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The effect of SK-896 on post-operative ileus in dogs: gastrointestinal motility pattern and transit

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Abstract

The aim of this study was to investigate the effect of SK-896 (Phe-Val-Pro-Ile-Phe-Thr-Try-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly-Gln-Hse), a new motilin analogue, on gastrointestinal motility and transit in dogs with post-operative ileus, and to compare the effects of this agent on these parameters with the effects of prostaglandin $F_{2\alpha}$, a well-known gastroprokinetic agent. We used chronically implanted force transducers to measure motility and radiography of radio-opaque markers to measure transit. Infusion of SK-896 1 μg/kg/h, for 20 min twice a day induced interdigestive migrating contractions-like motility. Infusion of prostaglandin $F_{2\alpha}$, 20 μg/kg/h, for 1 h twice a day induced continuous contractions in the distal part of the small intestine. The time of first appearance of interdigestive migrating contractions in the stomach (gastric-interdigestive migrating contractions) and the gastric emptying time of the solid marker with the administration of SK-896 were significantly less than those noted with the administration of prostaglandin $F_{2\alpha}$. It appears that gastric-interdigestive migrating contractions play an important role in the transit of substances, especially solid substances, in the gastrointestinal tract. We conclude that SK-896, which induced gastric-interdigestive migrating contractions, is effective to induce early recovery from post-operative ileus. © 2000 Published by Elsevier Science B.V.

Keywords: Gastrointestinal transit; Gastrointestinal motility; Interdigestive migrating contraction; Post-operative ileus; SK-896; Prostaglandin $F_{2\alpha}$; (Dog)

1. Introduction

Clinically, disorders of gastrointestinal motility are generally present after laparotomy, with several days required for recovery (Livingston and Passaro, 1990). Ileus after laparotomy is a major impediment to patient recovery, since it necessitates the use of a nasal tube for drainage of retained intragastric fluid and parenteral feeding, induces abdominal distention, pain and vomiting, and often results in pulmonary complications (Hinder and Kelly, 1977). Therefore, attempts have been made to reduce the duration of post-operative ileus in order to permit removal of the nasal gastric tube as early as possible and to enable normal feeding. There are many types of clinical treatment such as administration of gastroprokinetic agents, for example cholinergic agents like bethanachol (Furness and Costa, 1974; Ruwart et al., 1979), benzamide derivatives like metoclopramide or cisapride (James and Hume, 1968; Sparnon and Spitz, 1989; Springall and Spitz, 1989), somatostatin analogues (Cullen et al., 1993), and prostaglandin $F_{2\alpha}$ (Fiedler, 1980; Saito et al., 1993). Many other gastroprokinetic agents, dopamine receptor antagonists, various gastrointestinal peptides, macrolide antibiotics and opioid receptor antagonists have also been studied (Longo and Vernava, 1993).

Motilin is a gastrointestinal hormone, which was isolated and purified from porcine gastrointestinal mucosa by Brown et al. (1972). It is known that exogenous administration of motilin is able to induce interdigestive migrating contractions in dogs (Itoh et al., 1976). A recent study determined the amino acid sequence of motilin receptors identified in the human stomach (Feighner et al., 1999). Many studies have focused on the potent effects of motilin on gastrointestinal motor activity, and several trials of its use for treatment of various gastrointestinal disorders have been performed (Itoh, 1997). One such gastrointestinal disorder is post-operative ileus. Inatomi et al. (1993) re-

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ported that EM523, an erythromycin derivative and motilin agonist, induced migrating contractions from the stomach and duodenum to the lower gastrointestinal tract in conscious dogs with post-operative ileus. Yokoyama et al. (1995) reported that treatment with KW-5139, a motilin analogue, significantly shortened the time required to recover phase III contractions in the stomach as compared with treatment with prostaglandin $F_{2\alpha}$ in dogs with post-operative ileus. In addition, these authors reported that KW-5139 enhanced gastrointestinal motility significantly more than did prostaglandin $F_{2\alpha}$. These studies indicate that motilin, motilin agonists and motilin analogues are able to induce the pattern of gastrointestinal motility of the interdigestive period during post-operative ileus.

It is thought that interdigestive migrating contractions act as housekeepers in the gastrointestinal tract, and that food residues and secretions remaining in the gastrointestinal tract cause abdominal distention and disorders when this motility is lost, as in post-operative ileus. It is also thought that the cyclical enhancing of gastroprokinetic activity in the gastrointestinal tract during the interdigestive period is a preparative state for subsequent food intake rather than for performance of housekeeping functions (Code and Schlegel, 1974; Itoh, 1980). Therefore, the induction of gastrointestinal motility for transit of substances from the upper to the lower gastrointestinal tract may be important for early recovery from post-operative ileus, since abdominal surgery is performed under fasting conditions. Our previous results suggested that occurrence of phase III contractions in the stomach and interdigestive migrating contractions in the gastrointestinal tract play important roles in transporting liquid and/or solid substances from the upper to the lower gastrointestinal tract in dogs with post-operative ileus, and that such motility was principally responsible for recovery from ileus (Tsukamoto et al., 1999).

SK-896 (Phe-Val-Pro-Ile-Phe-Thr-Try-Gly-Glu-Leu-Gln-Arg-Leu-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly-Gln-Hse), in which Leucine replaces Metionine at position 13 of human motilin and Homoserine is added at the N-terminal, is a new human motilin analogue. We have previously investigated the pharmacological profile of SK-896 in vitro. SK-896 binds motilin receptors and induces Ca^{2+}- and dose-dependent contractions in isolated duodenal preparations from rabbits as does human motilin (Tsukamoto et al., 2000). Moreover, it is thought that SK-896 may be a useful and safe gastroprokinetic agent because it has a longer plasma concentration half-life than does human motilin and it induced no signs of anaphylactic shock in either mice or guinea pigs in a preliminary study (data not shown). In the present study, we investigated the effects of SK-896 on gastrointestinal motility and transit in dogs with post-operative ileus in order to clarify whether the interdigestive migrating contractions-like motility induced by motilin analogues in post-operative ileus is a motility to transport substances from the upper gastrointestinal tract to the lower. Moreover, in order to clarify what kind of motility is an effective treatment of post-operative ileus, we compared the gastrointestinal motility and transit induced by SK-896 with those induced by prostaglandin $F_{2\alpha}$, which is known to stimulate gastrointestinal motility in patients with ileus (Fukunishi et al., 1977; Saito et al., 1993).

2. Materials and methods

2.1. Animals

A total of 22 male beagle dogs (OBC, Shizuoka, Japan) weighing 8.7–13.0 kg were used in the experiments. The animals were housed in an air-conditioned room at 22°C with a 12-h light cycle, fed standard laboratory diet (Canine Diet #4360, Purina Japan, Tokyo, Japan) and given water ad libitum. The animals were fasted for 24 h before surgery (*ad libitum* intake of water was permitted).

2.2. Laparotomy

Laparotomy was performed according to the method described in a previous report (Tsukamoto et al., 1999). In brief, the dogs were anesthetized with 35 mg/kg i.v. of sodium pentobarbital, and the operation was performed aseptically. The external jugular vein was catheterized (ANTHRON®; Toray Medical, Tokyo, Japan) for drug administration. Then, 1 mg of atropine sulfate was administered through the catheter, and force transducers (F-12IS; Star Medical, Tokyo, Japan) were sutured with a silk thread to the serosal surface of the antrum of the stomach (5 cm orally from the pylorus), duodenum (15 cm anally from the pylorus), jejunum (3 points, 70, 170, and 220 cm anally through the entire length of 300 cm from the ligament of Treitz to the ileocecum), and colon (15 cm anally from ileocecum) to record contractile activities of the annular muscle. The leads from force transducers were passed under the skin to an incision between the scapulas, where they were exteriorized and fixed. Approximately 3 h was required from start to end of the operation. Post-operatively, a jacket was placed on the dog for protection of the leads and catheter, and 1 g of ceftriaxone sodium (Rocephin®; Japan Roche, Tokyo, Japan) was administered locally to the surgical wound on closing of laparotomy to prevent infection. In addition, 500 ml of KN® (Otsuka Pharmaceutical, Tokushima, Japan) fluid in which 0.5 g of ceftriaxone sodium was dissolved was infused at a rate of 500 ml/day. The dogs were given no food or water during the recording of gastrointestinal motility.

2.3. Gastrointestinal transit and motility

Gastrointestinal motility was recorded with a personal computer (PC-9801; NEC, Tokyo, Japan) continuously for 99 h after the operation using an organ motility analysis

system (ESC-820; Star Medical, Tokyo, Japan) with the dogs conscious and unrestricted. The three solid radio-opaque markers, with 5 ml barium sulfate (75% w/v) as contrast medium, and 20 ml barium sulfate (75% w/v) as a liquid marker were administered into the stomach through the gastric tube just before the end of the operation. SK-896 and prostaglandin $F_{2\alpha}$ were infused twice a day (0900 and 1700) at dosages of 1 μg/kg/h for 20 min and 20 μg/kg/h for 1 h, respectively. Abdominal X-rays were taken using X-irradiation equipment (CMB80 special type; SOFTEX, Tokyo, Japan) with an 80 kV peak, 20 mA, and 0.5 s under inhalation anesthesia with nitrous oxide–oxygen–fluothane gas (gas oxygen halothane; GOF) just after the end of operation, 30 min before and 3 h after drug administration, that is, four times in 1 day (0830, 1200, 1630 and 2000). The solid radio-opaque marker was made of enclosed wires in a low-density polyethylene tube 6 mm in diameter, 14 mm in length, 400 mg in weight, and with a specific gravity of about 1. The gastrointestinal tract was divided into the stomach, small intestine, colon, and rectum based on anatomical position on abdominal X-rays. Using the above division, a score was determined for the position of the solid radio-opaque marker or the distal and proximal points of barium sulfate (stomach: 0, small intestine: 1, colon: 2, rectum: 3, excretion: 4). The geometric mean as index of transit was calculated as the mean score for every point of measurement. Gastric emptying time was calculated as the mean time at which each score became 1. In the same fashion, small and whole intestinal transit times were calculated as the mean times at which each score became 2 and 3, respectively. When radio-opaque markers were not emptied from the stomach or had not passed the small intestine until 99 h after the operation, gastric emptying time and small intestinal transit time were regarded as 99 h. The time of first occurrence of interdigestive migrating contractions-like motility from the small intestine to the distal gastrointestinal tract (intestinal-interdigestive migrating contractions), from the duodenum to the distal gastrointestinal tract (duodenal-interdigestive migrating contractions), and from the stomach to the distal gastrointestinal tract (gastric-interdigestive migrating contractions) was read from the measurement motility chart.

2.4. Statistical analysis

The correlation between the time of gastric emptying, small or whole intestinal transit and the times of occurrence of intestinal-interdigestive migrating contractions, duodenal-interdigestive migrating contractions, and gastric-interdigestive migrating contractions were calculated. Results were expressed as the means ± S.E.M. The statistical significance of differences in geometric mean values was determined with the Mann–Whitney *U*-test, and the other parameters were evaluated with Student's *t*-test. *P* values less than 0.05 were considered significant. Coefficients of correlation (r) and their *P* values were also determined.

2.5. Drugs and chemicals

SK-896 ([Leu^{13}]motilin-Hse) was synthesized at Sanwa Kagaku Kenkyusho (Mie, Japan). Prostaglandin $F_{2\alpha}$ was purchased from Ono Yakuhin (Osaka, Japan). Sodium pentobarbital (Nembutal®) was purchased from Dainabot (Osaka, Japan). Atropine (atropine sulfate injection tanabe®) was purchased from Tanabe Seiyaku (Osaka, Japan). Ceftriaxone sodium (Rocephin®) was purchased from Japan Roche (Tokyo, Japan).

3. Results

3.1. Gastrointestinal motility

Weak irregular contractions were observed in all parts of the gastrointestinal tract for about 20 h after laparotomy in dogs. These weak contractions grew larger in amplitude and collected in clusters 1–2 min in length for about 20–30 h after laparotomy. During the early post-operative period up to 30 h after laparotomy, neither drug affected gastrointestinal motility in this model of post-operative ileus. Next, giant contraction groups termed phase III contractions were observed only in the lower part of the gastrointestinal tract and then, gradually, in the upper part. These phase III contractions were propagated to the lower part of the gastrointestinal tract as interdigestive migrating contractions-like motility from about 30 h after laparotomy on. Finally, phase III contractions were observed in the stomach, and these were propagated to the lower part of the gastrointestinal tract as interdigestive migrating contractions-like motility for about 60–70 h after laparotomy. Infusion of SK-896 for 20 min induced phase III contractions of the stomach and duodenum, and these contractions had spread to the small intestine at 40 h after laparotomy (Figs. 1 and 2). On the other hand, infusion of prostaglandin $F_{2\alpha}$ for 1 h induced continuous contractions, unlike those of phase III, in the small intestine but not in the upper gastrointestinal tract (Figs. 3 and 4).

3.2. Gastrointestinal transit of radio-opaque markers

Considering the geometric mean values of the solid markers, SK-896 significantly accelerated their transit as compared with prostaglandin $F_{2\alpha}$ at 43 h after the end of the operation. However, there was no difference between the two drugs for their effect on transit of the liquid marker at any time (Fig. 5). The gastric emptying time for solid markers was 44.9 ± 4.3 h with SK-896 significantly less than that with prostaglandin $F_{2\alpha}$ (Table 1). The small intestinal transit time and the whole intestinal transit time of solid markers with SK-896 were 54.9 ± 3.3 and 73.6 ± 3.5 h, respectively (Table 1). These transit times were also significantly less than those with prostaglandin $F_{2\alpha}$. On the other hand, gastric emptying time and small intestinal

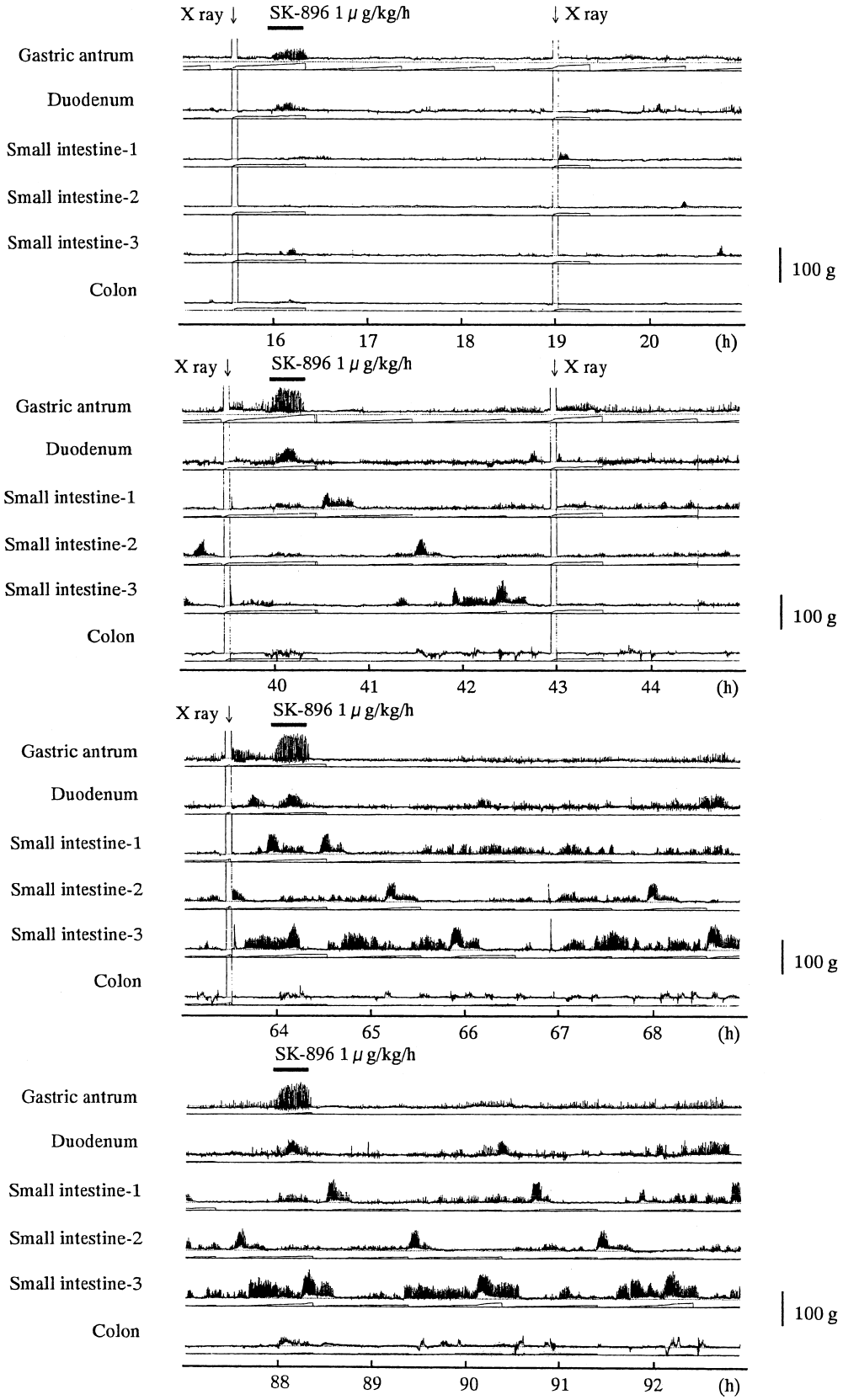

Fig. 1. A typical gastrointestinal motility chart for infusion of SK-896 in a dog with post-operative ileus given solid radio-opaque markers. SK-896 was infused at 1 μg/kg/h for 20 min at 16, 40, 64 or 88 h after laparotomy.

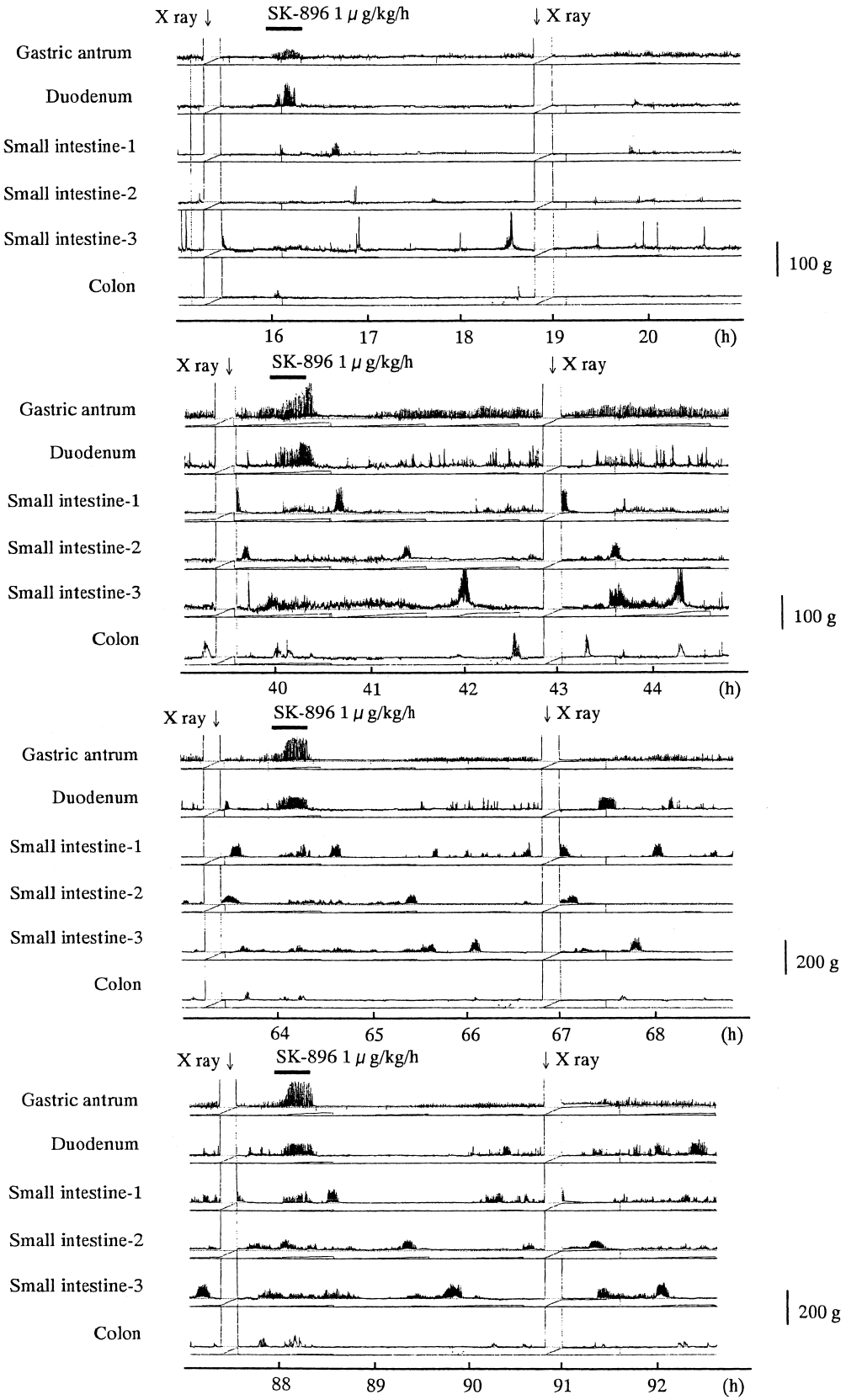

Fig. 2. A typical gastrointestinal motility chart for infusion of SK-896 in a dog with post-operative ileus given barium sulfate. SK-896 was infused at 1 μg/kg/h for 20 min at 16, 40, 64 or 88 h after laparotomy.

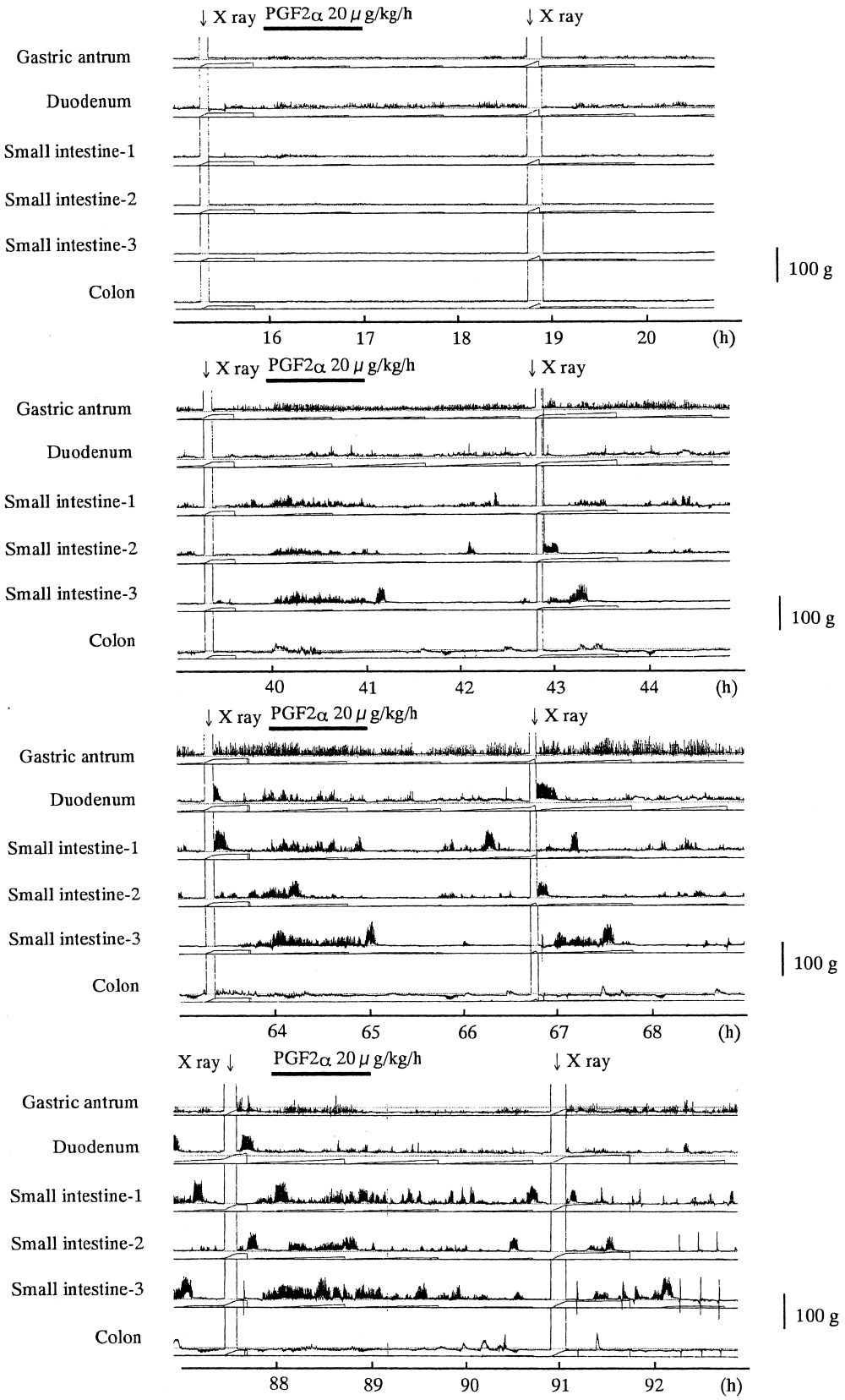

Fig. 3. A typical gastrointestinal motility chart for infusion of prostaglandin $F_{2\alpha}$ in a dog with post-operative ileus given solid radio-opaque markers. Prostaglandin $F_{2\alpha}$ was infused at 20 μg/kg/h for 60 min at 16, 40, 64 or 88 h after laparotomy.

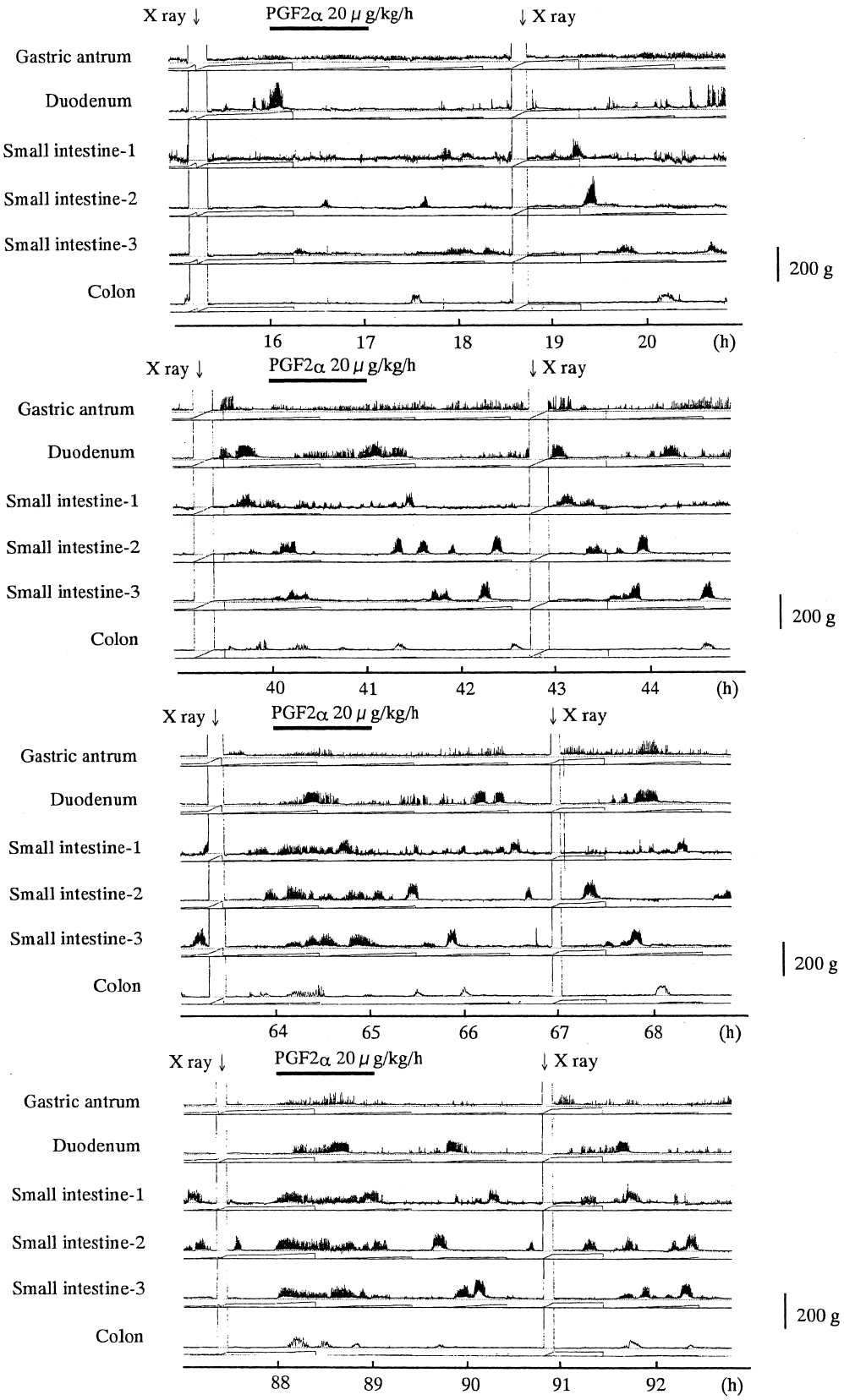

Fig. 4. A typical gastrointestinal motility chart for infusion of prostaglandin $F_{2\alpha}$ in a dog with post-operative ileus given barium sulfate. Prostaglandin $F_{2\alpha}$ was infused at 20 μg/kg/h for 60 min at 16, 40, 64 or 88 h after laparotomy.

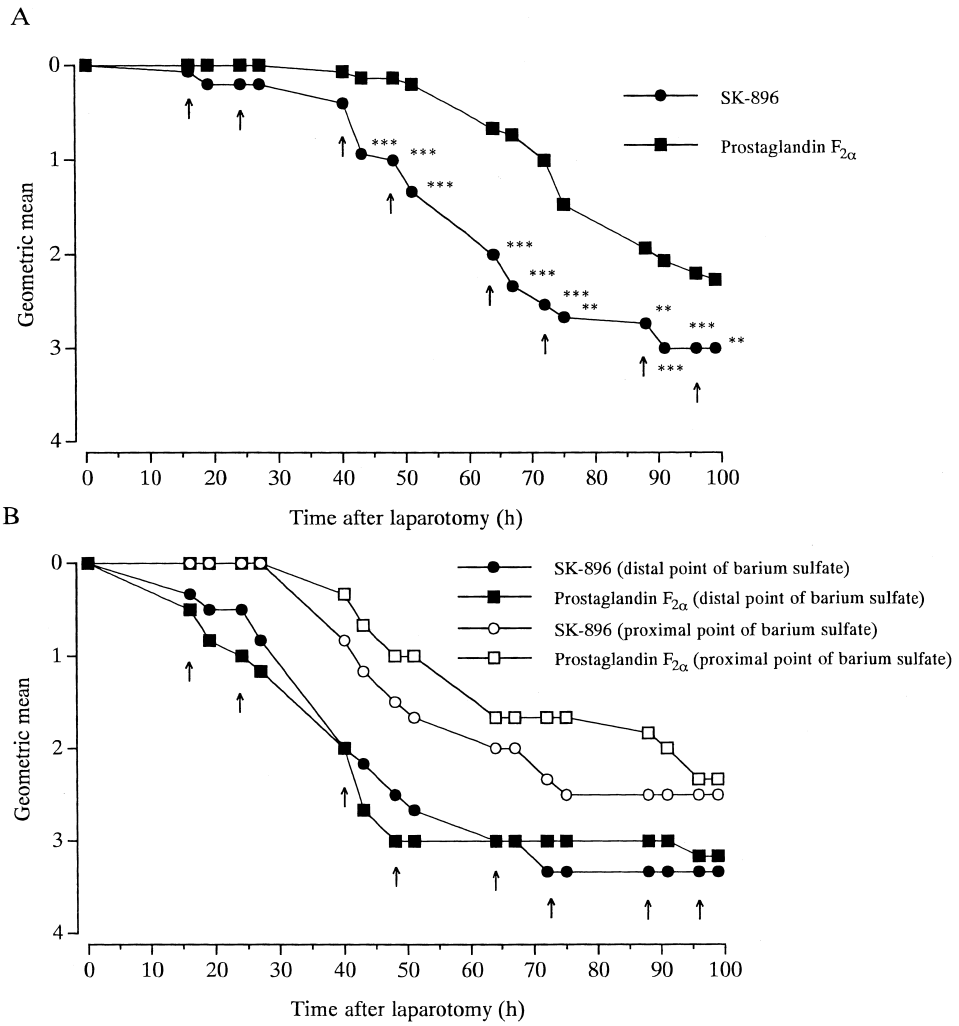

Fig. 5. The effects of SK-896 and prostaglandin $F_{2\alpha}$ on geometric mean values for solid marker (A) and liquid marker (B) in dogs with post-operative ileus. Each point represents the mean for 15 solid markers or six dogs. Each arrow represents the start of infusion of SK-896 or prostaglandin $F_{2\alpha}$ for 20 min or 1 h. $^{**}P < 0.01$, $^{***}P < 0.001$: significant difference determined with the SK-896 and prostaglandin $F_{2\alpha}$ as determined by Mann–Whitney *U*-test.

Table 1
Effects of SK-896 and prostaglandin $F_{2\alpha}$ on time parameters in dogs with post-operative ileus

	Time after laparotomy (h)		
	SK-896	Prostaglandin $F_{2\alpha}$	*P* value
Solid marker			
Intestinal-interdigestive migrating contractions	29.5 ± 3.1	42.2 ± 4.5	0.062
Duodenal-interdigestive migrating contractions	36.3 ± 1.9	46.2 ± 5.8	0.183
Gastric-interdigestive migrating contractions	40.0 ± 0.0	77.8 ± 6.4	0.0004
Gastric emptying	44.9 ± 4.3	74.7 ± 5.0	0.0001
Small intestinal transit	54.9 ± 3.3	78.5 ± 4.2	0.0001
Whole intestinal transit	73.6 ± 3.5	87.7 ± 3.4	0.0075
Liquid marker (barium sulfate)			
Intestinal-interdigestive migrating contractions	28.0 ± 3.2	31.7 ± 1.8	0.304
Duodenal-interdigestive migrating contractions	31.8 ± 3.2	42.8 ± 7.1	0.182
Gastric-interdigestive migrating contractions	36.0 ± 4.0	71.8 ± 9.5	0.0059
Gastric emptying	43.2 ± 2.0	57.0 ± 7.6	0.101
Small intestinal transit	50.3 ± 4.4	59.2 ± 7.5	0.334

Results are means ± S.E.M. for 15 solid markers or six dogs. *P* values were calculated by Student's *t*-test for comparisons between the SK-896-treated group and the prostaglandin $F_{2\alpha}$-treated group.

Table 2
Correlation coefficients between gastrointestinal transit times and the times of first occurrence of various types of interdigestive migrating contractions

Contrast	Solid marker		Liquid marker	
	r	*P*	*r*	*P*
The time of first occurrence of intestinal-interdigestive migrating contractions				
vs. Gastric emptying time	0.677	0.0001	0.510	0.0904
vs. Small intestinal transit time	0.670	0.0001	0.624	0.0302
vs. Whole intestinal transit time	0.613	0.0007	N.D.	N.D.
The time of first occurrence of duodenal-interdigestive migrating contractions				
vs. Gastric emptying time	0.604	0.0009	0.820	0.0011
vs. Small intestinal transit time	0.609	0.0008	0.838	0.0007
vs. Whole intestinal transit time	0.570	0.0019	N.D.	N.D.
The time of first occurrence of gastric-interdigestive migrating contractions				
vs. Gastric emptying time	0.754	< 0.0001	0.479	0.1150
vs. Small intestinal transit time	0.765	< 0.0001	0.391	0.2091
vs. Whole intestinal transit time	0.626	0.0002	N.D.	N.D.

N.D.: not detected. Correlation coefficients (r) were calculated by using linear regression.

transit time of the liquid marker with SK-896 did not differ from those with prostaglandin $F_{2\alpha}$ (Table 1). The whole intestinal transit time of the liquid marker was not determined because the barium sulfate diffused through the gastrointestinal tract over time after its administration.

3.3. Interdigestive migrating contractions and gastrointestinal transit activity

In dogs given the solid marker, SK-896 significantly shortened the time of the first occurrence of gastric-interdigestive migrating contractions. The gastric emptying time and the small and whole intestinal transit times showed good correlation with the time of first occurrence of gastric-interdigestive migrating contractions (Table 2). In the same fashion, SK-896 significantly shortened the time of the first occurrence of gastric-interdigestive migrating contractions in dogs given the liquid marker. However, only the gastric emptying time and the small intestinal transit time were correlated with the time of first occurrence of duodenal-interdigestive migrating contractions (Table 2).

4. Discussion

We now investigated the effects of SK-896 on the induction of gastrointestinal motility and transit in dogs with post-operative ileus. To observe the gastrointestinal motility under awake conditions and without restriction of the dogs, we sutured force transducers at various points in the gastrointestinal tracts. Therefore, it took about 3 h from start to end of the operation and physical damage to gastrointestinal tract from the operation was greater than after laparotomy alone. Furthermore, in order to take X-ray pictures and observe the gastrointestinal transit, we anesthetized the dogs with GOF, which allows early awakening and recovery from suppressed gastrointestinal motility (Tsukamoto et al., 1999). In a previous study, we found that the times of first occurrence of gastric-interdigestive migrating contractions in dogs given the solid and the liquid markers without drug administration to be, respectively, 73.8 and 62.0 h after laparotomy in the same model as in the present study (Tsukamoto et al., 1999). Yokoyama et al. (1995) reported a reappearance time of phase III contractions in the stomach with saline treatment of their model of 105.8 h. It was thought that our model was a milder case than theirs. Morris et al. (1983) observed the disappearance of phase III contractions 2 days after the operation and their reappearance 3 days after the operation. It was thought that our model was at the same level as theirs.

We investigated the dosage and administration frequency of SK-896 in dogs with post-operative ileus in a preliminary study. The times of first occurrence of gastric-interdigestive migrating contractions administered with 0.5, 1.0 and 2.0 $\mu g/kg/h$ of SK-896 for 20 min four-times a day were 37.0 ± 2.7, 36.0 ± 4.2 and 35.0 ± 2.5 h, respectively. The retention volumes of the gastric juice in stomach from 3 to 59 h after laparotomy under the same condition were 738.1 ± 92.8, 543.1 ± 74.4 and 534.7 ± 106.1 ml, respectively, while the time of first occurrence of gastric-interdigestive migrating contractions with twice daily administration of SK-896 (1.0 $\mu g/kg/h$ for 20 min) was 37.0 ± 3.8 h. The retention volume of gastric juice in the stomach from 3 to 59 h after laparotomy at this time was 415.8 ± 35.7 ml. There was no side-effect, such as vomiting under these condition for SK-896 administration. Moreover, prostaglandin $F_{2\alpha}$ is administered twice a day in clinical use. Therefore, we used SK-896 administered twice a day at the dosage of 1.0 $\mu g/kg/h$ for 20 min.

In this post-operative ileus model, SK-896 was able to induce interdigestive migrating contraction-like motility earlier than did prostaglandin $F_{2\alpha}$. In a previous study, we had confirmed that the first occurrence of gastric-interdigestive migrating contractions played an important role in transporting substances in the gastrointestinal tract in the dog with post-operative ileus (Tsukamoto et al., 1999). SK-896 was also able to induce the first occurrence of gastric-interdigestive migrating contractions earlier than that of untreated animals in the same model in the previous study.

The solid marker now used could pass through the gastric pyloric ring and was transported from the stomach to the duodenum by gastric-interdigestive migrating contractions motility; the gastric emptying time of this marker was correlated with the time of first occurrence of gastric-interdigestive migrating contractions. The small intestinal transit time of the solid marker was also correlated with the time of first occurrence of gastric-interdigestive migrating contractions. Moreover, the gastric emptying time, small intestinal transit time and whole intestinal transit time of the solid marker, measured as indexes of gastrointestinal transit ability, were reduced by SK-896, which induced interdigestive migrating contractions-like motility, compared with prostaglandin $F_{2\alpha}$, which induced continuous contractions. These findings confirmed that the gastrointestinal motility effective to transport substances from upper to lower gastrointestinal tract is interdigestive migrating contractions or interdigestive migrating contractions-like motility rather than just continuous contractions.

Clinically, the disorders of gastrointestinal motility referred to as ileus are generally present after laparotomy and require several days for recovery. During the period of post-operative ileus after laparotomy, problems arise with feeding, control of body fluids and wound healing because patients cannot eat. Early recovery from post-operative ileus would thus be beneficial. In addition, ileus after laparotomy is a major impediment to patient recovery, since it necessitates the use of a nasal tube for drainage of retained intragastric fluid and for parenteral feeding. Attempts have, therefore, been made to reduce the duration of post-operative ileus in order to permit removal of the nasal gastric tube as early as possible and to enable oral nutritional eating. It is thought that food residues and secretions remaining in the gastrointestinal tract during ileus cause abdominal distention and disorders. It has been reported that [Leu^{13}]motilin (KW5139), a motilin analogue, significantly decreased gastric juice output after pylorus-preserving pancreatoduodenectomy (Matsunaga et al., 1998). We observed that retention of gastric juice in the stomach from 3 to 59 h after laparotomy was increased without any drug treatment in dogs with post-operative ileus, and the value was 633.4 ± 71.3 ml in the preliminary study. We also confirmed that infused SK-896 was able to decrease the volume of juice, beginning 25 h after the end of laparotomy, and the value was 415.8 ± 35.7 ml. It is thought that this decreasing effect of SK-896 on retention of gastric juice in the stomach was the result of accelerated gastric emptying, subsequent to SK-896-induced gastric-interdigestive migrating contractions.

Prostaglandin $F_{2\alpha}$ may play an important role in the modulation of intestinal motility (Burakoff et al., 1990). It may decrease the neural secretion of norepinephrine and maintain the release of neural acetylcholine (Morris et al., 1983). It has a direct excitatory effect on intestinal smooth muscle, which is Ca^{2+} channel-dependent but independent of intrinsic nerves (Frantzides et al., 1992). It induces contraction of both the circular and longitudinal muscle layers of the intestine in humans (Bennett et al., 1976), and stimulates gastrointestinal motility. In addition, prostaglandin $F_{2\alpha}$ does not inhibit gastric secretion. Prostaglandin $F_{2\alpha}$ increases gallbladder pressure, as does cholecytokinin–pancreozymin, promotes bile acid excretion, and also stimulates duodenal motility (Nakano et al., 1975). It increases the secretion and pressure of jejunum and ileum, causes gastrointestinal motility, and finally induces diarrhea (Bennett, 1970; Cummings et al., 1973; Milton-Thompson et al., 1975). In the present study, prostaglandin $F_{2\alpha}$ enhanced the lower intestine motility but not gastric antrum motility. Imai et al. (1983) reported that infusion of 15 $\mu g/kg/h$ of prostaglandin $F_{2\alpha}$ for 1 h significantly decreased small intestinal transit time compared to that in a control group; however, even infusion of 45 $\mu g/kg/h$ of prostaglandin $F_{2\alpha}$ for 1 h did not affect gastric emptying time compared to that in normal humans. In a recent study, prostaglandin $F_{2\alpha}$ improved the recovery from post-operative ileus when administered after the reappearance of interdigestive migrating contractions (Shibata and Toyoda, 1998). Therefore, the reason why prostaglandin $F_{2\alpha}$ did not have a clear effect on the reappearance of gastric-interdigestive migrating contractions in this present study appeared to be either the difference between its potency in health and in the early period of post-operative ileus or the timing of prostaglandin $F_{2\alpha}$ administration.

In dogs with post-operative ileus, the plasma levels of motilin increased slightly and transiently with the onset of post-operative ileus, but the cyclical peaks in motilin usually found during fasting in healthy subjects were undetectable during the first three post-operative days (Cullen et al., 1994). These findings suggest that the absence of cyclical peaks in motilin results in ileus and that the production of cyclical peaks in motilin level induces recovery from ileus. Hall et al. (1984) reported that exogenously administered motilin induced an increase of the endogenous motilin level. We confirmed that SK-896 0.33 $\mu g/kg$ given i.v. twice a day to dogs with post-operative ileus induced 200–800 pg/ml of endogenous dog motilin 13 h after laparotomy in another study. The area under the curve (0–30 min) of the plasma concentration curve of SK-896 was 21.8–33.3 $ng \cdot min/ml$. Moreover, this endogenous dog motilin disappeared 30 min after the end of SK-896 administration. Therefore, it was thought that ad-

ministered SK-896 induced endogenous dog motilin in the present study. It thus appeared that periodic exogenous administration of motilin-like substances might be able to normalize the cyclical changes in motilin concentrations which are disturbed by laparotomy.

SK-896, a new human motilin analogue, enhanced gastrointestinal motility and shortened the time of first occurrence of gastric-interdigestive migrating contractions, gastric emptying time and the intestinal transit time of radioopaque markers. In conclusion, these results indicate that SK-896 is effective to induce recovery from post-operative ileus.

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