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• BASIC RESEARCH •

# Effect of enterokinetic prucalopride on intestinal motility in fast rats

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## Abstract

**AIM:** To evaluate the effects of prucalopride on intestinal prokinetic activity in fast rats and to provide experimental basis for clinical treatment of gastrointestinal motility diseases.

**METHODS:** Gastrointestinal propulsion rate was measured by the migration rate of activated charcoal, which reflexes gastrointestinal motility function. 120 Spraque-Dawley rats were randomly divided into four groups and received an intravenous injection of physiological saline (served as control), prucalopride 1 mg/kg, prucalopride 2 mg/kg and cisapride 1 mg/kg, respectively. The gastrointestinal propulsion rate was measured 1, 2 or 4 hours after intravenous injection of the drugs.

**RESULTS:** Significant accelerations of gastrointestinal propulsion rate in prucalopride 1 mg/kg and 2 mg/kg groups were found compared with control group at 2 and 4 hours (83.2 %±5.5 %, 81.7 %±8.5 % *vs* 70.5 %±9.2 %, $P<0.01$; 91.2 %±2.2 %, 91.3 %±3.9 % *vs* 86.8 %±2.6 %, $P<0.01$). The gastrointestinal propulsion rates at 1, 2 or 4 hours were faster in prucalopride 1 mg/kg and 2 mg/kg groups than in cisapride group (84.0 %±11.7 %, 77.1 %±11.9 % *vs* 66.3 %±13.6 %, $P<0.01$, $P<0.05$; 83.2 %±5.5 %, 81.7 %±8.5 % *vs* 75.4 %±5.9 %, $P<0.01$, $P<0.05$; 91.2 %±2.2 %, 91.3 %±3.9 % *vs* 88.6 %±3.5 %,$P<0.05$, $P<0.05$). No difference of gastrointestinal propulsion rate was found between prucalopride 1 mg/kg group and prucalopride 2 mg/kg group ($P>0.05$).

**CONCLUSION:** Prucalopride accelerates intestinal motility in fast rats, and has no dose dependent effect.

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## INTRODUCTION

Prucalopride is the first representative of the novel class of benzofurans,and is a highly specific and selective 5-$HT_4$ receptor agonist. Prucalopride can exert effect on intestinal prokinetic activity in fast rats.

## MATERIALS AND METHODS

### Experimental animals

One hundred and twenty healthy male Sprague-Dawley (SD) rats weighing 200-250 g were purchased from the Experimental Animal Center of Xi' an Jiaotong University. The rats were housed in rat cages at 22-25 ℃ with free access to standard rat pellet food and water for 10 days. They were fasted for 48 hours with free access to water.

### Chemicals

Prucalopride and cisapride were kindly provided by Janssen Research Foundation. Prucalopride was dissolved in sterile, and cisapride in 0.57 mol/L ascorbic acid. Activated charcoal was purchased from the Chemical Factory of the Forestry Science Institute of China. Arabic gum powder was purchased from the Third Chemical Factory of Tianjin. Diethyl ether was purchased from Xi' an Chemical Factory.

### Experimental procedure

The rats were randomly divided into four groups. Each group had 30 rats. The first group served as control and received intravenous injection of physiological saline under ether anaesthesia. The second group and the third received intravenous injection of prucalopride 1 mg/kg and 2 mg/kg under ether anaesthesia, and the fourth group received intravenous injection of cisapride 1 mg/kg in the same way. They then received intragastric injection of 100 g/L activated charcoal suspension (10 mg/kg, 100 g/L activated charcoal and 100 g/L Arabic gum powder respectively) through a specially designed orogastric cannula introduced through the mouth. The animals were killed 1, 2 and 4 hours respectively after ether anesthesia by cervical dislocation and decapitation. They had a laparotomy and migration of activated charcoal from esophagus-stomach junction to the most distal point of migration, and were expressed as distance (cm) migration by the stain. At 1 hour after injection, the most distal point of migration was in the small intestine and gastrointestinal(GI) propulsion rate was expressed as: gastrointestinal propulsion rate =the migration distance of activated charcoal(cm)÷the distance from esophagus-stomach junction to ileocecal opening (cm)×100 %. At 2 hours after injection, the most distal point of migration was all in the distal small intestine or proximal colon and at 4 hour after injection, the most distal point of migration was in the colon. So gastrointestinal propulsion rate was expressed as: gastrointestinal propulsion rate =the migration distance of activated charcoal (cm)÷the distance from esophagus-stomach junction to large intestine terminal (cm)×100 %.

### Statistical analysis

Data were expressed as $\bar{x}\pm s$. Statistical analyses used were unpaired *t* test. Statistical significance was taken as $P<0.05$.

## RESULTS

### One hour effect of prucalopride

At 1 hour after injection, the most distal point of migration was in the small intestine. Compared with control group, in prucalopride 1 mg/kg group and prucalopride 2 mg/kg group, GI propulsion rate had no difference ($P>0.05$). Prucalopride at a

dose of either 1 or 2 mg/kg had no significant effect on gastrointestinal motility. Compared with cisapride group, GI propulsion rate had differences in prucalopride 1 mg/kg group and prucalopride 2 mg/kg group ($P<0.01$, $P<0.05$, Table 1).

**Table 1** One hour effect of prucalopride on intestinal motility in SD rats ($\bar{x}\pm s$, $n=10$)

| Group | GI length (cm) | Migration of activated charcoal (cm) | GI propulsion rate (%) |
|---|---|---|---|
| Control | 82.9±12.2 | 63.8±10.5 | 77.9±7.5 |
| Prucalopride (1 mg/kg) | 70.9±4.1 | 59.7±9.5 | 84.0±11.7[b] |
| Prucalopride (2 mg/kg) | 73.8±11.7 | 57.0±12.8 | 77.1±11.9[a] |
| Cisapride (1 mg/kg) | 78.1±10.7 | 52.2±14.4 | 66.3±13.6 |

[a]$P<0.05$, [b]$P<0.01$, *vs* cisapride.

### *Two hour effect of prucalopride*

At 2 hours after injection, the most distal point of migration was in the distal small intestine or proximal colon. Compared with control group, GI propulsion rate had significant differences in prucalopride 1 mg/kg group and prucalopride 2 mg/kg group ($P<0.01$).

Prucalopride at a dose of either 1 or 2 mg/kg significantly increased GI propulsion, suggesting that prucalopride might enhance gastrointestinal motility. Compared with cisapride group, GI propulsion rate had differences in prucalopride 1 mg/kg group and prucalopride 2 mg/kg group ($P<0.01$, $P<0.05$,Table 2).

**Table 2** Two hour effect of prucalopride on intestinal motility in SD rats ($\bar{x}\pm s$, $n=10$)

| Group | GI length (cm) | Migration of activated charcoal (cm) | GI propulsion rate (%) |
|---|---|---|---|
| Control | 91.9±11.8 | 63.9±3.8 | 70.5±9.2 |
| Prucalopride (1 mg/kg) | 87.1±8.5 | 72.6±10.0 | 83.2±5.5[bd] |
| Prucalopride (2 mg/kg) | 100.1±12.2 | 81.9±14.0 | 81.7±8.5[ad] |
| Cisapride (1 mg/kg) | 95.4±12.3 | 72.0±6.9 | 75.4±5.9 |

[a]$P<0.05$, [b]$P<0.01$, *vs* cisapride; [d]$P<0.01$, *vs* control.

**Table 3** Four hour effect of prucalopride on intestinal motility in SD rats ($\bar{x}\pm s$, $n=10$)

| Group | GI length (cm) | Migration of activated charcoal (cm) | GI propulsion rate (%) |
|---|---|---|---|
| Control | 89.9±8.6 | 78.0±7.3 | 86.8±2.6 |
| Prucalopride (1 mg/kg) | 83.7±5.1 | 76.3±5.2 | 91.2±2.2[ad] |
| Prucalopride (2 mg/kg) | 97.4±9.8 | 87.3±10.4 | 91.3±3.9[ad] |
| Cisapride (1 mg/kg) | 99.5±12.7 | 88.1±13.7 | 88.6±3.5 |

[a]$P<0.05$, *vs* cisapride; [d]$P<0.01$, *vs* control.

### *Four hour effect of prucalopride*

At 4 hours after injection, the most distal point of migration was in the colon. Compared with control group, GI propulsion rate had significant differences in prucalopride 1 mg/kg group and prucalopride 2 mg/kg group ($P<0.01$). Prucalopride at a dose of either 1 or 2 mg/kg significantly increased GI propulsion, suggesting that prucalopride might enhance gastrointestinal motility. Compared with cisapride group, GI propulsion rate had differences in prucalopride 1 mg/kg group and prucalopride 2 mg/kg group ($P<0.05$, Table 3).

### *Response to different doses of prucalopride*

At 1, 2 and 4 hours after prucalopride injection, GI propulsion rate in prucalopride 1 mg/kg group was not different from that in prucalopride 2 mg/kg group ($P>0.05$, Table 1, 2 and 3). The effect of prucalopride was not clearly dose related.

## DISCUSSION

Prucalopride (R093877) is a newly synthesized enterokinetic agent which is a benzofuran derivative with the chemical structure of 4-animo-5-chloro-2, 3-dihydro-*N*-[1(3-methoxypropyl)-4-piperidinyl]-7-benzofurancarboxamide monochloride. It is a highly specific and selective 5-$HT_4$ receptor agonist[1]. *In vitro* animal experiments have shown facilitation of cholinergic[2] and excitatory non-adrenergic,non-cholinergic (NANC) neurotransmission. It is the first compound known to enhance NANC transmission in colonic preparations of guinea pig. Since cholinergic neurons and NANC neurons are known to play an important part in physiological regulation of colonic motility, it is likely that constipation will be favourably influenced by compounds facilitating NANC excitatory neurotransmission. Prucalopride is a specific and selective for 5-$HT_4$ receptor and is devoid of affinity to $M_3$ cholinoceptors, $5HT_{2A}$ and $5HT_3$ receptors, and cholinesterases. *In vivo* canine colonic studies confirmed the selectivity of the effects on 5-$HT_4$ receptors, as the selective and potent 5-$HT_4$ antagonist completely prevented the effects of prucalopride. But some 5-$HT_4$ agonist prokinetics stimulate $5HT_{2A}$ and $5HT_3$ receptors. *In vivo* and *in vitro* studies have shown that prucalopride can facilitate gastric, small intestinal, and colonic motility[3-5].

This study in fast rats showed that prucalopride had no significant effects on GI propulsion rate at 1 hour after intravenous injection. However, it significantly increased GI propulsion rate at 2, 4 hour after intravenous injection, suggesting that prucalopride might enhance gastrointestinal motility in the distal small intestine and colon instead of the stomach and proximal small intestine. This is consistent with the observations of Emmanuel *et al* in healthy volunteers. Emmanuel showed that 1 mg and 2 mg of prucalopride shortened orocaecal transit and whole gut transit,and suggested that prucalopride accelerated upper gut and colonic transit. Orocaecal transit was measured by lactoluse-hydrogen breath test. Whole gut transit was measured by radio-opaque markers. Bouras *et al*[6] reported that gastrointestinal and colonic transits were measured by scintigraphic techniques in healthy humans, and a daily dose of 0.5, 1, 2, or 4 mg prucalopride accelerated colonic transit, partly by stimulating proximal colonic empting, but did not alter gastric or small bowel transit. Poen *et al*[7] reported that prucalopride was well tolerated by healthy subjects and had a markedly consistent effect on stool frequency and colonic transit. Prucalopride, given orally or intravenously, altered colonic motility in the fast conscious dog in a dose-dependent manner. It induced signicant migrating contractions, stimulated proximal colon and inhihibed contractile motility patterns of distal colon by stimulating 5-HT4 receptors[4,8]. It deserves further study in patients with constipation. The fact that prucalopride did not affect stomach and proximal small intestine in fast rats does not preclude its potential beneficial effects in pathological states such as delayed gastric emptying. For example, in an animal model for delayed gastric emptying, prucalopride accelerated gastric emptying. In humans, Emmanuel *et al* observed that prucalopride shortened orocaecal transit, while Bouras *et al* found that prucalopride did not alter gastric or small bowel transit. This discrepancy probably was resulted from differences in methods used to measure transit. In Emmanuel *et al* studies, lactoluse-hydrogen breath test of a liquid marker

could measure orocaecal transit, but could not differentiate effects on stomach or small intestine. Whole gut transit was measured by radio-opaque markers. In Bouras *et al* studies, a scintigraphic technique was used to measure gastrointestinal and colonic transit[6]. The effects of prucalopride on stomach or small intestine deserves further study. Patients with idiopathic constipation had postprandial sigmoid mortor activity[9]. Prolonged colonic motility was recorded in patients with slow transit constipation[10]. Slow transit constipation was common[11-16]. Laxatives are often ineffective in treating constipation. An alternative therapeutic approach is to target serotonin-4 receptors, which are involved in initiating peristalsis[17-30]. Some Chinese herbal medicines can promote gastrointestinal motility and be used to treat constipation[31,32].

The reason for the lack of a dose-response effect of prucalopride on gastrointestinal motility is unclear. Maybe the dose groups were too few and the extent of doses was too narrow. It should design more dose groups to deserve the dose related effects. The dose dependent effects on significant colonic migrating have been more clearly shown by intravenous injection than by oral administration of prucalopride in dogs. Briejer *et al* observed a sigmoid dose-response curve in a dose of 0.001 to 1.25 mg/kg, the linear part of the curve was between 0.02 and 0.31 mg/kg. But Bouras *et al* reported that in healthy humans, a daily dose of 0.5, 1, 2, or 4 mg prucalopride was almost equally effective, and lack of dose-response effects[6]. The lack of stronger effects of 2 mg over 1 mg in this study might be resulted from turning off the signal: mechanisms that attenuate signaling by G protein-coupled receptors, by which serotonin receptors are characterized. In futher study, we shall investigate the dose related effects of prucalopride in patients with constipation and slow colonic transit.

This study showed that prucalopride whether 1 mg/kg or 2 mg/kg doses accelerated greater gastrointestinal propulsion rate compared with cisapride 1 mg/kg dose.

In conclusion, prucalopride can accelerate intestinal motility in fast rats, and maybe hold a promising new class of treatment for chronic constipation.

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