Effects of Cisapride on Gastrointestinal Motor Activity and Gastric Emptying of Disopyramide

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The effects of cisapride on the gastrointestinal contractile activity and pharmacokinetics of disopyramide were determined in beagle dogs and patients with arrhythmia.

In the animal experiments, the gastric motor index was significantly decreased by i.v. administration of disopyramide in a dose-dependent fashion. The peak decrease of the motor index was observed within 5 min after i.v. injection of disopyramide; the motor index then recovered gradually to the level present prior to drug administration. I.v. administration of cisapride (0.5 mg/kg) markedly increased gastrointestinal contractile activity following the decrease induced by disopyramide pretreatment (5 mg/kg, i.v.).

In the clinical studies, the gastric emptying test was performed using the acetaminophen method. A significant correlation between plasma concentrations of disopyramide and gastric emptying time has been found ($p<0.001$). The combination of disopyramide (100 mg t.i.d.) and cisapride (2.5 mg t.i.d.) significantly increased gastric emptying compared with that induced by disopyramide alone. The peak plasma concentration of disopyramide in association with cisapride oral administration was significantly higher, and the apparent absorption rate constant and lag time of disopyramide were about 2-fold higher and 2-fold shorter, respectively, than for disopyramide alone.

Cisapride, acting as a cholinergic agonist, may counteract the anticholinergic effect of disopyramide on gastric motility. As a factor influencing drug absorption, gastric emptying is of importance, as it determines the rate of drug delivery to the small intestine. Therefore, the oral administration of disopyramide with cisapride may be useful for patients with delayed gastric emptying.

Keywords — disopyramide; cisapride; drug interaction; motor index; gastric emptying; pharmacokinetics

Introduction

Disopyramide is an antiarrhythmic drug widely used for the prevention and treatment of supraventricular and ventricular arrhythmias. The most common adverse reactions to disopyramide are related to its anticholinergic activity and include dryness of the mouth, blurred vision, constipation and urinary retention.

Cisapride, a gastrointestinal prokinetic drug devoid of dopamine blocking effects, increases the resting release of acetylcholine from the myenteric plexus-longitudinal muscle.

In a previous study, we observed no significant correlation between dose per body weight and total plasma concentration of disopyramide following oral administration in patients with arrhythmias. In addition, Lima et al. have reported that the time-course of disopyramide concentration following oral administration was variable within and among patients. Changes in gastrointestinal motility are known to alter the absorption kinetics of several drugs. However, no precise studies of the effect of disopyramide on gastrointestinal motility have been carried out.

The purpose of the present study is to examine the effects of cisapride on the gastric motor activity of disopyramide in dogs and to evaluate further the alteration of disopyramide pharmacokinetics and gastric emptying by cisapride in patients with arrhythmia.
Methods

Animal Experiments — Four beagle dogs of either sex weighing 12—13 kg were used. The animal was anesthetized with sodium pentobarbital (35 mg/kg, i.v.) and the abdominal cavity was opened under aseptic conditions. Extraluminal force transducers (size 7 mm × 12 mm, F-121S, Star Medical, Tokyo, Japan) were sutured onto the serosa of the gastric antrum 3 cm proximal to the pyloric ring, the mid-duodenum and the small intestine 100 cm distal to the ligament of Treitz (jejunum) for the purpose of measuring circular muscle contraction, using methods reported previously. The lead wires of these transducers were led out of the abdominal cavity and through a skin incision made between the scapulae. The outer ends of the lead wires were sutured onto the skin adjacent to the skin incision. After the abdominal surgery, a Silastic tube (602-205, Dow Corning, Midland, MI, U.S.A.) was inserted into the superior vena cava through a branch of the right external jugular vein, and the outer end of this tube was sutured onto the adjacent skin. This tube was filled with heparin-containing saline, tipped with a plastic stopper, and used as the route for i.v. injection of drugs. After the operation, a jacket protector was placed on each dog in order to protect the lead wires and the Silastic tube. The animals were then permitted 3 weeks to recover from the surgery. During the experiments, they were housed individual experimental cages, fed once a day with dry meal (20 g/kg, CD-5, Clea Japan, Tokyo, Japan) and permitted water ad lib.

Gastrointestinal motor activity was recorded on a thermal pen-writing recorder (WR-3101, Graphtec, Tokyo, Japan) by connecting the lead wires of the force transducers to the connecting cables from the amplifiers (UG-16, Nihon Kohden, Tokyo, Japan) under the protective jacket. To measure motility quantitatively, the signals from the gastric antrum were relayed to a signal processor (7T18, Nihon Denki-Sanei, Tokyo, Japan) every 100 ms. The area surrounded by the contraction waves and the base line, i.e., the product of the amplitude (voltage) and the time in minutes during a certain fixed period, was calculated, expressed as percent of the area assuming that maximum contraction (amplitude) of the interdigestive migrating contraction lasted for 1 min, and used as the motor index. The motor index during 5 min before administration of the drug was designated as 100%, and the percent changes in gastric motility induced by test drugs were calculated every 5 min.

Either disopyramide (1.25—5 mg/kg) or saline (control) was administered i.v. 1 h after feeding. In separate experiments, cisapride (0.25—0.5 mg/kg) or its vehicle (control) was administered i.v. 5 min after administration of disopyramide (5 mg/kg).

Patients — Twenty patients with arrhythmia (mean age 60.5 years; mean body weight 57.0 kg) gave informed consent and participated in the gastric emptying test. Furthermore, nine of these patients (mean age 57.2 years; mean body weight 59.3 kg) participated in the simultaneous use test. All patients were hospitalized and had been receiving disopyramide treatment (100 mg t.i.d.) for more than one month.

Gastric Emptying Test — The gastric emptying test was performed using the acetaminophen method. After overnight fasting, the patients received disopyramide at 08:00 a.m., and a single 1.5 g dose of acetaminophen along with 200 ml of pasty test meal (Okunosu-A, Okuno Co., Ltd., Tokyo, Japan) were orally administered to each patient at 09:00 a.m. Venous blood samples were taken at 07:30 and 09:45 a.m. The patients were maintained in a semupright position throughout this test.

Pharmacokinetic Test — The patients were given the disopyramide at 08:00, 14:00 and 17:00 h. Blood samples were collected at the following times: 07:30, 09:00, 10:00, 12:00, 14:00 and 20:00 h.

Simultaneous Use Test — The tests of simultaneous use of disopyramide and cisapride were carried out using a cross-over design. With the first trial as control, nine patients took part in the gastric emptying test. Three days later, these patients participated in the pharmacokinetic test. In the second trial, each patient received a combination of a 2.5 mg cisapride tablet and a 100 mg disopyramide capsule three times daily for a period of 7 d. The gastric emptying test and
the pharmacokinetic test were carried out on the 5th and 7th days of this period, respectively. No side effects were seen during the test period.

Drugs — For i.v. administration in animal experiments, disopyramide phosphate (Roussel-Uclaf, Paris, France) was dissolved in saline, and cisapride was solubilized in 100 mM tartaric acid contained in 4% dimethyl sulfoxide. In the clinical trials, the disopyramide free base, cisapride and acetaminophen were obtained as 100 mg capsules (Searle Yakuhin, Osaka, Japan), 2.5 mg tablets (Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan) and powder (Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan), respectively.

Analysis — Blood samples were separated by centrifugation and the extracted plasma fraction was stored at -20 °C until analysis. Total plasma concentrations of disopyramide and acetaminophen were determined by fluorescence polarization immunoassay (Abbott Laboratories, Chicago, U.S.A.). The concentration–time data obtained from pharmacokinetic tests were fitted to a one-compartment open model with first-order absorption. The pharmacokinetic parameters were calculated by using the least-squares fit program, MULTI. The simulation program of multiple dosing was established by modifying the MULTI subroutine in order to predict the plasma level after multiple-dosing at non-uniform dosing intervals, using methods reported previously. The theory of this subroutine is as follows: the plasma concentration-time curves are described by Eq. 1.

\[
C_p = \frac{k_a \cdot F \cdot D}{V \cdot (k_a - K)} (e^{-k_t'} - e^{-k_a \cdot t'})
\]

where, \(C_p\) is the plasma concentration, \(D\) is the dose, \(F\) is the fraction of the dose absorbed, \(V\) is the apparent volume of distribution of the drug, \(k_a\) is the apparent absorption rate constant, \(K\) is the elimination rate constant and \(t'\) is any time within the dosing intervals. The \(F\) and \(V\) values could not be estimated, since calculated only as the \(F/V\) value.

When the drug is repeatedly administered in various doses \((D_1, D_2, \cdots D_n)\) at various time \((T_1 = 0, T_2, \cdots T_n)\), the plasma concentration of the drug at any time \(t\) \((t \geq T_n)\) after the start of dosing can be calculated using Eq. 2.

\[
C_p = \sum_{m=1}^{n} C_p(m)(t)
\]

where,

\[
C_p(1)(t) = \frac{k_a \cdot F \cdot D_1}{V(k_a - K)} (e^{-k_{t,1}} - e^{-k_a \cdot t_1})
\]

\[
C_p(2)(t) = \frac{k_a \cdot F \cdot D_2}{V(k_a - K)} (e^{-k_{t,2}} - e^{-k_a \cdot t_2})
\]

\[
C_p(n)(t) = \frac{k_a \cdot F \cdot D_n}{V(k_a - K)} (e^{-k_{t,n}} - e^{-k_a \cdot t_n})
\]

and

\[
t_1' = t - T_1 - \text{lag time}
\]

\[
t_2' = t - T_2 - \text{lag time}
\]

\[
\cdots
\]

\[
t_n' = t - T_n - \text{lag time}
\]

If the value of \(C_p(n)(t)\) at \(t_n'\) is minus, it is defined as being equal to zero.

Results were expressed as mean \(\pm\) S.E. Statistical analysis was performed using a one-way analysis of variance coupled with Dunnett's test of paired \(t\)-test. Obtained \(p\) values of less than 0.05 were considered to indicate statistical significance.

Results

Effects of Disopyramide and Cisapride on Gastrointestinal Contractile Activities

Three weeks postoperatively, two main patterns of gastrointestinal contractile activity were present in dogs, the interdigestive and the digestive states. In the interdigestive state, strong contractions (interdigestive migrating contractions, IMC) were observed to occur at regular intervals of 100 to 120 min in the stomach, duodenum and jejunum. In all animals tested, feeding disrupted the regular IMC pattern and initiated a digestive pattern of activity characterized by regularly
Fig. 1. Effects of Disopyramide and Cisapride on Gastrointestinal Contractile Activities in Dogs
(A) saline, (B) disopyramide at 5 mg/kg, (C) cisapride at 0.5 mg/kg following i.v. administration of disopyramide (5 mg/kg).
Saline or disopyramide was administered 1 h after feeding. Cisapride was given 5 min after administration of disopyramide. a) feeding, b) saline, c) disopyramide 5 mg/kg, d) cisapride 0.5 mg/kg.
Disopyramide and Cisapride Interaction

Fig. 2. Dose Related Effects of Disopyramide on the Gastric Motor Index in Dogs
Saline (○) or disopyramide (●, 1.25 mg/kg; ▲, 2.5 mg/kg; ■, 5 mg/kg) was i.v. administered 1 h after feeding. The posttreatment values are expressed as a percentage of changes from the level immediately before drug administration. Each point represents the mean of 4 observations. Vertical bars show mean ± S.E. a) saline or disopyramide. b) p<0.05, c) p<0.01 compared with the control group at the same time by Dunnett’s test.

Fig. 3. Effects of Cisapride on the Gastric Motor Index Following Administration of Disopyramide in Dogs
100 mM tartaric acid containing 4% dimethyl sulfoxide (vehicle, ○) or cisapride (●, 0.25 mg/kg; ▲, 0.5 mg/kg) was i.v. administered 5 min after administration of disopyramide (5 mg/kg, i.v.). Disopyramide was given 1 h after feeding. The post-treatment values are expressed as a percentage of changes from the level immediately before drug administration. Each point represents the mean of 4 observations. Vertical bars show mean ± S.E. a) disopyramide 5 mg/kg, b) vehicle or cisapride. c) p<0.05, d) p<0.01 compared with the group treated with vehicle at the same time by Dunnett’s test.

occuring contractile activity without quiescence in the stomach and irregularly occurring contractile activity in the small intestine (Fig. 1).

Intravenous administration of saline 1 h after feeding did not affect gastrointestinal contractile activity (Fig. 1A), whereas disopyramide given i.v. at 5 mg/kg decreased the amplitude of the gastric and small intestinal contractions (Fig. 1B). The gastric motor index was significantly decreased by disopyramide administration in a dose-dependent fashion. Peak decrease in the motor index was observed within the 5 min period following injection of disopyramide; the motor index subsequently recovered gradually to the level present prior to drug administration (Fig. 2).

Cisapride administered i.v. at 0.5 mg/kg markedly increased gastrointestinal contractile activity following the decrease by disopyramide pretreatment (5 mg/kg, i.v.) in dogs (Fig. 1C). The effect of cisapride at a dosage of 0.25 mg/kg on the gastric motor index was not significantly different from that of the vehicle (100 mM tartaric acid containing 4% dimethyl sulfoxide), whereas the motor index was significantly increased by administration of 0.5 mg/kg of cisapride (Fig. 3).

Effect of Cisapride on Gastric Emptying Caused by Disopyramide

Figure 4 shows the relationship between plasma concentrations of disopyramide and

Fig. 4. Relationship between Plasma Concentration of Disopyramide and Acetaminophen in 20 Patients with Arrhythmia
The solid line represents the values calculated by regression analysis. Y=0.082X + 1.017, r=0.728, p<0.001, n=20.
acetaminophen during the gastric emptying test; a significant correlation was found between the two \((p<0.001)\). The mean plasma concentrations of disopyramide at 105 min and acetaminophen at 45 min after oral administration were 1.86 \(\mu g/ml\) (range, 0.57 to 2.83 \(\mu g/ml\)) and 10.22 \(\mu g/ml\) (range, 2.30 to 20.88 \(\mu g/ml\)), respectively.

The effect of disopyramide with or without cisapride on gastric emptying is summarized in

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**Fig. 5.** Effects of Disopyramide with or without Cisapride on Gastric Emptying Test

The open circle represents the mean plasma concentrations of acetaminophen at 45 min and disopyramide at 105 min after oral administration. Vertical bars indicate \(\pm S.E\). from 9 patients. Control; disopyramide alone, Cisapride; disopyramide with cisapride. \(a) p<0.05\) compared with disopyramide alone.

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**Fig. 6.** Simulated Plasma Concentration Curves of Disopyramide after Multiple Oral Dosing with (●) or without (○) Cisapride

Each point represents the average value and vertical bars indicate \(\pm S.E\). from 9 patients. \(a) p<0.05\) compared with disopyramide alone. The administration of the drugs is indicated by the arrow.

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**Fig. 5.** Cisapride induced a significant rise in the mean plasma concentration of acetaminophen (disopyramide alone, 7.76 \(\pm\) 3.39 \(\mu g/ml\); disopyramide with cisapride, 10.48 \(\pm\) 2.51 \(\mu g/ml\); \(p<0.05\)). The mean plasma concentration of disopyramide seemed to be increased by cisapride administration, although the difference between trials with and without cisapride was not significant (1.68 \(\pm\) 0.59 \(versus\) 2.14 \(\pm\) 0.40 \(\mu g/ml\)).

**Effect of Cisapride on the Pharmacokinetics of Disopyramide**

Figure 6 shows the plasma concentration-time courses of disopyramide after oral administration of disopyramide with or without cisapride. At 2 h after oral administration of disopyramide with cisapride, the plasma concentration of disopyramide was significantly higher than for disopyramide alone \((p<0.05)\). The lines mean the fitted curves by MULTIP program using the one-compartment open model. The pharmacokinetic parameters estimated from these curve fitting are listed in Table I. The apparent absorption rate constant and lag time of disopyramide associated with cisapride oral administration were both significantly greater and shorter than those of disopyramide alone \((p<0.05)\), respectively.
**Table I.** Pharmacokinetic Parameters of Disopyramide after Multiple Oral Dosing

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$k_a$ (h$^{-1}$)</th>
<th>$K$ (h$^{-1}$)</th>
<th>Lag time (h)</th>
<th>$t_{1/2}$ (h)</th>
<th>$AUC_{\infty}$ (μg·h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.991 ± 0.211$^b$</td>
<td>0.089 ± 0.010</td>
<td>0.966 ± 0.100</td>
<td>8.346 ± 0.655</td>
<td>18.098 ± 1.298</td>
</tr>
<tr>
<td>Cisapride</td>
<td>1.913 ± 0.273$^c$</td>
<td>0.100 ± 0.008</td>
<td>0.587 ± 0.095$^c$</td>
<td>7.446 ± 0.829</td>
<td>18.205 ± 1.237</td>
</tr>
</tbody>
</table>

Control, disopyramide alone; cisapride, disopyramide with cisapride. $a$) Theoretical values converted to a single oral dose. $b$) Mean ± S.E. (n = 9). $c$) Significantly different from control (p < 0.05).

**Discussion**

The results of these animal experiments demonstrated that disopyramide inhibits gastric motility. Anticholinergic drugs are known to inhibit gastrointestinal motor activity. It therefore seems likely that the inhibitory effect of disopyramide on gastrointestinal motor activity may be due to its anticholinergic activity. Cisapride is a prokinetic agent and correspondingly facilitates or restores motility in the gastrointestinal tract. It acts in part through a mechanism thought to involve enhancement of physiological release of acetylcholine from postganglionic nerve endings of the myenteric plexus in gastrointestinal smooth muscle. The inhibitory effect of disopyramide on gastric motor activity was almost completely abolished by treatment with cisapride in beagle dogs. Therefore, cisapride, acting as a cholinergic agonist, may counteract the anticholinergic effect of disopyramide on gastric motility. However, the molecular mechanism for the indirect cholinergic effects of cisapride is unknown. There is evidence as well that cisapride acts as an antagonist of serotonin, although agonist effects have also been reported. The mechanism of interaction of disopyramide and cisapride awaits clarification of the relation of receptors for these agents to gastrointestinal motility.

The gastric emptying has been measured by various methods, such as using X-ray, a radiotelemetric capsule and aspiration of the residue in the stomach. These methods, however, require expensive instruments or special techniques. On the other hand, the gastric emptying correlates with the plasma concentration of acetaminophen administered orally and the drug has been used for measuring the gastric emptying by clinicians. In the clinical studies, a significant correlation between plasma concentrations of disopyramide and acetaminophen as a marker for measuring gastric emptying was observed (Fig. 4). However, a large magnitude of gastric emptying time was observed in patients receiving disopyramide therapy. These results indicate that the inhibitory effect of disopyramide on gastric motility was less clearly present in clinical patients than in the experimental animals tested.

Gastric emptying time associated with the combination of disopyramide and cisapride was significantly shorter than that associated with disopyramide alone (Fig. 5). It has been reported that cisapride is effective in shortening or normalizing gastric emptying time, and our results are consistent with these findings. As shown in Fig. 6, the peak plasma concentration of disopyramide obtained with cisapride administration was significantly higher than that obtained with disopyramide alone. Moreover, the apparent absorption rate constant and lag time of disopyramide with cisapride were about 2-fold higher and 2-fold shorter, respectively, than those associated with disopyramide alone (Table I). Because they accelerate gastric emptying, gastrokinetic drugs such as cisapride have the potential to affect the rate of absorption of other drugs. Our results therefore indicate that since disopyramide is absorbed from the small intestine, the significant increase in the rate of disopyramide absorption may be due to the significant increase in the rate of gastric emptying induced by the combination of disopyramide and cisapride.

In conclusion, the results of this study suggest that although disopyramide is useful for the control of atrial and ventricular arrhythmias, slow absorption may leave some patients at risk during the first few hours after the onset of symptoms: This is a serious disadvantage if the drug
is to be used orally for prophylaxis. In addition, a similar finding has been reported for the use of mexiletine in coronary care unit patients.  

As a factor influencing drug absorption, gastric emptying is of importance, as it determines the rate of drug delivery to the small intestine, where absorption is most rapid. Therefore, the oral administration of disopyramide with cisapride may be useful for patients with delayed gastric emptying.

References


