56 (15) ^b	18.51 (5) ^b
Cisapride	24	37.50 (9)	50.00 (12)	12.50 (3)

^aNE: noticeable efficiency, E: efficiency, IE: inefficiency; ^b*P*>0.05 v Cisapride group.

Gastric liquid emptying

Gastric liquid emptying tests were done in 10 healthy volunteers and 39 FD patients. Half gastric emptying time (GET₋₅₀) and total gastric emptying time (GET) of health controls were 36.12 min ± 10.22min and 87.07 min ± 21.11 min. Those of FD patients were 52.95 min ± 13.49 min and 120.74 min ± 23.80min, both of which were longer than those of healthy controls ($P < 0.001$). If the normal GET₅₀ range was set as from 16.09 to 56.15 (mean ± 1.96 SD), there were 14 (35.90%) patients with delay of gastric emptying.

Both Zhishi Xiaopiwan and Cisapride could shorten the gastric liquid emptying time (Table 4). After treatment, there was still significant difference between the gastric emptying time of Herbal group and control group ($P < 0.05$), but there was no significant difference between those of Cisapride group and control group ($P > 0.05$). The median difference of GET₅₀ and GET of Herbal group before and after treatment were 5.75 min and 13.22min respectively, and those of Cisapride group were 17.18 min and 33.54 min ($0.25 < P < 0.05$). So the effect of Zhishi Xiaopiwan in enhancing gastric emptying is less than that of Cisapride.

Table 4 Comparison of gastric emptying time between before and after treatment

Group	Cases	GET ₅₀ (min)	GET (min)
Control	10	36.12±10.22	87.07±21.11
Herbal	Before treatment	51.63±13.15 ^a	117.34±23.29 ^a
	After treatment	45.62±10.82 ^{b,c}	103.26±22.19 ^{b,c}
Cisapride	Before treatment	54.66±14.14 ^a	125.01±24.47 ^a
	After treatment	40.95±11.29 ^{b,d}	95.49±22.31 ^{b,d}

^a $P < 0.01$ v control group, ^b $P < 0.01$ v before treatment, ^c $P < 0.05$ v control group, ^d $P > 0.05$ vs Control group.

DISCUSSION

In this study, we found 35.9% of FD patients had delayed gastric liquid emptying, which is similar to the results of 23%-55% reported previously^[3,4]. This indicates that quite a few FD patients have gastric hypomotility. Gastrointestinal manometric techniques^[1,5] showed that during fasting, the cycles of Migrating Motor Complex (MMC) of FD patients are less than those of healthy subjects. No matter during fasting or digestive period, the amplitude and frequency of the contractions of antrum and duodenum of FD patients are all less than those of healthy subjects. During digestive period, the numbers of duodenal propulsive peristalsis and the coordinating contractions between antrum and duodenum are less than those of healthy subjects.

Ultrasonographic techniques^[6] also showed that the postprandial antrum contractions of FD patients are incomplete with small waves of irregular rhythm, as compared to the complete, even and rhythmical peristalsis of healthy subjects. The gastrointestinal hypomotility and the incoordination between antrum and duodenum may induce delay of gastric emptying. As an agonist of 5-HT₄ receptor, Cisapride can act on the receptors of the intermediate and terminal neurons of myenteric nerve plexus in gastrointestinal smooth muscle and improve the gastrointestinal motility by promoting cholinergic nerves to release acetylcholine. It can increase the amplitude and frequency of the gastric contractions and the numbers of coordinating contractions between antrum and duodenum to accelerate gastric emptying.

Symptomatology of FD is very similar to that of "Piman Zheng", a name of disease in Traditional Chinese medicine with bloating as the chief complaint. Zhishi Xiaopiwan is the commonly used Chinese medicine for "Piman Zheng". So we chose this medicine to treat FD and compared it with Cisapride. The results showed that Zhishi Xiaopiwan could effectively ameliorate the symptoms of FD, and its total efficiency rate (81.49%) was not significantly different from that of Cisapride (87.5%). Gastric emptying examinations indicated that Zhishi Xiaopiwan also could accelerate the gastric liquid emptying, although its effect was less than that of Cisapride. Its effect on enhancing gastrointestinal motility was proven in previous animal experiments. The main ingredient of Zhishi Xiaopiwan-*Citrus aurantium* L. could prolong the canine intestinal active duration of MMC by reducing the duration of the phase I and prolonging the duration of the phase II^[7]. Other ingredients, such as *Tangshen Asiabel Root*, *Rhizome Atractylodes macrocephalae*, *Ternate Pinellia Tuber* and *Golden Thread Rhizome*, could increase the frequency of rat gastric electric spikes and amplitude of gastric contractions and regulate the disturbance of gastric electric rhythm. *Rhizome Atractylodes macrocephalae* might act on cholinergic receptors to activate the gastric movement^[8,9].

Not all FD patients had delayed gastric emptying. This indicates that gastrointestinal hypomotility is not the sole pathogenesis of FD, other factors such as hypersensitiveness of gastric mucosa, disturbance of gastric accommodation and failure of gallbladder contraction might also be involved in the pathogenesis^[10]. The inconsistency between the symptomatic relief and improvement of gastric emptying by Zhishi Xiaopiwan also suggests

that the action of the herbal medicine to improve symptoms might be through mechanisms other than promoting gastric motility, which should be further studied in the future.

In conclusion, we found that delay of gastric emptying was one of the pathogenetic factors of FD, and both Zhishi Xiaopiwan and Cisapride could ameliorate the symptoms of FD and accelerate the gastric liquid emptying in certain percentage of patients. In this aspect, Cisapride is better than the herbal medicine we used.

REFERENCES

- 1 Stanghellini V, Ghidini C, Maccarini MR, Paparo GF, Roccrinaldesi, Barbara L. Fasting and postprandial gastrointestinal motility in ulcer and non-ulcer dyspepsia. *Gut*, 1992;33(2):184-190
- 2 Marzio L, Giacobbe A, Conoscitore P, Facciorusso D, Frusciante V, Modoni S. Evaluation of the use of ultrasonography in the study of liquid gastric emptying. *Am J Gastroenterol*, 1989;84(5):496-500
- 3 Marizo L, Difelice F, Grazia M, Imbimbo B, Lapenna D, Cuccurullo F. Gallbladder hypokinesia and normal gastric emptying of liquids in patients with dyspeptic symptoms. A double-blind placebo-controlled clinical trial with cisapride. *Dig Dis Sci*, 1992;37(2):262-267
- 4 Wang BE, Liang XM, Jia BQ, Chen BW, Ke MY, Lin SL *et al.* A controlled multicentre clinical trial on Cisapride in treatment of functional dyspepsia. *Chin J Internal Med*, 1995;34(3):180-184
- 5 Zhang SL, Wang ZH. Effect of *Helicobacter pylori* on the motility of antrum and duodenum in FD patients. *Chin J Digest*, 1995;15(Suppl):76-77
- 6 Jin ZD, Zhou DW, Xu GM. Clinical study on measuring gastric motility with real time ultrasonography. *Chin J Digest*, 1997;17(1):59
- 7 Bi QH, Yang DZ, Yin CZ, Ding AL. Effect of Zhishi on the small intestinal myoelectric activity. *Acta Medica Sinica*, 1991;6(1):39-42
- 8 Chen Z, Li SR, Han Y, Tian GQ, Yuan GC, Chen XY. Clinical and experimental study on non-ulcerative dyspepsia treated with Shenxia Heweining. *Chin J Intergrated Tradit Western Med*, 1994;14(2):83-85
- 9 Ma XS, Fan XP, Chen Z, Li CW, Xin YS. Effect and mechanism of Rhizome *Atractylodes Macrocephalae* on gastrointestinal motility in animals. *Chin J Digestion*, 1996;16(5):261-264
- 10 Lin J. Advance in the pathogenesis of FD. *Chin J Gastroenterol*, 1997;2(1):51-53