Gastrointestinal Peptide Hormones During Postoperative Ileus
Effect of Octreotide

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The hypothesis was that postoperative ileus might be caused by a disturbed balance between the motor-stimulating hormones, motilin and substance P, and the motor-inhibitory hormone, vasoactive intestinal polypeptide, and that octreotide might prevent this disturbance and so ameliorate the ileus. In 15 conscious dogs with chronic gastrointestinal electrodes, electrical activity was recorded and blood was drawn for radioimmunoassay of motilin, substance P, and vasoactive intestinal peptide (VIP) during fasting and after a liquid meal. Ileus was then induced by celiotomy and intestinal abrasion. During and after operation, five dogs received 154 mM NaCl only, five dogs octreotide, 0.19 μg/kg/hr, and five octreotide, 0.83 μg/kg/hr. Plasma levels of motilin, substance P, and VIP were changed little by operation, but cyclical increases in plasma motilin, which occurred preoperatively during phase III of the interdigestive myoelectric complex, were completely abolished postoperatively during ileus, as was the complex itself. Octreotide ameliorated the ileus and restored the interdigestive complexes, but it decreased plasma motilin and did not restore the cyclic increases in motilin found in health, nor did it alter plasma substance P and VIP. In conclusion, octreotide ameliorates postoperative ileus, but it does not do so by increasing plasma motilin or substance P or decreasing plasma VIP.

KEY WORDS: ileus; motilin; substance P; vasoactive intestinal peptide; octreotide.

We demonstrated recently that octreotide shortens the duration of postoperative ileus in the small bowel and colon of dogs (1). The result suggested that octreotide ameliorates ileus by preventing a disturbance in the balance of gastrointestinal peptides that stimulate and those that inhibit gastrointestinal motility and transit. The disturbed peptides might include motilin, a stimulating hormone that initiates the interdigestive migrating myoelectric complex (MMC) in the duodenum (2); substance P, another stimulating hormone; and vasoactive intestinal peptide (VIP), an inhibitory neuropeptide (3–5). Others have also suggested that these three peptides have a role in the disrupted motility and transit characteristic of postoperative ileus (6–9).

Plasma motilin concentrations vary cyclically with the phases of the interdigestive MMC, with peak concentrations occurring during phase III (10–13). The interdigestive MMCs are abolished during postoperative ileus (14), but the effect of ileus on
plasma motilin has not been fully evaluated. In regard to substance P, rats treated with capsaicin, which defunctionalizes afferent sensory neurons and presumably prevents substance P release and subsequent inhibitory transmitter release, had more rapid gastrointestinal transit following induction of ileus than control animals (6, 7). Moreover, animals treated with antibodies to VIP maintained gastric motility after an intraabdominal operation (8). The beneficial action of octreotide in postoperative ileus could be due in part to the inhibition of VIP release. Octreotide is known to inhibit VIP release (15).

The aim of this experiment was to measure the plasma concentrations of motilin, substance P, and VIP in healthy dogs and in dogs with postoperative ileus. Some of the dogs with ileus received no specific treatment, while others received octreotide.

**MATERIALS AND METHODS**

Fifteen adult female dogs weighing 16–24 kg had Ag–AgCl monopolar recording electrodes placed on the serosal surface of the stomach, 2 and 4 cm orad to the pylorus, on the duodenum 5 and 20 cm aborad to the pylorus, and on the jejunum at four sites spaced at 30-cm intervals (Figure 1). All electrodes were connected by insulated copper wires to a multioutlet connector in a stainless steel cannula positioned in and anchored to the left inferior abdominal wall. Five of the dogs underwent additional placement of a heparinized, permanent, indwelling, silastic catheter through a branch of the splenic vein into the portal venous system. The catheter was connected to a stainless steel cannula and positioned in and anchored to the left superior abdominal wall for repeated portal venous blood sampling. The dogs were allowed to recover from the operation for 12 days before studies were begun. All procedures and animal care were carried out according to guidelines set forth by the Institutional Animal Care and Use Committee of the Mayo Foundation, Rochester, Minnesota, which approved the protocol on March 25, 1991.

**Preoperative Studies**

Each dog underwent two complete preoperative studies of gastrointestinal myoelectric activity and peripheral blood sampling for radioimmunoassay of motilin. Additionally, the dogs with the indwelling silastic catheters underwent portal venous blood sampling for radioimmunoassay of substance P and VIP.

After an overnight fast, each dog's electrodes were connected to an amplifier and a pen recorder (Gould model 2600, Gould Inc., Wilmington, Massachusetts) that ran at a paper speed of 1.5 cm/min. Myoelectric activity was recorded during fasting for 4 hr to determine the individual phases of the MMC. The dogs were then given a meal consisting of 250 ml of 5% dextrose and 50 ml of beef broth (Campbell Soup, Inc., Paris, Texas), and gastrointestinal myoelectric activity was recorded for another 2 hr. Peripheral blood for motilin radioimmunoassay was drawn during phases I, II, and III of the MMC as identified by the criteria of Code and Marlett (16), and then every half hour following the ingestion of the liquid meal. Portal venous blood was drawn at the beginning and end of each study. Both peripheral venous blood and portal venous blood were collected into glass tubes containing 4.5 mg of ethylene diamine tetraacetic acid (EDTA). The plasma was isolated and stored at −76 °F for future analysis.

**Induction of Ileus**

After an overnight fast, the dogs were anesthetized with methohexital sodium (12.5 mg/kg), and a 10-cm midline lower abdominal incision was made. A 15-cm segment of small bowel was exteriorized, rubbed for 5 min with a sterile sponge, and then left exposed to air for 30 min. This operation consistently produces ileus (1, 14). After returning the bowel to the abdomen and wound closure, the dog was allowed to recover for 2 hr and then fasting and fed studies repeated. The dogs were given butorphanol tartrate, 5 mg intramuscularly for pain, immediately after wound closure and on the evening of the operative day.

The 15 dogs were randomized into three groups consisting of five dogs per group. The first group (controls) was given 0.9% NaCl 2 ml/8 hr subcutaneously. The