Effects of Trimebutine on Intestinal Motility after Massive Small Bowel Resection

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Abstract

Effects of trimebutine maleate (TM) on intestinal motility in short bowel syndrome (SBS) were studied in conscious canines in both acute and chronic phases following 80% massive distal small bowel resection (MSBR). TM was administered orally to beagles with MSBR or as controls in the postprandial and fasting states, and given simultaneously with meals. Intestinal motility was measured using bipolar electrodes for approximately 1 month after the electrodes were implanted in each beagle and the data compared between treatment groups. When TM was given with meals, the postprandial period without duodenal migrating myoelectric (or motor) complexes (MMCs) was shorter than in those given meals only. When TM was given in the postprandial state in short bowel beagles, the initial duodenal MM Cs occurred earlier, i.e. the postprandial period was shorter. Diarrhea did not occur in these beagles. When TM was given in the fasting state, duodenal MM Cs occurred and propagated to the distal intestine. In conclusion, oral TM administration can produce a more appropriate intestinal condition for the next food intake and make enteral nutrition possible even in the acute phase after MSBR. Such feeding can be carried out without overloading gut function as a result of the modulation of gastrointestinal motility by TM.

Key words: intestinal motility, small intestine, trimebutine (TM), short bowel syndrome (SBS), massive small bowel resection (MSBR)

Introduction

Massive small bowel resection (MSBR) is inevitably performed in certain pediatric surgical diseases, including midgut volvulus, multiple intestinal atresia, necrotizing enterocolitis, intestinal functional obstruction, gastroschisis, or strangulation ileus. After MSBR, patients suffer from serious symptoms of malabsorption and malnutrition, which constitute the short bowel syndrome (SBS), sometimes necessitating long-term hyperalimentation. To prevent severe diarrhea and malabsorption in the acute phase after MSBR, optional surgical procedures have
been tried to delay food transit time and to expand absorption area (Thompson and Rikkers, 1987).

On the other hand, to attenuate the more rapid transit time, drug therapy in SBS has been attempted with some efficacy (Grosfeld, et al., 1986). In this study, we have investigated the effects of trimebutine maleate (TM; Cerekinor®: a drug which modulates bowel motility) on postoperative malabsorption in SBS during the acute and chronic phases following surgery.

There have been a limited number of reports of studies of intestinal motility after MSBR using myoelectric electrodes or strain gauge force transducers (Wittman, et al. 1984; Kitahara, 1986; Wada, et al. 1989; Uchiyama, et al. 1992, 1996, 2000). In the present study, motility of the remnant intestine was continuously measured using myoelectric activity in postoperative conscious beagles. The usefulness of TM for treating MSBR in terms of intestinal motility is evaluated and discussed.

**Materials and Methods**

**Surgical Procedures**

Experimental subjects: Beagle dogs weighing 9 to 12 kg underwent laparotomy under sodium pentobarbital anesthesia with ventilatory support and intravenous infusion. Intestinal length was measured at the antimesentric side after atropine sulfate injection, and sites for electrode placement and the length of resection were determined.

Acute phase after MSBR; Group I (n=3): The distal small bowel was massively resected (80%) and an end-to-end jejunoileal anastomosis was performed, preserving about 50 cm of the proximal jejunum from the ligament of Treitz and 10 cm of the terminal ileum (MSBR). Bipolar electrodes were then implanted in the following sites: the duodenum (D), the proximal jejunum (J1: 10 cm distal to the ligament of Treitz), the jejunum 5 cm above the anastomosis (J2), and the terminal ileum 5 cm below the anastomosis (TI).

Chronic phase after MSBR; Group II (n=3): Beagle dogs that underwent MSBR were housed in our animal experiment facility. After a period of about one year, three beagles had further surgery to implant electrodes at equivalent intestinal sites to those described above (D, J1, J2, TI).

Controls (n=3): Laparotomy was performed and electrodes implanted in the duodenum (D), the proximal jejunum (J1), the jejunum at 45 cm from the ligament of Treitz (J2), the middle jejunum (J3, J4), and the terminal ileum 5 cm above the ileocolic junction (TI).

**Recording condition and intestinal motility analysis**

Electromyograms of intestinal motility were recorded from the day following the electrode implantation operation. Gut motility was continuously recorded and analyzed for a month postoperatively. Beagles were kept in cages that permitted physiologic activity and sleeping, and were supplied with food once a day with water freely available.

Migrating myoelectric (or motor) complexes (MMCs) periodically propagate from the proximal to the distal bowel in the fasting state (Szurszewski, 1969; Carlson et al., 1972; Ito, 1981; Sarna, 1985). We analyzed the interval between MMCs at various sites in the intestine,
the propagation pattern of the duodenal MMCs to the distal intestine, and the postprandial period without duodenal MMC activity (the interval between food intake and the initial duodenal MMC). Ryan's multiple comparison test was used to evaluate the statistical significance of the results. Data is described as mean±SD.

**Oral administration of TM**

A TM tablet coated with a small amount of meat, or TM mixed with meat as a meal, was administered orally to beagles of each group from the 10th day postoperative. The effects of trimebutine were observed as follows. 1; The duration of postprandial period without duodenal MMC activity was measured after a meal (200 g of meat containing 170 Kcalories) with TM in a dose of 200 mg (20 mg/kg), and was compared with that in beagles only given a meal. 2; During the postprandial state, TM in a dose of 100 mg was administered, with measurement of the interval from TM administration to the occurrence of duodenal MMC activity compared with the interval from meal intake alone to MMC appearance. 3; In the fasting period while duodenal MMCs were occurring, 100 mg of TM was given, and the interval until further duodenal MMC occurrence was measured.

**Ethical Considerations**

All procedures were performed within the guidelines of and with the approval of the Ethical Committee on Animal Experimentation of the university.

**Results**

1. **Intestinal motility in each group**
   
   Group I;
   
   Acute phase after MSBR. For 3 days postoperative, propagating duodenal MMCs did not occur, and solitary MMC tended to occur in the jejunum. The basic electric rhythm (BER) of the resting phase was dominant while small amplitude activity occurred sporadically. On the other hand, diarrhea often occurred even after ingestion of some milk. During such periods of diarrhea, intestinal MMCs did not occur. At 4–5 days, isolated MMC occurred in the duodenum or the jejunum (Fig. 1). At 6–8 days, duodenal MMCs tended to propagate to the distal intestine. After 8–10 days postoperatively, feces gradually formed a paste, while duodenal MMCs occurred periodically and migrated to the terminal ileum beyond the anastomosis. Defecation occurred 2–3 times a day. In the fasting state, MMCs originating in the duodenum (duodenal MMCs) occurred at a mean interval of 153.6 minutes. This interval was significantly longer than that in Group II or in controls (Table 1). The postprandial period without duodenal MMCs was markedly increased to an average of 19.6 hours (with a range of 17–25 hours), which was significantly longer than those in Group II and in controls (Table 2).
   
   Group II;
   
   Chronic phase after MSBR. After electrode implantation, solitary MMC occurred at the jejunum on the first day postoperative, especially at the terminal ileum. Jejunal MMCs started to migrate to the distal intestine at 2–3 days. Duodenal MMCs occurred at 3–4 days. After
Fig. 1. Small intestinal motility in a beagle in the acute phase after MSBR (Group I). Recording speed: 2.5 mm/min. A: At 3 days after MSBR, the basic electric rhythm (BER) occurs but spike potentials (SP) do not superimpose. The frequency of BER is 20/min at the duodenum (D), 19/min at the proximal jejunum (J1), 18/min at the jejunum above anastomosis (J2), and 10/min at the terminal ileum (TI). Diarrhea occurs easily in this period. B: At 5 days after MSBR, isolated MMC events occur at J1, J2 or TI in the fasting state, but myoelectric SP is of low amplitude. Jejunal MMCs propagate to J2 and TI beyond the anastomosis.

Table 1. Interval between duodenal MMCs in the fasting state, and time for duodenal MMCs to occur after oral administration of TM.

<table>
<thead>
<tr>
<th></th>
<th>Interval between duodenal MMCs in the fasting state (min)</th>
<th>Time to duodenal MMC after TM giving in the fasting state (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (acute phase after MSBR)</td>
<td>153.6±56.7 (n=55)</td>
<td>39.2±18.3 (n=6)</td>
</tr>
<tr>
<td>Group II (chronic phase after MSBR)</td>
<td>126.9±54.2 (n=71)</td>
<td>30.8±10.3 (n=6)</td>
</tr>
<tr>
<td>Controls (laparotomy)</td>
<td>123.1±34.6 (n=56)</td>
<td>38.8±20.3 (n=4)</td>
</tr>
</tbody>
</table>

TM: trimebutine maleate  
*n, no. of intervals or TM giving.  
Values are given as mean±SD.  
Significance vs. Group I: *p < 0.01 (Ryan's multiple comparison test)

Table 2. The length of the postprandial period without duodenal MMCs, comparison between beagles after meals only, after meals with TM and after oral administration of TM.

<table>
<thead>
<tr>
<th>Postprandial period without duodenal MMC</th>
<th>after meals (h)</th>
<th>after meals with TM (h)</th>
<th>after TM giving in the postprandial state (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (acute phase after MSBR)</td>
<td>19.6±3.1 (n=11)</td>
<td>16.3±2.6a (n=12)</td>
<td>13.8±2.7a (n=7)</td>
</tr>
<tr>
<td>Group II (chronic phase after MSBR)</td>
<td>13.9±2.7 (n=12)</td>
<td>11.2±2.2c (n=9)</td>
<td>9.7±1.6b (n=7)</td>
</tr>
<tr>
<td>Controls (laparotomy)</td>
<td>8.2±2.1 (n=7)</td>
<td>4.5±3.4c (n=14)</td>
<td>7.8±0.8 (n=3)</td>
</tr>
</tbody>
</table>

TM: trimebutine maleate  
*n, no. of meals or TM giving.  
Values are given as mean±SD.  
Significance vs. each other: *p < 0.01 (Ryan's multiple comparison test)  
Significance vs. after meals in each Group: *p < 0.01, *p < 0.05 (Ryan's multiple comparison test)
that period, duodenal MMCs propagated to the terminal ileum smoothly. Diarrhea was not
symptomatic after oral intake even at 5 days postoperatively. Intestinal motility was stable
and periodic on day 5 and defecation was observed once or twice a day. In the fasting state,
duodenal MMCs were repeated with a mean interval of 126.9 minutes, which was significantly
shorter than in Group I, but similar to that in control (Table 1). The mean postprandial period
was 13.9 hours (with a range of 10–15 hours), which was significantly shorter than that in Group
I, but still longer than that in controls (Table 2).

Controls;

MMCs occurred at the jejunum on the 1st day postoperatively. Usually, duodenal MMCs
occurred and propagated to the distal intestine after 3 days. In the fasting state, duodenal
MMCs occurred periodically at a mean interval of 123.1 minutes (Table 1). After meals, the
myoelectric complex disappeared and remained suppressed for 6 to 10 hours. The mean
postprandial period was 8.2 hours (Table 2). Beagles usually defecated once a day soon after
a meal. All the data were statistically not significantly different to those previously reported

2. Intestinal motility after administration of TM with meals

After TM with meals, duodenal MMCs appeared with an average interval of 16.3 hours in
Group I and 11.2 hours in Group II, which was significantly shorter than that after the intake of
a meal alone (Table 2). In controls, duodenal MMCs occurred occasionally just after TM with
meals with a mean interval of 37 minutes. The postprandial period was 4.5 hours which was
statistically shorter than that after food intake alone (Table 2; Fig. 2, 3). Diarrhea did not
occur in any group.

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![Graph of small intestinal motility](image-url)

Fig. 2. Small intestinal motility in a postprandial state beagle in the acute phase after MSBR
(Group I). Recording speed; 2.5 mm/min. After TM (trimebutine maleate) administration at a dose of 200 mg (20 mg/kg) with meat, intestinal MMCs disappear, and irregular
low or high amplitude activity continues in every intestine. The postprandial period
without duodenal MMCs became shorter than in cases when only meat is given.
3. **Effect of TM administration in the postprandial state**

The timing of administration of TM after meals in each group was determined by previous results (Uchiyama et al., 1996). Since having a postprandial period without duodenal MMCs is favorable for the study of the effect of TM, the most suitable timing of TM administration after MSBR was considered to be around 10 hours after meals in the acute phase (Fig. 4) and 8 hours in the chronic phase, and 5 hours in control beagles. After administration of TM, the average postprandial period without duodenal MMCs after MSBR was 13.8 hours in the acute phase and 9.7 hours in the chronic phase, and was 7.8 hours in control beagles. The postprandial period was significantly shorter by giving TM in the acute and chronic phases after MSBR (Table 2). Diarrhea was not observed in these conditions.

4. **Effect of TM administration in the fasting state**

TM was administered orally while periodic MMCs were occurring. The timing of the drug administration was at 20, 19, and 19 hours in groups I, II after MSBR, and in controls respectively. After oral intake of TM, intestinal MMCs were evoked in every group. Duodenal MMCs which propagated to the distal intestine occurred with an average of 39.2 minutes (with a range of 15 to 66 minutes) in Group I, 30.8 minutes (with a range of 16 to 42 minutes) in Group II, and 38.8 minutes (with a range of 17 to 56 minutes) in controls (Table 1,
Effects of TM on short bowel syndrome

**- postprandial state -**

<table>
<thead>
<tr>
<th>Location</th>
<th>Activity</th>
<th>Time Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum: D</td>
<td>TM</td>
<td>0.03 sec.</td>
</tr>
<tr>
<td>Proximal jejunum: J1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jejunum above anastomosis: J2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal ileum: TI</td>
<td></td>
<td>60 min.</td>
</tr>
</tbody>
</table>

Fig. 4. Small intestinal motility in a postprandial state beagle in the acute phase after MSBR (Group I). Recording speed: 2.5 mm/min. After TM administration of 100 mg (10 mg/kg), duodenal MMCs do not occur but strong myoelectric activity occurs sporadically at J1 and J2. Initial duodenal MMCs occurred earlier, and the postprandial period became shorter than in cases when only meat was given. TM; trimebutine maleate

**- fasting state -**

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<td>60 min.</td>
</tr>
</tbody>
</table>

Fig. 5. Small intestinal motility in a fasting state beagle in the acute phase after MSBR (Group I). Recording speed: 2.5 mm/min. After TM administration at a dose of 100 mg (10 mg/kg), duodenal MMCs occur, and migrate to the distal jejunum. TM; trimebutine maleate

Diarrhea did not occur in any group.

**Discussion**

We have reported that duodenal MMCs are suppressed soon after MSBR while severe
diarrhea is liable to happen even with a small amount of enteral feeding. After several days, duodenal or jejunal MMCs tend to occur and to propagate to the distal intestine, and then, diarrhea tends to cease as long as enteric overload is avoided. Usually around 10 days following MSBR, duodenal MMCs propagated periodically to the distal small intestine, but the interval between duodenal MMCs was prolonged, and the propagation velocity of duodenal MMCs was slowed in every segment of the intestine. The postprandial period without duodenal MMCs after meals was extremely prolonged in the acute phase. These changes in motility would compensate for the more rapid transit time and for the reduced surface area for digestion and absorption. Moreover, these changes might reflect sensory vagal nerve activity, and the altered condition of the intrinsic nervous system (Kumar and Wingate, 1993; Uchiyama, 1996). In the chronic phase, the interval between periodic duodenal MMCs was significantly shorter than in the acute phase and similar to controls. The postprandial period in the chronic phase was shorter than that in the acute phase, but still longer than that in controls. These changes in motility would reflect postoperative adaptation. Usually defecation becomes stable after MSBR, occurring 2-5 times a day for 1-6 months. Studies have shown a functional adaptation and a morphologic compensation (proliferation of the mucosa and enlargement of the remnant intestine) that increases nutrient absorption over the long-term after MSBR (Grosfeld, 1986).

In short bowel syndrome, with the decrease of digesto-absorbtional capacity and stagnation of bowel contents, enteral nutrition results in an overload of the function of the remnant gut, consequently diarrhea and malabsorption occur. Restriction of enteral nutrition and hyperalimentation are the principal treatment to prevent diarrhea or malnutrition (Grosfeld, 1986). To improve these conditions, operative procedures (Thompson, 1987; Uchiyama, 1992, 2000) or medications to modulate intestinal motility or to promote absorptive ability have been considered. With such a background, we analyzed the effect of TM administration, and demonstrated that TM provides improved intestinal motility without diarrhea. This allows for the possibility of earlier enteral feeding in short bowel syndrome.

In the modulation of gut motility, TM has been reported to have a dual action on gastrointestinal smooth muscle (Furukawa, et al. 1984; Nagasaki, et al. 1989, 1993; Takenaga, et al. 1982, 1984; Taniyama, et al. 1991; Yamada, et al. 1982). Namely, it has been reported to have a stimulatory effect on the hypomotile gastrointestinal tract, but an inhibitory effect on the hypermotile tract. These effects are believed to be a direct action on the intestinal smooth muscle without the intervention of extrinsic nerves. In this study, when TM was given with meals in control beagles, duodenal MMCs occasionally appeared during postprandial intestinal activity, a period when stimulated vagal nerve activity would be expected to be dominant.

Clinical studies of TM in irritable bowel syndrome or other functional disorders suggest that this drug has a beneficial effect that enhances gastric emptying and inhibits propulsive electromechanical activity in the colon (Frexinos, et al. 1985; Matsueda, et al. 1990). After MSBR, gastric emptying time after feeding is extremely prolonged and gut motility is suppressed for a long time as a compensating phenomenon. But by overloading the gut with enteral nutrition, hyperactivity of the gastro-colic reflex and hypersecretion of the gut mucosa are evoked. In the conditions after MSBR, TM is expected to modulate gut motility by having a
stimulatory effect on the inhibited gastrointestinal motility and an inhibitory effect on the accelerated colonic motility especially after enteral feeding. In this study, in the acute phase after MSBR, the prolonged postprandial period was shortened by oral intake of TM with meals and by intake of TM alone in the postprandial state. MMCs were also provoked in each small intestine in the fasting state by oral intake of TM without causing diarrhea. This indicates that oral TM intake can moderate intestinal motility even in the acute phase after MSBR. In conclusion, oral administration of TM improves the intestinal condition for the next intake of food and makes enteral nutrition possible even in the acute phase after MSBR without overloading gut function or without resultant diarrhea.

References


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