

GHRELIN AGONIST ACTIVITY IN A RAT MODEL OF POSTOPERATIVE ILEUS AND OPIOID-DELAYED GASTROINTESTINAL MOTILITY

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Acute postoperative ileus (POI) is the product of two main mechanisms: (1) disruption of spinal and supraspinal signaling pathways as a consequence of surgical injury and (2) reduction in propulsive gastrointestinal motility as a side effect of opioid analgesics administered for post-surgical pain. Although opioid antagonists may be used to treat the latter mechanism, no single agent has been reported to potently address both aspects of POI. TZP-101 is a novel ghrelin receptor agonist with selective gastroprokinetic activity. The aim of this study was to determine whether TZP-101 could effectively treat both the individual and combined components of acute POI in a rat model. **Methods.** POI was induced by surgery [i.e. laparotomy and manipulation of the bowel, model 1], pretreatment with morphine (3 mg/kg s.c.) [model 2] or a combination of both [model 3]. The role of ghrelin receptors in POI was investigated by examining the ability of TZP-101 to reverse delayed gastric emptying in all 3 models. Gastric retention was measured 15-min after co-incident, intragastric administration of ^{99m}Tc labeled methylcellulose and intravenous administration of TZP-101 (30-1000 µg/kg) in fasted rats. **Results:** As expected, gastric emptying of the radiolabeled meal was delayed in all 3 models in vehicle-treated subjects (Table 1) in comparison to non-operated, morphine-naïve controls (30.4±4.7%, n=8). TZP-101 dose-dependently normalized gastric emptying with similar efficacy and potency in all 3 models (Table 1). **Summary:** Selective activation of ghrelin receptors resulted in a complete recovery of impaired gastric emptying induced by surgery alone, morphine alone or a combination of surgery and morphine. The unique finding that there was no diminution of TZP-101 potency in the combination model suggests that the therapeutic effect of TZP-101 against the delay in GI transit consequent to morphine treatment and surgery is due to the activation of a common prokinetic pathway.

Table 1

Treatment (6-8 rats per dose)	Gastric Emptying (% gastric residue)		
	Surgery	Morphine	Surgery + Morphine
Vehicle	73.8±4.6	67.0±5.8	70.5±5.6
TZP-101 30 µg/kg	54.9±6.6	-	52.0±6.9
TZP-101 100 µg/kg	50.0±7.5*	-	45.7±1.5** -
TZP-101 300 µg/kg	43.4±7.8**	45.4±12.4*	37.1±6.3***
TZP-101 1 mg/kg	28.2±7.7***	29.8±6.8***	28.3±6.7***

One-way ANOVA with Bonferroni's MCT. * p<0.05, ** p<0.01, ***p<0.001 compared to vehicle