

A clinical audit of the efficacy of tegaserod as a prokinetic agent in the intensive care unit

Dianne P Stephens, Jane H Thomas, Sarah J Collins,
Paul B Goldrick and Stephen Fowler

Tegaserod is a novel selective serotonin receptor type 4 (5HT₄) partial agonist that stimulates motility in the entire gastrointestinal tract. Serotonin receptors are located throughout the gastrointestinal tract and have a role in the regulation of motility, ion secretion and perception of bowel distension and pain. Activation of the 5HT₄ receptors has been shown to stimulate chloride ion secretion and the peristaltic reflex. Tegaserod has proven efficacy in irritable bowel syndrome with constipation.¹ It has been shown to significantly accelerate gastric emptying, and to reduce small-bowel and colonic transit times in healthy volunteers. The most striking prokinetic effects were observed in the upper gastrointestinal tract (stomach and small intestine), and the effects were seen in both male and female subjects.²

The delivery of adequate nutrition is an important component of management in all critically ill patients. The preferred route of feeding is enteral.³ Unfortunately, intolerance of enteral feeding is common because of multiple disease- and drug-related factors that combine to impair gastrointestinal motility. Strategies to improve this motility, and consequent tolerance of enteral nutrition, include placement of small-bowel feeding tubes and use of prokinetic agents such as metoclopramide, cisapride and erythromycin.⁴ These agents have variable effectiveness, and there are concerns about their side effects. Metoclopramide is associated with prolonged QT syndrome, life-threatening arrhythmias and adverse extrapyramidal effects. Cisapride and erythromycin have also been associated with prolonged QT syndrome and ventricular arrhythmias. Cisapride is no longer available in Australia because of its side-effect profile.

Tegaserod is potentially safer than the currently available prokinetic agents, as it has minimal affinity for other serotonin receptors and no affinity for dopaminergic, opioid or α -receptors, which is a concern with other prokinetic agents. Tegaserod does not have cardiac or extrapyramidal side effects. The two main side effects reported are diarrhoea and headache.⁵ There have been rare reports of ischaemic colitis occurring in patients taking tegaserod for irritable bowel syndrome, although a direct causal effect has not been established, and the group in whom this side effect was reported have a threefold higher risk of ischaemic colitis than the general population. There have been encouraging case reports of tegaserod improving gastroin-

ABSTRACT

Objective: To formally document the effectiveness of tegaserod as a prokinetic agent in intensive care patients.

Methods: The audit was designed in consultation with the Northern Territory Drug and Therapeutics Committee. Tegaserod was added to the feeding protocol and prokinetic algorithm in the ICU, and a prospective audit was performed of patients receiving the medication between May and September 2006.

Results: Over the 5-month period, 40 patients received tegaserod after failing to respond to two doses of metoclopramide. Median daily volume of gastric aspirate was reduced from 1220 mL in the 24 hours before tegaserod to 887.5 mL in the first 24 hours after its introduction, and to 280 mL in the second 24 hours ($P=0.01$ and $P<0.001$, respectively). Tegaserod was an effective prokinetic agent in 85% (34) patients. Attributable diarrhoea occurred in 13% (5) patients, but did not require intervention.

Conclusions: Tegaserod is an effective alternative prokinetic agent for ICU patients with a safer side-effect profile. We believe it warrants further investigation.

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testinal motility in critically ill patients,⁶ but no large studies are yet available.

Audit background

The intensive care unit at Royal Darwin Hospital has used tegaserod on an ad-hoc basis for improving bowel motility for several years. The only side effect noted was occasional diarrhoea that may have been attributable to tegaserod. Anecdotally, senior clinicians have found it be effective in many patients in whom conventional agents have failed. The Northern Territory Drug and Therapeutics Committee requested that the ICU audit the use of tegaserod to inform its decision about placing tegaserod on the formulary. The audit was designed as a quality project to document the efficacy of tegaserod in improving tolerance of enteral feeding in ICU patients and to document the frequency of adverse events, such as diarrhoea.

Figure 1. Standard feeding protocol for ICU patients at Royal Darwin Hospital

Feeding protocol

Patient commences enteral feeding on admission to ICU

↓
Not tolerating feeds?

↓
Start metoclopramide 10 mg IV 6/24
Give at least 2 doses to see if it works

↓
Still not tolerating feeds?

↓
Start tegaserod 6 mg (nasogastric) 8/24
Give at least 3 doses to see if it works

↓
Still not tolerating feeds?

↓
Start erythromycin 100 mg (intravenous) 6/24
Give at least 2 doses to see if it works

↓
Still not tolerating feeds?

↓
Consider placing a nasojejunal tube

Checking enteral feed tolerance by gastric residual volumes

- Commence enteral feeds at 20 mL/h, increase by 20 mL/h to target rate over first 4 hours.
- Aspirate nasogastric tube every 4 hours.
- If aspirate is high (> 200 mL + 4 × feeding rate), aspirates are discarded, and rate reduced to half.
- If subsequent aspirate remains high (> 200 mL + 4 × feeding rate), aspirates are discarded, and rate reduced to 10 mL/h.
- Where aspirates are high, ensure prokinetic protocol is being followed as above.
- If aspirates are acceptable (< 200 mL + 4 × feeding rate), return aspirate, and continue at target rate or increase by 20 mL/h until target rate is met.

Methods

The audit was conducted in the ICU over a 5-month period from 1 May to 30 September 2006. It included all patients who were given tegaserod during this period.

The hospital's standard feeding flow chart was revised to include tegaserod; all other aspects of the chart and protocol had been in place for many years (Figure 1). Metoclopramide is the traditional first-line therapy in the ICU and remained the first-line prokinetic agent, as tegaserod was traditionally used only when metoclopramide failed to reduce the volume of gastric aspirate.

The feeding flow chart describes a stepped introduction of prokinetics based on the volume of gastric aspirate as a measure of feeding tolerance. Patients are defined as not tolerating feeds if their gastric aspirates are "high" — defined in our institution as a 4-hourly aspirate > 200 mL + 4 × feeding rate.

Table 1. Patient characteristics on entry to the audit

Variable	Number*
Total no. of patients	40
Males	29
Indigenous patients	18
Average age (years)	51.4
Average APACHE II score	21.6
Average standardised mortality ratio	0.41
Trauma patients	11
Sepsis patients	21
Other diagnoses	8
Inotropes received	34
Aperients received†	33

* Unless otherwise indicated.

† Coloxyl and Senna (Fawns & McAllan), lactulose or Movicol (Norgine) prescribed.

The number of doses of each prokinetic drug in the algorithm was decided by consensus among the senior clinicians based on previous experience with tegaserod use in patients in whom metoclopramide therapy failed. A full 24 hours of tegaserod therapy was included in the algorithm, as this was the drug of interest to us. The audit was not designed to make any conclusions about the relative efficacy of the different prokinetic agents, but to establish whether tegaserod was an effective prokinetic agent.

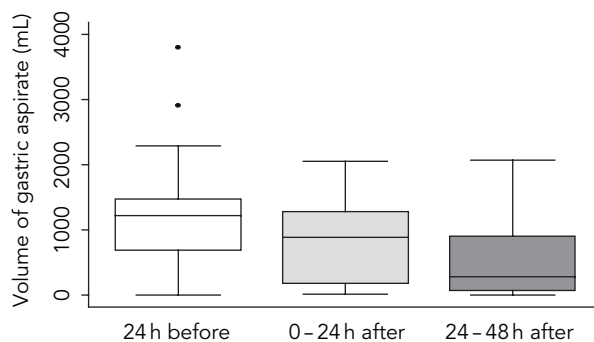
The ICU staff were educated on the new flow chart that included tegaserod, and the new chart replaced the old chart in the nursing instruction booklet in each ICU bay. Data were collected by the ICU Research Coordinator, including de-identified patient demographic characteristics, enteral feeds, gastric aspirates, episodes of diarrhoea, prokinetics and aperients used, and any attributable adverse events. Diarrhoea was defined as more than three watery liquid stools in a 24-hour period.

The first-line prokinetic used was metoclopramide. If this failed after two doses, then tegaserod was started at a dose of 6 mg enterally every 8 hours. Previous studies used doses of 6 mg every 12 hours, but as tegaserod has an elimination half life of 7.5 hours, and its oral bioavailability is 10% and reduced by food, we decided that 8-hourly dosing was more likely to be effective in the ICU setting.

Statistical analysis

The median volume of gastric aspirate was compared between the 24-hour periods immediately before tegaserod was given, and 0–24 hours and 24–48 hours after it was begun using the Wilcoxon signed-rank test for matched pairs (STATA 8.0, Stata Corp, College Station, Tex, USA).

Figure 2. Volume of gastric aspirate per 24 h period before and after introduction of tegaserod



Key: For each time period, box = interquartile (25%–75%) range; horizontal bar = median; whiskers = range; discrete points = values more than three standard deviations from the median. ♦

Table 2. Volume of gastric aspirate (mL) per 24-hour period before and after introduction of tegaserod

	24 h	After tegaserod	
	before tegaserod	0–24 h	24–48 h
Minimum	0	12	0
25% (1st quartile)	691.5	178.5	70.0
50% (median)	1220.0	887.5*	280.0 [†]
75% (3rd quartile)	1472.5	1280.0	905.0
Maximum	3800	2055	2070
Mean	1189.4	862.4	516.9
No. of patients	40	40	39

* Significant difference between 1220 mL and 887.5 mL ($P=0.01$).

[†] Significant difference between 1220 mL and 280 mL ($P<0.001$). ♦

Results

Forty patients were included in the audit over the 5-month period. Their demographic characteristics are shown in Table 1.

Results of the audit are outlined in Figure 2 and Table 2. Median daily volume of gastric aspirate was reduced from 1220 mL before tegaserod to 887.5 mL in the first 24 hours after tegaserod was begun, and from 1220 mL to 280 mL in the 24–48 hours after tegaserod was begun ($P=0.01$ and $P<0.001$, respectively). The results demonstrate that volume of gastric aspirate was reduced by the addition of tegaserod as a prokinetic agent. Nine patients received erythromycin in addition to tegaserod, but in three cases this was a protocol violation. Tegaserod was effective (no further motility agents indicated according to our protocol) in 34 patients (85%). Most patients received a standard 1 cal/mL (4.2 kJ/mL) fibre-containing enteral formula (30,

Nutrison Multifibre [Nutricia]; 2, Jevity [Abbott]; 3, Impact with Fibre [Novartis]). Five patients received a 1.5 cal/mL (6.3 kJ/mL) formula (Impact 1.5 [Novartis]) or 2 cal/mL (8.4 kJ/mL) formula (Renal Novasource [Novartis]).

Nine patients had documented diarrhoea or a rectal tube in place in the 24–48 hour period after tegaserod was added to their medications. Five cases of diarrhoea could be attributed to tegaserod (started after tegaserod was administered). In some cases, the aperient regimen was not halted despite documented presence of loose stools. The diarrhoea did not result in the cessation of tegaserod. No other adverse events were recorded.

Discussion

Tegaserod is a novel prokinetic agent with a safer side-effect profile than prokinetic agents currently in use. Our previous experience and this audit demonstrate that tegaserod is effective in reducing the volume of gastric aspirate and improving tolerance of enteral nutrition in most patients in whom metoclopramide therapy has failed. The occasional side effect of diarrhoea is limited and manageable. There were no serious adverse effects observed in this audit. We conclude that tegaserod appears to be an effective prokinetic agent that warrants further investigation.

Author details

Dianne P Stephens, Director of ICU

Jane H Thomas, ICU Research Coordinator

Sarah J Collins, ICU Staff Specialist

Paul B Goldrick, ICU Supervisor of Training

Stephen Fowler, Critical Care Pharmacist

Royal Darwin Hospital, Darwin, NT.

Correspondence: dianne.stephens@nt.gov.au

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