

## MOTILIN RECEPTOR ANTAGONISM ATTENUATES NATURALLY OCCURRING MMCs AND REVERSES MOTILIN-IMPAIRED GASTRIC ACCOMMODATION IN CONSCIOUS DOGS

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**Background:** Motilin has been postulated to have a role as an interdigestive hormone regulating antral migrating motor complex (MMC) in various species, including dog and man. A potent and selective antagonist is required to establish motilin's physiological role, but no such antagonist has yet been described. The aim of this study was to investigate the role of motilin in the interdigestive and post-prandial periods in conscious dogs using a novel, selective and potent motilin antagonist (JTZ-2002). **Methods:** Gastrointestinal motility was measured for 24h by telemetry in freely moving Beagle dogs (F) instrumented with strain gauges on antrum and duodenum. In a second series of experiments, fundic accommodation in response to a 200ml milk meal was measured using a bartostat. **Results:** Following an overnight fast, JTZ-2002 (0.1, 0.3, 1 mg/kg, i.v.) suppressed the regular occurrence of phase III activity of the MMC in a dose-dependent manner. Baseline MMC-interval during the 4h period before drug was  $86 \pm 5$  min and average contraction amplitude (CA) was  $276.7 \pm 66.0$  mN (mean  $\pm$  SEM, n=6). After 1 mg/kg dose, time to first MMC was  $225 \pm 31$  min vs.  $99 \pm 15$  min in controls ( $P < 0.01$ , n=4) and CA was reduced to  $5 \pm 2\%$  of baseline CA over the first hour and recovered to  $52 \pm 21\%$  after 4h. The 0.1 and 0.3 mg/kg doses also suppressed MMC activity where CA returned to baseline levels after 3h (n=2). After a standard 75g meal, JTZ-2002 (0.3 mg/kg, i.v., admin. 2h after meal) suppressed post-prandial CA during the first hour to  $58 \pm 4\%$  of pre-drug baseline (n=2) whereas vehicle treatment maintained CA at  $106 \pm 10\%$  (n=4). Although JTZ-2002 (1 mg/kg, i.v.) did not influence normal fundic accommodation in response to a milk meal ( $AUC_{1h}$   $296 \pm 39$  vs.  $365 \pm 26$  ml.h in control,  $P > 0.05$ , n=5), JTZ-2002 (0.3 mg/kg, i.v.) did antagonize the fundic contraction induced by infusion of exogenous motilin (0.01 mg/kg/h, i.v.); AUC of fundic relaxation (0-to-5 min.) for vehicle administration was  $18.7 \pm 3.3$  vs.  $27.3 \pm 3.5$  ml.h after JTZ-2002 (n=4,  $P < 0.05$ ). **Conclusions:** These data provide the first pharmacological evidence that motilin is an endocrine regulator of the phase III contraction of the MMC and further suggest that motilin also has a role in stimulating antral and duodenal contractions in the post-prandial period. Thus, motilin antagonists may have a role in the treatment of gut motility disorders characterized by heightened spontaneous activity in the upper gut and/or poor gastric accommodation.