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Salutary Effects of Tachykinin Receptor Antagonists in a Rat Model of Postoperative Ileus[1]

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Background. **Postoperative ileus (PI) is a common surgical complication treated mainly with supportive measures. Tachykinins control gastrointestinal motility and modulate somatic and visceral pain sensation; therefore, the effect of tachykinin receptor antagonists in a rat model of PI using NK_{1-3} antagonists, SR140333, SR48968, and SR142801, was investigated.**

Materials and methods. **Intestinal transit was measured as Evans blue migration after varied nociceptive stimuli: skin incision (SI), laparotomy (LAP), or laparotomy plus gut manipulation (L + M) in anesthetized rats.**

Results. **Diethyl ether anesthesia and SI did not influence the intestinal transit of the dye in comparison to untreated animals—UN: 61.17 ± 5.47, 62.10 ± 8.30, and 56.70 ± 4.10 cm, respectively. In contrast LAP and L + M have significantly reduced intestinal motility to 26.40 ± 2.07 and 9.70 ± 1.15 cm, respectively. SR140333 (3–30 μg/kg), SR48968 (1–30 μg/kg), and SR142801 (3–10 μg/kg) reversed the additional inhibitory effects of gut manipulation subsequent to LAP dose-dependently, the dye transit returning with the use of the most effective antagonist doses up to 25.28 ± 1.08, 21.70 ± 0.19, and 25.0 ± 1.34 cm. The combinations of submaximal doses of NK_1 and NK_3, NK_2 and NK_3 and NK_1, and NK_2 and NK_3 antagonists were not more effective than a single-agent regimen. On the other hand SR140333 and SR48968 (NK_1 + NK_2 antagonists) acted additively, the intestinal transit reaching 26.60 ± 0.85 cm. SR140333, SR48968, and SR142801 have not affected the intestinal passage in UN rats or those undergoing SI or LAP.**

Conclusions. **SR140333, SR48968, and SR142801 exert a salutary action on suppressed gut motility following surgical manipulation of the gut, the combination of NK_1 and NK_2 antagonists being most beneficial.**

Key Words: **postoperative ileus; rats; tachykinin receptor antagonists.**

INTRODUCTION

Postoperative ileus (PI) is a spontaneously reversible, transient inhibition of propulsive bowel motility occurring after major surgical interventions and especially those that involve an open technique abdominal operation leading to an increased morbidity and higher hospitalization costs [1]. Due to an unclear etiology, supportive measures remain the cornerstone of the current therapy despite achieving some progress with multimodal postsurgical rehabilitation programs and the introduction of peripherally acting opioid antagonists [1, 2].

It seems that the inhibitory neuronal arches, with afferent capsaicin-sensitive unmyelinated fibers and efferent adrenergic and nitrergic neurons, play a prominent role in the development of PI. In concert with this hypothesis, thoracic epidural anesthesia improved PI outcome in humans, whereas the inhibition of nitric oxide synthase (NOS) reversed the intestinal transit migration in rodents [3, 4].

The enteric nervous system produces a number of inhibitory (e.g., NO, VIP, CO) and stimulatory neurotransmitters (e.g., substance P) [5]. Tachykinins belong to the largest peptide family with three main subtypes of

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receptors present in rat intestinal smooth muscle cells: NK_1, NK_2, and NK_3 [6]. Major tachykinins such as substance P (SP) and neurokinins A and B (NKA and NKB) bind to all of these the receptors with varied degrees of affinity [7]. Tachykinins are most frequently an excitatory transmitters in the gut; however, their net effect depends on the animal species, gut segment, the profile of activated receptors, and other mediators acting at target sites. The main sources of neuronal tachykinins in the gut are the intrinsic enteric neurons of myenteric and the submucosal plexuses together with the extrinsic primary afferent fibers. Moreover many C-afferent fibers possess tachykinin receptors that can be sensitized by mechanical stimulation or an induction of an inflammatory process [8]. NK_1, NK_2, and NK_3 receptors are involved in the modulation of visceral hypersensitivity evoked by colorectal distension or inflammation [9, 10]

Octreotide, VIP, SP, and CGRP antagonists ameliorate the postsurgical inhibition of gastric and small intestine motility in dogs and rats, implying that multiple tachykinin substances are involved in the pathogenesis of PI [11, 12].

The activity of tachykinins in the gut and the availability of potent synthetic tachykinin receptor antagonists, SR140333, SR48968, and SR142801, enabled a study of the effect of NK_{1-3} receptor blockade in a rat model of PI. Due to conflicting reports in the literature, it was investigated whether in a combination of NK_{1-3} receptor antagonists could potentially exert an additive salutary effect on the small bowel motility following a surgical insult.

MATERIALS AND METHODS

Surgical Protocol

The Bioethics Committee of the Medical University of Gdańsk approved the experimental procedures. Male albino Wistar rats (180–250 g) were fasted for 48 h, maintaining free access to tap water. Rats were randomly divided into four groups: one control group (untreated animals) and three groups exposed to surgical insult under diethyl ester anesthesia as previously described [3]. Rats from the second group underwent skin incision after having abdominal hair shaven and skin disinfected with 70% ethanol. In the third group, the animals underwent laparotomy. Animals from the fourth group were exposed to laparotomy and subsequent gut evisceration followed by mechanical stimulation of cecum and small intestine. Briefly, the small intestine and cecum were pulled out of the abdominal cavity and gently spread between two layers of damp, sterile gauze. The small intestine was carefully touched by two wet cotton bud applicators from cecum upward, until the duodenal end of the intestine was reached. This procedure was repeated six times within 10 min, and then the cecum and small intestine were returned to the abdominal cavity and the surgical wound was sutured. After the operation, the rats recovered for 1 h. Recovery time was based on the findings of the pilot experiments that diethyl ester anesthesia affects gastrointestinal (GI) motility for approximately 1 h. Subsequently, all animals received 0.15 ml Evans blue via an orogastric tube and 30 min later the animals were sacrificed by cardiotomy under deep ether anesthesia. The small intestines were excised and, to avoid tissue stretching, gently laid on corkboard for measurements, which consisted of establishing the most distal point of dye migration from the pylorus. A blinded observer, unaware of the treatment the animals were receiving, performed measurements. The intestinal transit was measured from the pylorus to the most distal point of dye migration. Experimental details are depicted in Fig. 1.

The Effects of Tachykinin Receptor Antagonists on the Intestinal Transit

Initially the effects of intraperitoneally (i.p.) injected SR 140333 (3–100 μg/kg), SR 48968 (1–30 μg/kg), and SR142801 (3–30 μg/kg) were investigated in untreated or anesthetized rats and animals exposed to skin incision, laparotomy, laparotomy, and gut manipulation. Subsequently, a combination of submaximal doses of NK_1 + NK_2 (SR140333 + SR48968; 10 + 3 μg/kg), NK_1 + NK_3 (SR140333 + SR142801; 10 + 6 μg/kg), NK_2 + NK_3 (SR48968 + SR142801; 3 + 6 μg/kg), or NK_1 + NK_2 + NK_3 receptor antagonists (SR 140333 + SR48968 + SR142801; 10 + 3 + 6 μg/kg) were investigated in rats undergoing laparotomy followed by gut manipulation. Respective controls in each experimental group received an equal volume of saline (0.9% NaCl) instead of test article. All tested agents or saline was administered 1.5 h before surgical procedures.

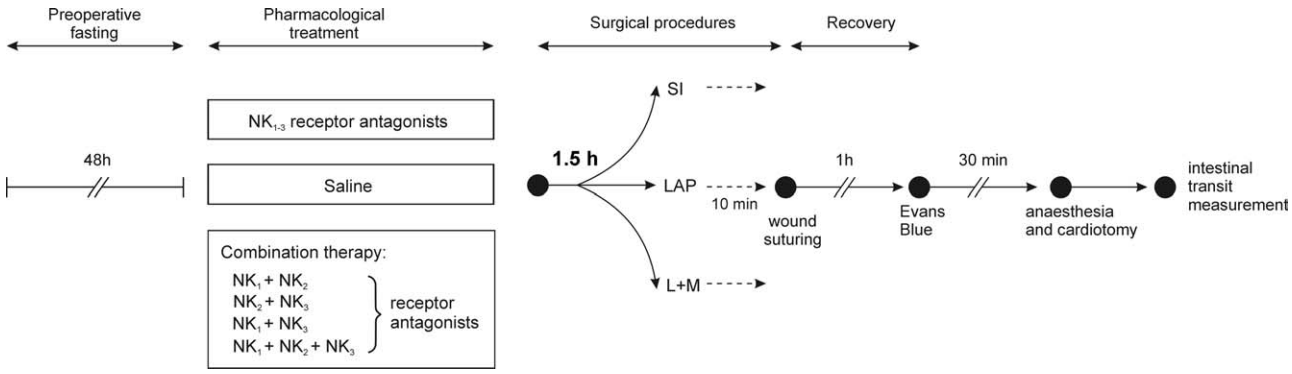

FIG. 1. The effects of NK_{1-3} antagonists, SR140333 (3–100 μg/kg), SR48968 (1–30 μg/kg), SR142801(3–30 μg/kg), administered separately or in combination were tested on the intestinal transit of Evans blue, after surgical intervention in rats subjected to different nociceptive stimuli: skin incision (SI), laparotomy (L), or laparotomy followed by gut handling (L + M). Respective controls in each experimental group received an equal volume of saline (0.9% NaCl) instead of test article. All tested agents or saline were administered 1.5 h before surgical procedures.