Effects of 5-HT$_4$ selective receptor agonist, mosapride citrate on electrocardiogram in dogs

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Abstract: Mosapride stimulated dietary motility was introduced because of the arrhythmogenic effect of cisapride. Cisapride, 5-HT receptor agonist, induces prolongation of QT interval. Additionally, this condition can raise the possibility of acute, “malignant” arrhythmias such as torsade de pointes. It is hard to find any reports about effects of mosapride on cardiac parameters in dogs. By confirming electrocardiogram (ECG) parameters, the surface extremity leads ECG that was obtained from the four-limb electrodes and which was recorded by an ECG recorder after administration of mosapride 3 mg/kg PO b.i.d, and mosapride 3 mg/kg with itraconazole 5 mg/kg PO b.i.d, respectively. QT interval was shortened on the days of 3, 5, and post-day 1 in both mosapride 3 mg/kg administrated group and mosapride with itraconazole group. Heart rate increased significantly. QTc was slightly prolonged in mosapride administration group and mosapride with itraconazole group. However, all dogs of QTc were in normal variation (150~250 msec). Besides, the dogs showed no side effects reported in human medicine during the administration with these drugs. Although mosapride can increase the heart rate, this study suggest that mosapride may be useful for the dogs with disorders of gastrointestinal motility because of no fatal arrhythmogenic effect inspite of administration with itraconazole in dogs.

Keywords: electrocardiogram, itraconazole, mosapride, QTc, QT interval

Introduction

The greatest scientific and clinical advances in gastroenterology over the past two decades have addressed the functional aspect of digestion, especially in gastrointestinal motility. With the smooth muscle contraction of gastrointestinal system, peristalsis tends to propel digestive contents along the gastrointestinal tracts. Delayed gastric emptying is a significant cause of upper gastrointestinal tract symptoms in dogs and cats [4].

Some gastrointestinal prokinetic agents have effects throughout the gastrointestinal tract. The gastrointestinal prokinetic agents work with many different mechanisms of action [2]. Prokinetic agents, including metoclopramide, cisapride and mosapride increase digestive motility by, stimulating serotonin 5-HT$_4$ receptors in the gastrointestinal plexus, consequently increasing the release of acetylcholine and enhancing gastrointestinal motility as well as gastric emptying [2]. Metoclopramide stimulates upper gastrointestinal tract than colonic motility that has more potent as antiemetic than upper gastrointestinal motility [7, 9]. Animals show unusual behavior, extrapyramidal side effect after administration rarely because this drug originally marketed as a dopamine transporter receptor antagonist [7, 8]. Besides, metoclopramide is excreted mostly in the urine, and severe renal failure makes adverse effects more likely [8]. Cisapride is an oral gastrointestinal prokinetic agent that stimulates normal motility from the lower esophageal sphincter to the anus. It has about 8 times more potent than metoclopramide as a prokinetic agent does [12]. However, cisapride, which acts on serotonin receptors 5-HT$_3$ to 5-HT$_4$, has been associated with potentially fatal heart rhythm abnormalities [7]. Cisapride induces prolongation of QT interval. Furthermore, this condition can raise the possibility of such acute, “malignant” arrhythmias as torsade de pointes and ventricular fibrillation [13]. Concomitant use of imidazole class antifungal agent or macrolide antibiotics has also been found to inhibit the cytochrome P-450 enzyme system that affects cisapride metabolism and results in increased serum cisapride levels and more arrhythmogenic [13]. For that reason, this drug has not been available from several markets including Korea [2].

Many alternative gastrointestinal prokinetic agents have been introduced in market like itopride, and mosapride which are a structurally related benzamide, because of arrhythmogenic effect of cisapride. Mosapride enhances upper gastrointestinal motility in conscious dogs [6, 14]. In rabbits, rats, guinea pigs, and conscious cats, mosapride does not show arrhythmogenic effect [1, 5]. Although mosapride can

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be possible to alternate the uses of cisapride and metoclopramide, there is little information about side effects of mosapride in dogs. There is no report about effects on cardiac parameters in dogs. This study is to investigate the cardiac effects of mosapride citrate on electrocardiogram (ECG) in dogs.

Materials and Methods

Preparation of experimental animals

The use of animals in this experiment was approved by the Institute of Laboratory Animal Resources, Seoul National University (SNU-110722-1), Korea. All the beagle dogs (6 dogs) were cared for in accordance with the Animal Care and Use Guidelines (Institute of Laboratory Animal Resources, Seoul National University). The animals used in our experiment were male or female beagle dogs weighing 6–10 kg. All the dogs were determined to be healthy after a routine physical examination, complete blood count, serum biochemistry analysis. Each dog was kept in its cage at a room temperature (approximately 25°C). Food was available twice a day and water was continuously available. The animals were divided into 2 groups: mosapride 3 mg/kg administration group (A group: n = 3, 2 males and 1 female), and mosapride 3 mg/kg with itraconazole 5 mg/kg group (B group: n = 3, 2 males and 1 female). Dogs were orally and repeatedly administered for 5 days with water, mosapride 3 mg/kg or mosapride with itraconazole 5 mg/kg twice a day. From the 1st to 5th day of administration, drugs were administered twice a day (8–9 a.m. and 8–9 p.m.).

ECG measurement

The surface ECG was obtained from the four-limb electrodes and recorded by using an ECG recorder (Cardiofax GEM ECG-9020K; Nihon Kohden, Japan). From the 1st to 5th day of administration, ECG was measured on day 1, day 3 and day 5 at least 3 times at each point (0, 1 and 3 h after administration). ECG was also evaluated post drug administration of 1 day and 2 days. Heart rate was measured before and after the administration of mosapride. ECG signals were read for 10–15 sec, and recorded on ECG paper. The signals were automatically analyzed by an interpretive ECG Analysis for dogs and cats (Veterinary ECG Software Kit QP-992E; Nihon Kohden). We also checked the end of T wave and analyzed ECG manually, and then QT intervals were measured. The QT interval begins with the onset of the QRS complex and ends when the T wave returns to baseline. Even though the QT interval does not vary during respiratory sinus arrhythmia, measured QT interval was corrected for the effect of heart rate using the Bazett formula: QTc = QT interval/square root of RR interval (in seconds).

Drugs

Mosapride was obtained from the commercial source (Gasmotic; Daewoong Pharmaceutical, Korea). Itraconazole was also obtained from the market (Hitrazole; JW Pharmaceutical, Korea). Administration dose of mosapride was decided by motility index of recent study [6]. Dogs were orally administered mosapride or mosapride with itraconazole twice a day for 7 days.

Statistical analysis

All data are expressed as the mean ± SD statistically significant differences between the values in drug-treated group were analyzed by One-Way ANOVA using the PASW 18 statistics (IBM, USA). All differences with values of $p \leq 0.05$ were considered significant.

Fig. 1. Effects of mosapride on electrocardiogram at the 5 day (d) of repeated administration in conscious dogs. There are no fatal arrhythmogenic effects in mosapride (3 mg/kg) administration group and mosapride (3 mg/kg) with itraconazole (5 mg/kg) group. Lead as marked, 25 mm/sec, 5 mm/mV.