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Constipation Evoked by 5-HT_3-Receptor Antagonism: Evidence for Heterogeneous Efficacy among Different Antagonists in Guinea-pigs

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Abstract—The abilities of selective 5-HT_3-receptor antagonists to evoke constipation were examined in conscious guinea-pigs and in preparations of guinea-pig isolated colon. Compared with vehicle-treated guinea-pigs, acute doses of granisetron (0·1, 1 and 10 mg kg^{-1}, i.p.) and tropisetron (10 mg kg^{-1}, i.p., but not 1 and 0.1 mg kg^{-1}, i.p.) significantly ($P < 0·05$) reduced the total number of faecal pellets excreted during a 12-h observation period. By contrast, BRL 46470 (0·1–10 mg kg^{-1}, i.p.) had no significant effect on the incidence of defecation. Mid-to-distal lengths of guinea-pig isolated colon spontaneously expelled faecal pellets. Granisetron (0·1 and 1 μM) and tropisetron (1 μM) reduced or prevented the rate at which they were spontaneously expelled. Morphine (0·1 μM) and clonidine (10 nM) also slowed faecal pellet transit time. Naloxone (0·1 μM) had no effects alone, but reversed the actions of granisetron, morphine and clonidine. BRL 46470 (1 μM) had no significant effect on the transit of faecal pellets in guinea-pig isolated colon. In segments of guinea-pig isolated colon which did not contain faecal pellets, granisetron, tropisetron and BRL 46470 antagonized the ability of 5-HT to evoke cholinergically-mediated contractions of the longitudinal muscle. The respective pA_2 values and slopes of the Schild plots were 8·5 ± 0·05, slope 1·06 ± 0·03; 8·5 ± 0·1, slope 0·91 ± 0·04; and 7·9 ± 0·1, slope 0·93 ± 0·05. Our experiments suggest that not all 5-HT_3-receptor antagonists are the same. In particular, BRL 46470 does not prevent defecation or faecal pellet expulsion in guinea-pig colon, even though this compound is an effective 5-HT_3-receptor antagonist in the same tissue. For the 5-HT_3-receptor antagonists which did cause constipation, the effects can be at least partly attributed to an indirect opioid-dependent action within the colonic enteric nervous system.

Within the gastrointestinal tract, 5-hydroxytryptamine (5-HT) 5-HT_3 receptors are involved in the mechanisms of cytotoxic-induced nausea and vomiting (Sanger 1993), visceral pain (Moss & Sanger 1990; Banner & Sanger 1992) and the watery diarrhoea evoked by medullary carcinoids, cholera toxin or by 5-HT (Anderson et al 1987; Coupar et al 1988; Buchheit 1989).

5-HT_3-receptor antagonists usually have little or no effect on the motility of the healthy upper gastrointestinal tract (Sanger 1992). However, acute doses of these drugs are reported to cause constipation in volunteers (e.g. tropisetron and granisetron: Stacher et al (1989); Upward et al (1990)), suggesting a role for the 5-HT_3 receptor in the normal physiology of defecation. We have, therefore, investigated the actions of granisetron, tropisetron and a new 5-HT_3-receptor antagonist, BRL 46470 (endo-*n*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)3,2-dihydro-3,3-dimethylindole-1-carboxamide (Blackburn et al 1993)), on both the frequency of defecation in conscious guinea-pigs and on the ability of the guinea-pig isolated colon to expel faecal pellets. The resultant pharmacology supports our previous view (Moss & Sanger 1990) that not all 5-HT_3-receptor antagonists behave in the same way.

Materials and Methods

Faecal pellet output from conscious guinea-pigs

Male guinea-pigs (Dunkin Hartley, 250–450 g) were transferred to a constant low-level light room seven days before experimentation (with free access to food and water), where they remained throughout the experiment. Twenty-four hours before each experiment, the guinea-pigs were weighed and split randomly into four groups, each containing six animals. Guinea-pigs were then transferred, in pairs, to wire-bottom metabolic cages, again with free access to food and water. On the day of the experiment (0900 h), each group of guinea-pigs was injected intraperitoneally (i.p.) with volumes of warmed 0·9% NaCl (saline) (0·25–0·45 mL; 37°C) or with 0·1, 1·0 or 10·0 mg kg^{-1} of either granisetron, tropisetron or BRL 46470. The number of faecal pellets produced by each pair of guinea-pigs at 1, 3, 5, 8, 10, and 12 h post dosing was then monitored. A minimum of four pairs of animals was used to study each concentration of each antagonist.

Faecal pellet output from guinea-pig isolated colon

The mid-to-distal colon (about 25 cm) was removed from adult male albino guinea-pigs (250–450 g). These were then immediately placed in a horizontal organ bath (50-mL volume) containing Krebs solution (mM: NaCl 121·5, $CaCl_2$ 2·5, KH_2PO_4 1·2, KCl 4·7, $MgSO_4$ 1·2, $NaHCO_3$ 25·0, glucose 5·6) bubbled with 5% CO_2 in O_2 and maintained at 37°C; the Krebs solution was then perfused through the bath at a constant rate of 5 mL min^{-1} throughout the experiment.

The colon was secured within the bath by frog heart clips attached at regular intervals along a stainless steel bar fitted to the base of the organ bath. Care was taken to ensure that

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faecal pellet movement was not obstructed by the clips. Movement of the faecal pellets always occurred in an anal direction. The times taken for each successive pellet to arrive at a transducer fixed approximately two thirds along the intestine was then recorded. After approximately consistent control readings were obtained (after 30–40% of the pellets were expelled; n = 3 minimum), the bath was drained and refilled with warmed Krebs solution containing the compound under investigation. If the compound failed to prevent or inhibit pellet movement, the colon was allowed to empty. If the compound reduced or prevented pellet movement, the compound was left in contact with the colon for 60 min. If the colon had not discharged its contents within this period, the bath was drained, re-filled and then perfused for 60 min with Krebs solution containing the same compound plus naloxone (0·1 μM). Preparations containing less than 12 pellets were disregarded. Each drug was investigated in a minimum of six colons.

5-HT-evoked contractions of guinea-pig isolated colon

Segments of distal colon (2–3 cm in length) were suspended under a 1 g load in 10 mL-tissue baths containing Krebs solution. Tissues were maintained at 37 ± 1°C and gassed with 5% CO_2 in O_2. Responses were registered and magnified 6–18 times with isotonic transducers. All experiments were carried out in the presence of methiothepin (0.1 μM) to block effects of 5-HT at the 5-HT$_1$-like and 5-HT$_2$ receptors and 5-methoxytryptamine (5-MeOT, 10 μM) to desensitize the 5-HT$_4$ receptor (Craig et al 1990).

In each tissue, two non-cumulative concentration-response curves were constructed to 5-HT (0·1–100 μM) using a 30-s contact time and a 15-min dose cycle. One hour was allowed before construction of the second concentration-response curve to 5-HT, during which time the tissues were washed every 15 min with Krebs solution containing the appropriate concentration of antagonist under observation. Responses were expressed as a percentage of the maximum 5-HT-evoked contraction obtained in the control curve in each tissue. All agonist concentration-effect curves were fitted using a non-linear iterative fitting program (Kaleidagraph, Synergy Software, PCS Inc., Reading, PA, USA) according to the following relationship (Parker & Waud 1971):

$$E = \frac{M[A]^p}{[A]^p + [K]^p}$$

This relationship describes a curve with maximum response M, an EC50 equal to K and a slope determined by the power p. [A] represents agonist concentration and E is response. Values of pA_2 were calculated using the method of Arunlakshana & Schild (1959).

Statistical analysis

For the in-vivo experiments, the results are expressed as mean ± standard error of the mean (s.e.m.) and the effects of the 5-HT$_3$-receptor antagonists were compared with the effects of saline (dosed on the same day) using the Student's unpaired *t*-test. A *P* value of 0·05 or less was taken to be significant.

For the in-vitro experiments on faecal pellet output, the effects of the various treatments were compared with the faecal pellet transit times measured before any drug addition to the bathing solution. Analysis was carried out using a weighted analysis of variance method on log-transformed data. The mean ± s.e.m. was calculated and re-expressed in the original scale (i.e. antilog of mean = geometric mean).

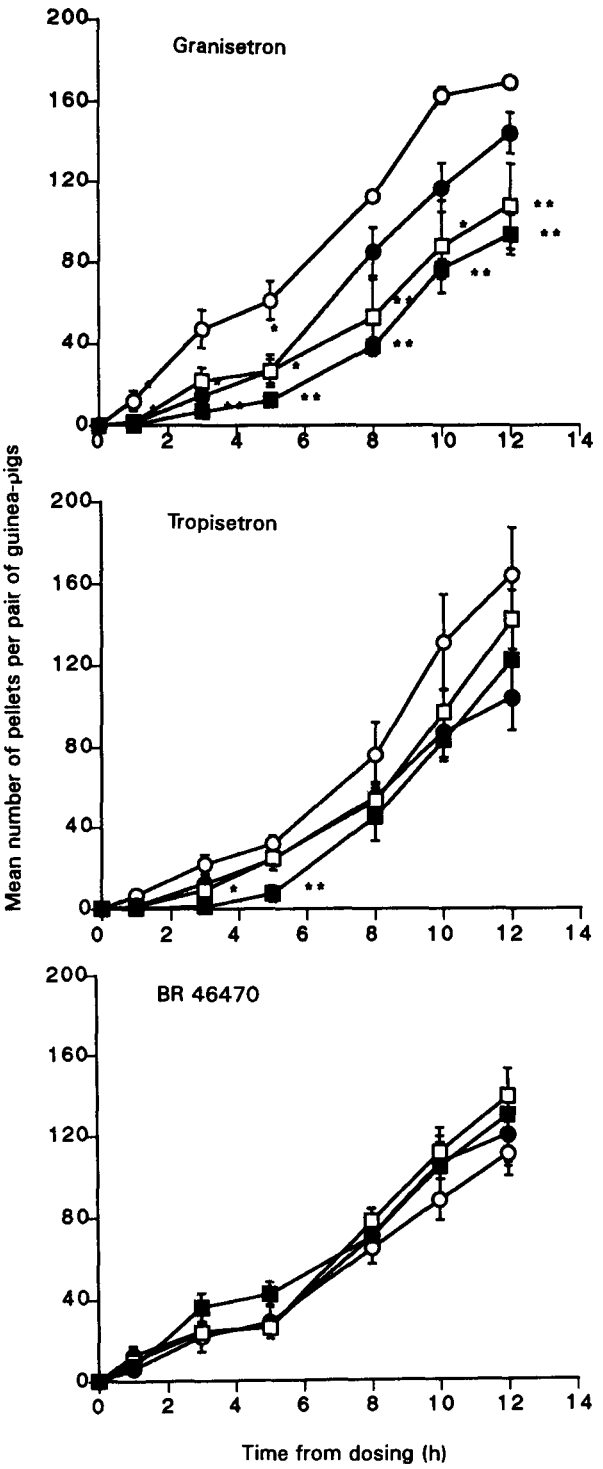

FIG. 1. The effects of granisetron, tropisetron and BRL 46470 on faecal pellet output over a 12-h period in conscious guinea-pigs. Each compound was tested at 0·1 (●), 1 (□) and 10 (■) mg kg^{-1} and results were compared with saline controls (○). The number of pellets produced per pair of guinea-pigs was expressed as mean ± s.e.m. A minimum of four pairs of animals was used in each study. *P < 0·05, **P < 0·01.

Table 1. The effects of solvent, naloxone, granisetron, tropisetron, BRL 46470, morphine and clonidine on faecal pellet transit time in isolated sections of guinea-pig mid-to-distal colon.

Drug	Concn (μM)	Faecal pellet transit time (s)
Control		52 ± 7
Solvent		57 ± 5
Naloxone	0·1	52 ± 6
Granisetron	0·1	102 ± 15*
	1	190 ± 23**
Tropisetron	1	105 ± 21*
BRL 46470	1	83 ± 15
Morphine	0·1	403 ± 96***
Clonidine	0·01	1945 ± 588***

Analysis was carried out using a weighted analysis of variance method on log-transformed data. Results are expressed as mean ± s.e.m. Each drug was examined in a minimum of six colons. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

For the in-vitro tissue bath experiments, pA_2 values for granisetron, tropisetron and BRL 46470 vs 5-HT were determined on individual curves by the method of Arunlakshana & Schild (1959). The slope and the intercept of the resulting straight line with the abscissa were determined by linear regression. Results were then expressed as a mean ± s.e.m. for a minimum of four tissues.

Drugs used

The following drugs were dissolved in Krebs solution: 5-hydroxytryptamine creatinine sulphate (Sigma, Poole, UK), 5-methoxytryptamine hydrochloride (Aldrich, Milwaukee, USA), morphine sulphate (Sigma), clonidine hydrochloride (Boehringer Ingelheim, Lewes, East Sussex, UK), naloxone hydrochloride (Sigma), methiothepin maleate (Roche), granisetron, tropisetron (synthesized in-house) and BRL 46470 (endo-*n*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)3,2-dihydro-3,3-dimethylindole-1-carboxamide, synthesized in-house).

Results

Faecal pellet output from conscious guinea-pigs

Granisetron and tropisetron significantly reduced the number of faecal pellets excreted over a 12-h period. In this action, granisetron was active at 0·1, 1 and 10 mg kg^{-1} (i.p.) whereas only 10 mg kg^{-1} (i.p.) tropisetron significantly reduced the number of faecal pellets excreted. By contrast, BRL 46470 had no consistent ability to reduce faecal pellet excretion at any of the doses tested (0·1, 1 and 10 mg kg^{-1}, i.p.; Fig. 1).

Table 2. The ability of naloxone (0·1 μM) to reverse the constipatory effects of granisetron, morphine and clonidine in the guinea-pig isolated mid-to-distal colon.

Drug	Concn (μM)	Faecal pellet transit time (s)	
		Without naloxone	With naloxone
Krebs solution		82 ± 20	
Granisetron	1	292 ± 65**	73 ± 12
Krebs solution		62 ± 8	
Morphine	0·1	387 ± 112***	97 ± 21
Krebs solution		87 ± 15	
Clonidine	0·01	1945 ± 588***	148 ± 37*

Analysis was carried out using a weighted analysis of variance method on log-transformed data. Results are expressed as mean ± s.e.m. Each drug was examined in a minimum of six colons. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

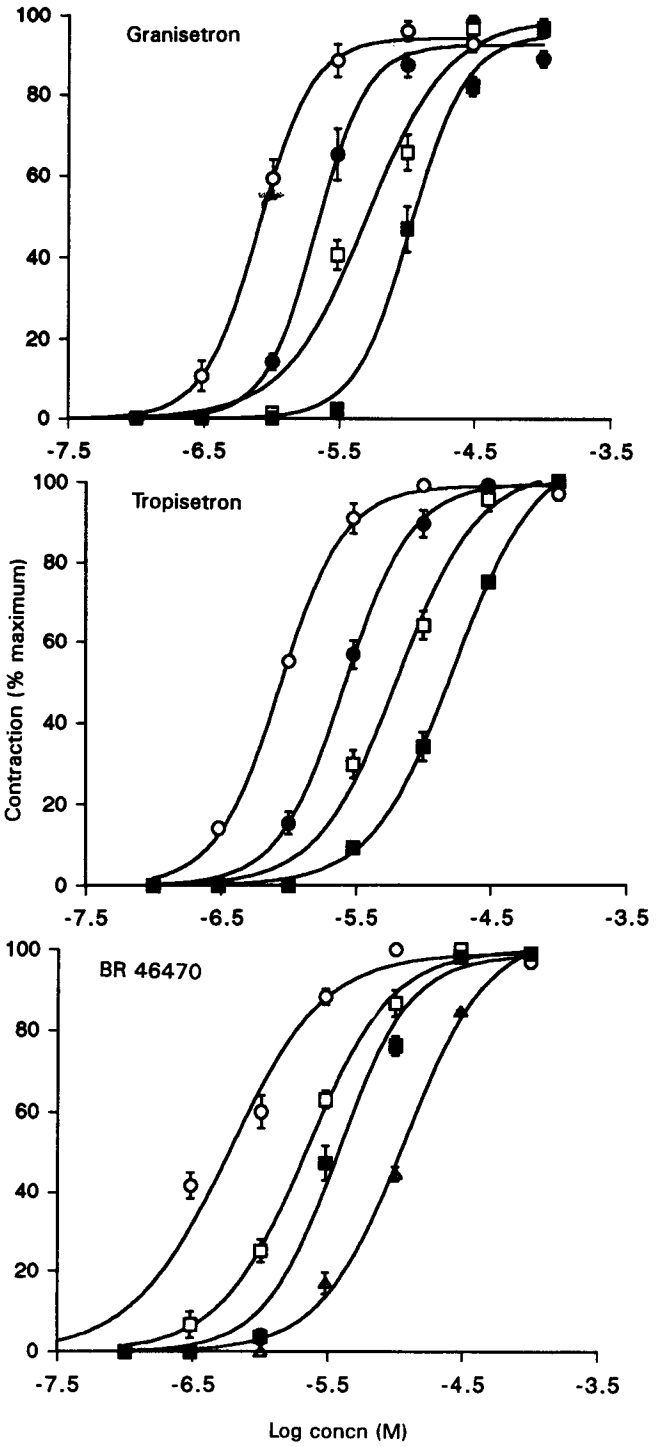

FIG. 2. The effects of granisetron, tropisetron and BRL 46470 on the concentration-response curve to 5-HT in guinea-pig isolated distal colon. Concentration-response curves to 5-HT were constructed on the absence (○) and presence of 10 nM (●), 30 nM (□), 0·1 μM (■) and 0·3 μM (△, BRL 46470 only) of each antagonist. Results are expressed as mean ± s.e.m. of a minimum of four observations.

Faecal pellet output from guinea-pig isolated colon

Faecal pellet transit times (control; 52 ± 7 s between each successive pellets) were unaffected by adding solvent (Krebs; 57 ± 5 s) or naloxone (0·1 μM, 52 ± 6 s) to the bathing solution (Table 1). Granisetron (0·1 and 1 μM) concentration-dependently and significantly slowed the faecal pellet transit times (102 ± 15 s and 190 ± 23 s, respectively). Tropisetron (1 μM) also significantly slowed faecal pellet transit time (105 ± 21 s), but at 0·1 μM was inactive (results not shown). BRL 46470 (1 μM) had no statistically significant effect on transit time (83 ± 15 s).

In addition to granisetron and tropisetron, morphine (0·1 μM) and clonidine (0·01 μM) also significantly slowed faecal pellet transit time (403 ± 96 and 1945 ± 588 s, respectively; Table 1)).

This inhibitory effect of granisetron (1 μM), morphine (0·1 μM) and clonidine (0·01 μM) was prevented or greatly reduced by the concomitant addition of naloxone (0·1 μM; Table 2).

5-HT-evoked contractions of guinea-pig isolated colon

In the presence of methiothepin (0·1 μM) and 5-MeOT (10 μM), 5-HT (0·1–100 μM) evoked a monophasic concentration-response curve. Granisetron (10 nM, 30 nM and 0·1 μM), tropisetron (10 nM, 30 nM and 0·1 μM) and BRL 46470 (30 nM, 0·1 μM and 0·3 μM) each produced a concentration-dependent shift to the right of the 5-HT curve, with pA_2 values and slopes of Schild plots of 8·5 ± 0·05 (slope 1·06 ± 0·03), 8·5 ± 0·1 (slope 0·91 ± 0·04) and 7·9 ± 0·1 (slope 0·93 ± 0·05), respectively (Fig. 2).

Discussion

The present study set out to investigate the mechanism underlying the constipation evoked by certain 5-HT$_3$-receptor antagonists (e.g. granisetron, ondansetron and tropisetron) in healthy volunteers. In normal human subjects, these compounds have little or no effect on the motility of the stomach and small intestine (Staniforth & Corbet 1987; Gore et al 1989; Talley et al 1989), but there have been consistent reports of a change in lower bowel function after their administration. These changes include mild constipation (Gore et al 1989; Stacher et al 1989; Upward et al 1990) and colonic stasis (Gore et al 1989; Talley et al 1989). For this reason the present study has focused on the effects of 5-HT$_3$-receptor antagonists on colonic motility.

In agreement with findings in volunteers (Stacher et al 1989; Upward et al 1990), granisetron and tropisetron when dosed acutely caused an inhibition of defecation in conscious guinea-pigs. Similar results have previously been obtained with ondansetron (Sanger et al 1991). BRL 46470, on the other hand, failed to significantly inhibit faecal pellet output at all concentrations tested. The doses at which the constipatory effects were observed are generally higher than those required to antagonize the 5-HT$_3$-receptor-mediated Von Bezold-Jarisch reflex in the anaesthetized rat (Richardson et al 1985; Sanger & Nelson 1989; Cohen et al 1989). However, the 5-HT$_3$ receptor in guinea-pig isolated tissues has an affinity for antagonists that is consistently lower than for the 5-HT$_3$ receptor in isolated tissues from rats and other species (Butler et al 1990). Hence this observation in the present study may be attributed simply to species variation. Granisetron and tropisetron were also shown to reduce the rates at which faecal pellets were expelled from guinea-pig isolated colon.

Morphine and clonidine reduced or stopped the expulsion of faecal pellets from the isolated colon. These inhibitory actions, and those of granisetron, were each reversed by the addition of naloxone to the bathing solution, at a dose which had no effects on the expulsion of faecal pellets when dosed alone. This suggests a fundamental involvement of opioids in the regulation of colonic constipation, supporting clinical findings in which naloxone has been shown to reverse constipation (Kreek et al 1983), increase faecal wet weights in geriatric patients (Kreek et al 1984) and accelerate colonic transit in normal volunteers (Kaufman et al 1988). The mechanism by which naloxone reversed the constipatory action of granisetron is believed to be one of functional antagonism. It has previously been shown that granisetron has no affinity for opiate receptors (Van Wijngaarden et al 1990) and does not modify morphine-induced emesis (Wynn et al 1993).

Initial studies investigated the effects of granisetron, tropisetron and BRL 46470 on faecal pellet expulsion in-vitro at a concentration of 1 μM. Such a concentration was believed to be supramaximally effective at antagonizing the 5-HT$_3$ receptor in guinea-pig tissue (Sanger & Nelson 1989; Butler et al 1990). At this concentration, granisetron displayed clear activity, reducing by half the rate at which faecal pellets were expelled. Granisetron 0·1 μM was therefore tested and was shown to produce a reduced, but still significant, effect. Tropisetron (1 μM) showed small but significant activity, whereas reducing the concentration of tropisetron to 0·1 μM resulted in a loss of activity. Higher concentrations of tropisetron were not investigated since they have also been shown to reduce the amplitude of electrically-evoked contractions in the guinea-pig ileum (Wardle & Sanger 1989) and to inhibit potassium and sodium currents in guinea-pig cardiac tissue (Scholtysik 1987). BRL 46470 was inactive at 1 μM. Higher concentrations were not investigated since they have previously been shown to reduce the amplitude of electrically-evoked contractions in the guinea-pig isolated ileum (in-house data). These results suggest that, in-vitro, 5-HT$_3$-receptor antagonists have varying abilities to evoke constipation. This observation is supported by a recent in-vivo study (Kishibayashi et al 1993) in which a series of quinolinecarboxylic acid-derived 5-HT$_3$-receptor antagonists have been shown to produce varying degrees of slowing of faecal pellet output in a stress-induced defecation model in rats.

These differences cannot easily be explained by an inability of the compounds to antagonize 5-HT$_3$ receptors within the isolated colon. Thus, in common with the other antagonists, BRL 46470 potently antagonizes cholinergically-mediated contractions of the longitudinal muscle evoked by exogenous 5-HT. In this model, the effective concentrations of BRL 46470 were considerably lower than the concentration which failed to prevent faecal pellet expulsion. Since faecal pellet movement along the colon is predominantly a result of circular, rather than longitudinal muscle contraction, these results may suggest that the 5-HT$_3$

receptor on the circular muscle of the guinea-pig colon differs from that on the longitudinal muscle, either in its pharmacology or in its accessibility to compounds that are added to the intact ileum via an external bathing solution. Thus, the variation in the abilities of compounds to slow faecal pellet expulsion in-vitro may be attributed to variations in their ability to reach equilibrium with the receptor in the time it takes for the colon to empty. Such a conclusion, however, would require further investigation.

Our experiments, therefore, provide support for the concept that, in the guinea-pig, not all 5-HT_3-receptor antagonists have the same ability to evoke constipation. If these results are applicable to man, they may also suggest that, compared with other 5-HT_3-receptor antagonists, acute doses of BRL 46470 could have a lower propensity to cause constipation.

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