

Gut

Leading article

What comes after macrolides and other motilin stimulants?

Delayed gastric emptying is often considered the major pathophysiological mechanism underlying symptoms in both functional dyspepsia and diabetic gastroparesis. Studies have reported a significant delay in the gastric emptying rate of solids in up to 50% of patients with functional dyspepsia and in up to 75% of patients with type 1 diabetes.^{1,2} Prokinetic agents, including metoclopramide, domperidone, and cisapride, have traditionally been used to enhance gastric emptying rate and to improve symptoms in these patients. However, their prokinetic effect was moderate and the symptomatic response was often poor.¹

Development of motilides

In view of the limited options to treat these patients, the report of the strong gastrokinetic effect of erythromycin³ was met with great enthusiasm. This surprising effect of erythromycin relates to its ability to act as a motilin receptor agonist,⁴ and several motilides (motilin agonists) lacking antibiotic activity were developed, including ABT-229. However, the outcomes of clinical trials with ABT-229 were unequivocally disappointing with regard to symptom improvement. In a large double blind placebo controlled study of 612 patients with functional dyspepsia assigned to placebo, or 1.25, 2.5, 5.0, or 10 mg of ABT-229, symptoms did not improve. On the contrary, an inverse dose-response occurred for postprandial fullness and ABT-229 apparently prevented the beneficial placebo effect.⁵ Similarly, as reported in this issue of *Gut* by Talley *et al*, a study with a comparable design in 270 patients with diabetes mellitus had an adverse effect and increased the severity of dyspeptic symptoms (see page 395).⁶ This led the authors to conclude that motilides will not be helpful in treating gastroparesis, and that acceleration of gastric emptying is apparently not the right therapeutic target. These are far reaching conclusions which may not be warranted. Several factors may have contributed to the negative outcome of both studies.

Relevance of delayed gastric emptying

Large studies have established that delayed gastric emptying is present in no more than one third of patients with functional dyspepsia⁷⁻⁹ and this is associated with symptoms of postprandial fullness, vomiting, and nausea.^{7,9} Although less systematically studied, the relationship between dyspeptic symptoms and gastroparesis appears at least as inconsistent in diabetic patients.² In keeping with the relatively low prevalence of delayed gastric emptying in both patient groups, ABT-229 failed to provide symptomatic relief in unselected patients. However, even when only the subgroup of patients with delayed gastric emptying was analysed, no symptomatic benefit was obtained.^{5,6}

Relevance of ABT-229 pharmacology

The authors assume that in the phase II trials the prokinetic activity was not lost over time although no repeated measurement of gastric emptying rate at the end of the treatment period was provided. The literature provides strong indications that ABT-229 may lose its potency during prolonged treatment. In an animal study, one month treatment with ABT-229 caused complete tachyphylaxis to ABT-229 and to motilin, apparently caused by severe downregulation of the motilin receptor.¹⁰ The plasma half life of ABT-229 is estimated to be 20 hours which may contribute to receptor downregulation. In a study involving nine healthy volunteers, the effect of 4 and 16 mg doses on gastrointestinal motility and on gastric emptying of two consecutive meals was evaluated. This study confirmed the effect on the emptying of the first meal but emptying of a second identical meal taken four hours after the first meal was not affected. The amplitude and number of antral contractions were increased after the first but not after the second meal.¹¹ However, at the time of the second meal, plasma levels of ABT-229 were still elevated in the absence of any prokinetic effect, confirming that tachyphylaxis had occurred.¹¹ Thus tachyphylaxis is a real problem and it may have contributed to the absence of a therapeutic benefit after four weeks of treatment, although this does not explain the worsening over placebo.

Relevance of other pathophysiological mechanisms

Recent studies provide further evidence that functional dyspepsia is a heterogeneous disorder in which different underlying pathophysiological disturbances are associated with specific symptom patterns. As mentioned above, delayed gastric emptying, present in up to 33% of patients, is associated with postprandial fullness, nausea, and vomiting.^{7,9} Impaired gastric accommodation to a meal is found in 40% of patients and is associated with early satiety and weight loss.¹² Hypersensitivity to gastric distention, occurring in 35% of patients, is associated with symptoms of epigastric pain, excessive belching, and weight loss.¹³ Impaired accommodation and increased sensitivity to gastric distention have also been reported in diabetic patients.^{14,15} A number of observations suggest that motilide prokinetics may have an adverse effect on gastric accommodation to a meal and on sensitivity to gastric distention.

Administration of erythromycin causes a significant increase in tone and phasic contractile activity in the proximal stomach.^{16,17} Both tonic and phasic contractions are accompanied by increases in the active wall tension of the proximal stomach which plays a crucial role in gastric mechanosensitivity.^{17,18} In healthy subjects, spontaneous phasic contractions of the proximal stomach can be

perceived. Erythromycin increases the intensity and frequency of these contractions, resulting in a significant increase in perceived contractions.¹⁷ During administration of erythromycin, subjects reported significantly higher perception scores at identical distending volumes or pressures, thereby mimicking hypersensitivity to gastric distention.¹⁷ In addition, administration of motilin or of erythromycin reduces meal induced relaxation of the proximal stomach,^{15,19} thereby mimicking impaired accommodation to a meal. Although similar specific data are not available for ABT-229, it is conceivable that both mechanisms contributed to the worsening of dyspeptic symptoms during treatment.

Future directions

In view of the heterogeneity of the underlying pathophysiological mechanisms, it seems unlikely that any form of treatment will be beneficial to all dyspeptic patients. In theory, patients with impaired accommodation should benefit from drugs that induce relaxation of the proximal stomach whereas patients with hypersensitivity to gastric distension should benefit from drugs that inhibit visceral perception or drugs that decrease gastric wall tension. Studies addressing these hypotheses are currently in progress.

The disappointing outcome of the clinical studies with ABT-229 might tempt one to conclude that motilin agonists will not be therapeutically useful to treat symptoms in patients with functional or diabetic dyspepsia and delayed gastric emptying. However, several factors associated with the drug and with the study design may have contributed to the negative outcome. It is unclear to what extent tachyphylaxis played a role in the therapeutic failure in patients with delayed gastric emptying, and whether this problem affects all motilides. Motilides with a short half life may be less likely to induce tachyphylaxis. Another point to keep in mind is the mechanism of action of motilin and the motilides. Pharmacological studies leave no doubt that motilin receptors are expressed both on nerves and smooth muscle, and neural effects seem to occur at lower concentrations.^{20,21} Whether these are truly different receptors remains to be proved but the recent cloning of a human motilin receptor²² may allow characterisation at the molecular level. In the rabbit duodenum, ABT-229 activates a smooth muscle motilin receptor, while in the antrum ABT-229 acts on both neural and muscular receptors.²⁰ At the doses used in the clinical trials it is most likely that if the situation in humans is comparable, both smooth muscle and neural effects were induced. It is important to note that the effect of erythromycin on the human fundus is a direct smooth muscle effect¹⁶ while the effect of low doses of erythromycin on the antrum is neurally mediated.²¹ Both effects may contribute to acceleration of gastric emptying but the effect on the fundus may affect accommodation, sensitivity, and dyspeptic symptoms.¹⁷ Motilides with a different selectivity profile, with perhaps a smaller prokinetic effect, could be devoid of an effect on the fundus.

Several other prokinetic drugs are currently under development or under investigation. When selecting prokinetic drugs for clinical application, the issue of tachyphylaxis as well as effects on the proximal stomach should be considered. Prokinetic agents do not necessarily impair meal induced relaxation of the proximal stomach as the 5-HT₄ agonist/5-HT₃ receptor antagonist cisapride was shown to enhance gastric accommodation to a meal.²³ Cholecystokinin A receptor antagonist inhibited gastric accommodation to a meal, and the effects of newer prokinetic agents such as the selective 5-HT₄ agonist tegaserod or the muscarinic autoreceptor inhibitor Z-338 on the

proximal stomach remain to be assessed.²⁴⁻²⁶ The limitations of the clinical studies with ABT-229 do not allow the conclusion that acceleration of gastric emptying is not a valid therapeutic target. Final proof or disproof of this hypothesis will require a study performed in patients with delayed gastric emptying which assesses symptoms associated with delayed emptying (fullness, nausea, and vomiting) and which provides proof of prokinetic efficacy in a repeat gastric emptying study at the end of the treatment period. For now, in the absence of specific drugs that enhance accommodation or reduce gastric mechanosensitivity, prokinetics are likely to remain our principal treatment option in patients with functional or diabetic dyspepsia.

J TACK

Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, Belgium and Centre for Gastroenterological Research, University of Leuven, Leuven, Belgium

T PEETERS

Centre for Gastroenterological Research, University of Leuven, Leuven, Belgium

Correspondence to: J Tack. Jan.Tack@med.kuleuven.ac.be

- Talley NJ. Review article: functional dyspepsia—should treatment be targeted on disturbed physiology? *Aliment Pharmacol Ther* 1995;9:107–15.
- Horowitz M, Wishart JM, Jones KL, et al. Gastric emptying in diabetes: an overview. *Diabet Med* 1996;13(suppl 5):S16–22.
- Janssens J, Peeters TL, Vantrappen G, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin: preliminary studies. *N Engl J Med* 1987;322:1028–31.
- Peeters TL, Matthijs G, Depoortere I, et al. Erythromycin is a motilin receptor agonist. *Am J Physiol* 1989;257:G470–4.
- Talley NJ, Verlinden M, Snape W, et al. Failure of a motilin receptor agonist (ABT-229) to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying: a randomized double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 2000;14:1653–61.
- Talley NJ, Verlinden M, Geenen DJ, et al. Effects of a motilin receptor agonist (ABT-229) on upper gastrointestinal symptoms in type 1 diabetes mellitus: a randomised, double blind, placebo controlled trial. *Gut* 2001;49:395–401.
- Stanghellini V, Tosetti C, Paternico A, et al. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996;110:1036–42.
- Maes BD, Ghoos YF, Hiele MI, et al. Gastric emptying rate of solids in patients with nonulcer dyspepsia. *Dig Dis Sci* 1997;42:1158–62.
- Sarnelli G, Caenepeel P, Geypens B, et al. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. 2001 (submitted).
- Depoortere I, Verlinden M, Thijs T, et al. The motilide ABT-229 selectively downregulates motilin receptors in different tissues. Evidence for motilin receptor subtypes. *Gastroenterology* 1999;116:A1061.
- Verhagen MA, Samsom M, Maes B, et al. Effects of a new motilide, ABT-229, on gastric emptying and postprandial antroduodenal motility in healthy volunteers. *Aliment Pharmacol Ther* 1997;11:1077–86.
- Tack J, Piessevaux H, Coulie B, et al. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 1998;115:1346–52.
- Tack J, Caenepeel P, Fischler B, et al. Hypersensitivity to gastric distention is associated with symptoms in functional dyspepsia. *Gastroenterology* 2001 (in press).
- Undeland KA, Hausken T, Aanderud S, et al. Lower postprandial gastric volume response in diabetic patients with vagal neuropathy. *Neurogastroenterol Motil* 1997;9:19–24.
- Samsom M, Salet GA, Roelofs JM, et al. Compliance of the proximal stomach and dyspeptic symptoms in patients with type I diabetes mellitus. *Dig Dis Sci* 1995;40:2037–42.
- Bruley des Varannes S, Parys V, Ropert A, et al. Erythromycin enhances fasting and postprandial proximal gastric tone in humans. *Gastroenterology* 1995;109:32–9.
- Piessevaux H, Tack J, Wilmer A, et al. Perception of changes in wall tension of the proximal stomach in humans. *Gut* 2001;49:203–8.
- Distruiti E, Azpiroz F, Soldevilla A, et al. Gastric wall tension determines perception of gastric distention. *Gastroenterology* 1999;116:1035–42.
- Tack J, Peeters T, Vos R, et al. Influence of motilin on meal-induced satiety in man. *Neurogastroenterol Motil* 1999;11:294.
- Van Assche G, Depoortere I, Thijs T, et al. In the rabbit gastric antrum the neurogenic and myogenic effects of the motilide ABT-229 are mediated via motilin receptors. *Neurogastroenterol Motil* 1998;10:106.
- Coulie B, Tack J, Peeters T, et al. Involvement of two different pathways in the motor effects of erythromycin on the gastric antrum in humans. *Gut* 1998;43:395–400.
- Feighner SD, Tan CP, McKee KK, et al. Receptor for motilin identified in the human gastrointestinal system. *Science* 1999;284:2184–8.
- Tack J, Broekaert D, Coulie B, et al. Influence of cisapride on gastric tone and on the perception of gastric distension. *Aliment Pharmacol Ther* 1998;12:761–6.
- Scott LJ, Perry CM. Tegaserod. *Drugs* 1999;58:491–6.
- Zerbib F, Bruley Des Varannes S, Scarpignato C, et al. Endogenous cholecystokinin in postprandial lower esophageal sphincter function and fundic tone in humans. *Am J Physiol* 1998;275:G1266–73.
- Nakajima T, Nawata H, Ito Y. Z-338, a newly synthesized carboxamide derivative, stimulates gastric motility through enhancing the excitatory neurotransmission. *J Smooth Muscle Res* 2000;36:69–81.