Research Article

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Granisetron Transdermal System for Gastroparesis: A Prospective Study using the GCSI-Daily Diary

Jason Heckert, Ron Schey and Henry P Parkman*

Gastroenterology Section, Temple University School of Medicine, Philadelphia, Pennsylvania, USA

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***Correspondence:** Henry P Parkman, Gastroenterology Section, Temple University School of Medicine, 3401 North Broad Street, Philadelphia, PA 19140, USA, Tel: 215-707-7579, Fax: 215-707-2684; E-mail: henry.parkman@temple.edu

Abstract

Granisetron transdermal system (GTS; Sancuso®), a patch delivering a 5-HT₃ receptor antagonist, has been shown to improve nausea and vomiting in gastroparesis. Recent FDA guidance on gastroparesis suggests daily scoring of symptoms to show efficacy.

Aim: Determine the efficacy and onset of therapeutic response of GTS in improving specific symptoms and overall symptoms of gastroparesis in patients with gastroparesis using a daily symptom diary for gastroparesis.

Methods: Symptomatic patients with diabetic or idiopathic gastroparesis with nausea and/or vomiting were enrolled. Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD) captured severity of symptoms at baseline for one week and during two weeks of treatment with GTS.

Key results: 14 patients (age 41.5 ± 17 years; 13 females) with refractory gastroparesis (5 idiopathic, 9 diabetic) participated in this open label study. Nausea, early satiety, postprandial fullness, abdominal pain, GCSI-DD composite score, and overall symptom severity significantly improved ($p < 0.05$) during treatment when compared to the baseline week. Nausea significantly decreased on day 5 ($p < 0.01$) of treatment. Episodes of vomiting did not significantly change. Side effects included pruritus (2 patients) and redness (1) at the patch site, headache (1), constipation (1), and poor patch adherence (5).

Conclusions and Inferences: GTS significantly reduced nausea severity in patients with gastroparesis. There were also significant improvements in early satiety, postprandial fullness, and abdominal pain. Nausea improvement occurred on the fifth day of treatment. Thus, GTS has therapeutic effect on nausea, as well as other gastroparesis symptoms, in patients with gastroparesis as captured using a daily diary for gastroparesis.

Key Points: Granisetron transdermal system (GTS; Sancuso®), a patch delivering a 5-HT₃ receptor antagonist, has been shown to improve nausea and vomiting in gastroparesis.

Daily symptom scoring, using a patient reported outcome, may help document efficacy for agents to treat gastroparesis: determining which symptoms improve and when.

GTS has therapeutic effect on nausea, as well as other gastroparesis symptoms, in patients with gastroparesis as

captured using a daily diary for gastroparesis. Nausea improvement occurred on the fifth day of treatment.

Keywords: Granisetron; Gastroparesis; Idiopathic gastroparesis; Diabetic gastroparesis

Introduction

Symptoms of gastroparesis, a chronic motility disorder of the stomach characterized by delayed gastric emptying, include nausea, vomiting, early satiety, postprandial fullness, and abdominal pain [1]. Treatment for gastroparesis includes diet modifications followed by the use of antiemetic and/or prokinetic agents [2].

Nausea and vomiting are important symptoms in gastroparesis, as these symptoms impact on quality of life. Nausea and vomiting are mediated by a number of neural pathways, including serotonergic (5-HT) receptors [3]. Serotonin 5-HT₃ receptor antagonists, such as ondansetron and granisetron, are approved for nausea and vomiting related to chemotherapy, radiation, and postoperative conditions [4,5].

Granisetron transdermal system (GTS; Sancuso®) is a cutaneous patch that provides continuous administration of granisetron (3.1 mg per day for up to 1 week). Many patients with gastroparesis have nausea and vomiting which may make oral medication administration problematic; the transdermal route may be helpful for these patients. GTS has improved nausea and vomiting in 50-76% of gastroparesis patients [6,7]. Some patients reported improvement in other gastroparesis symptoms such as early satiety, loss of appetite, abdominal pain, and postprandial fullness [7].

Recently, there has been a move to evaluate the therapeutic response in gastroparesis clinical trials with a daily symptom diary [8,9,10], as they can capture daily variability of gastroparesis symptoms and reduce recall bias that may be present asking about symptoms over a 2 week period, as done in the conventional Gastroparesis Cardinal Symptom Index (GCSI) [11]. The Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD) is one such symptom instrument that meets the specifications of the FDA guidance for clinical trials in gastroparesis [8-10]. The therapeutic response to GTS has not yet been evaluated with a daily diary.

The aim of this study was to evaluate the efficacy of GTS in reducing gastroparesis symptoms using a daily diary, to determine the specific symptoms that improve with treatment with GTS, to determine the duration of

treatment until symptom reduction, and to document the side effects of GTS.

Methods

Patients

This prospective clinical study included patients with nausea and/or vomiting from refractory gastroparesis at Temple University Hospital. Enrollment into this open label treatment protocol with GTS was over a 3 year period from June 2013 to October 2016. The protocol was approved by our IRB and FDA (FDA IND Number: 70,582 and Temple IRB Protocol Number: 21086). Patients had delayed gastric emptying with continued symptoms despite therapy with prokinetic agents and antiemetic agents. Many had failed treatment or had side effects with metoclopramide, domperidone, botulinum toxin injection into the pylorus.

Protocol

Patient inclusion criteria for this study included 1) Age 18 to 65 years of age; 2) diagnosed gastroparesis patients with symptoms of gastroparesis for at least 3 months; 3) symptoms of nausea and vomiting of at least moderate severity using the GCSI; 4) prior history of delayed gastric emptying as determined by scintigraphy; 5) gastroparesis from either diabetic or idiopathic etiologies; and 6) symptoms of nausea and vomiting that had not responded adequately to conventional antiemetic agents (Compazine®, Tigan®, Reglan®, Zofran®). Exclusion criteria for this study included 1) post-surgical gastroparesis; 2) prolonged QTc on EKG; 3) prior intolerance to 5HT₃ antagonists (ondansetron or granisetron); 4) known hypersensitivity to granisetron or to any of the components of the patch; 5) current treatment with ondansetron or granisetron; 6) use of ketoconazole, a medications with known drug-drug interactions with granisetron; 7) Women known to be pregnant, as determined on enrollment by a urine pregnancy test; 8) Women of childbearing potential who do not agree to use a medically approved form of contraception; and 9) nursing mothers.

Patients signed informed consent. The treatment protocol assesses symptoms and side effects. Patients undergo EKG, potassium, magnesium monitoring before

treatment. Patients were initially given a placebo patch for one week, while symptoms were being monitored with the GCSI-DD. Patients were then treated with GTS for two weeks with weekly follow-up. Patients filled out Patient Assessment of Upper GI Symptoms (PAGI-SYM) assessing symptom severity prior to treatment and during treatment, and answered the Clinical Patient Grading Assessment Scale (CPGAS) question after two weeks of treatment. Patients filled out the GCSI-DD for one week prior to starting GTS therapy as well as two weeks on GTS therapy.

Questionnaires

The Patient Assessment of GI Symptoms (PAGI-SYM) questionnaire includes the nine symptoms of the Gastroparesis Cardinal Symptom Index (GCSI) (nausea, retching, vomiting, stomach fullness, inability to finish a normal meal, feeling excessively full after meals, loss of appetite, bloating and stomach visibly larger) as well as additional symptoms of abdominal pain, constipation, and diarrhea [11,12]. The PAGI-SYM Masks the patient to assess the severity of symptoms over the past 2 weeks using a Likert scale from 0 (none) to 5 (very severe).

The Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD) was used to capture the severity of symptoms at baseline and during two weeks of treatment with GTS. The GCSI-DD includes questions about severity of nausea, early satiety, postprandial fullness, upper abdominal pain, and overall symptoms. Patients rated their symptom severity on a scale of 0 (no symptom), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe) and recorded the number of vomiting episodes per day. A daily composite score was calculated as the average of the five symptom scores (not including overall symptom severity) with a cap of 4 vomiting episodes per day.

The Clinical Patient Grading Assessment Scale (CPGAS; +7=completely better; 0=no change; -7=very much worse) asks patients about the therapeutic response of their gastroparesis symptoms at the follow up visit on treatment [13].

Gastric emptying scintigraphy (GES)

Gastric emptying scintigraphy was performed according to the standardized consensus protocol [14,15]. Patients were instructed to stop medications that could affect gastrointestinal motility for 48 hours prior to the study arriving in the morning after fasting overnight. Diabetics had their glucose checked at the beginning

of the study, with appropriate treatment measures being taken if low blood sugar (hypoglycemia <60 mg/dl) or high blood sugar (hyperglycemia >250 mg/dl) is detected. Gastric emptying scintigraphy was performed using a standard low-fat, Eggbeaters® meal to measure solid emptying. The meal consisted of the equivalent of two large eggs radiolabeled with 0.5-1 mCi Tc-99m sulfur colloid served with two pieces of white bread and jelly. Patients were given 120 ml of water. Following ingestion of the meal, imaging was performed at 0, 1, 2 and 4 hours with the patient upright for measuring gastric emptying of Tc-labeled solids. Gastric emptying was analyzed as percent of radioactivity retained in the stomach over time using the geometric center of the decay-corrected anterior and posterior counts for each time point. Gastric retention of Tc-99m >60 % at 2 hours and/or >10% at 4 hours was considered delayed gastric emptying.

Statistical analysis

Data were compiled in a Microsoft Excel database. Daily GCSI-DD symptom scores of the first two weeks of GTS treatment were compared to the baseline week on placebo patch using paired t-tests in order to determine when significant improvement occurred. Additionally, mean symptom score during the each week of treatment was compared to baseline using a paired t-test in order to determine if symptom improvement during the study period was significant. Results are expressed as a mean $\pm$ SEM or mean $\pm$ SD (where annotated).

Results

Patients

14 patients (age 41.5 ± 17 years; 13 females) with refractory gastroparesis (5 idiopathic, 9 diabetic) participated in this open label study from June 2013 to October 2016. All patients had delayed gastric emptying using gastric emptying scintigraphy. Main symptoms were nausea in 7 patients, retching 2, gas/bloating 3, abdominal pain 1, early satiety 1.

Efficacy

Mean daily symptom scores improved over the course of treatment for each symptom except for episodes of vomiting. Nausea (2.31 ± 0.17 vs 1.14 ± 0.32 , $p < 0.01$) and early satiety (2.51 ± 0.25 vs 1.79 ± 0.30 ; $p < 0.01$) significantly improved on day 5 of treatment with GTS and remained significantly improved throughout the remainder of the GTS treatment period. Improvement in postprandial fullness was significant after five days of GTS treatment

as well, however the improvement fluctuated over the treatment period. Abdominal pain significantly improved after four days of treatment; however, the response also fluctuated over the treatment period. Improvement in overall gastroparesis symptoms was significant on the fifth day of treatment; however, that improvement fluctuated over the treatment period.

To better understand the therapeutic effects of GTS over the treatment period, each patient's symptoms during their baseline period was compared with their symptoms during their first and second week of treatment (Table 1). Overall, the GCSI-DD composite score decreased from 1.89 ± 0.15 to 1.34 ± 0.21 , a significant decrease of 0.55 ± 0.12 ($p < 0.01$). There was strong correlation between

Table 1: Weekly symptoms during the study as assessed by the GCSI-DD – both at baseline and during the first and second weeks of treatment.

	Baseline Period	Week 1 of Treatment	P value	Week 2 of Treatment	P value
Nausea	2.31 ± 0.17	1.69 ± 0.28	<0.01	1.30 ± 0.27	<0.01
Early Satiety	2.51 ± 0.25	2.13 ± 0.27	0.02	1.83 ± 0.25	<0.01
Postprandial Fullness	2.52 ± 0.25	2.07 ± 0.23	<0.01	1.89 ± 0.21	<0.01
Upper Abdominal Pain	1.56 ± 0.33	1.31 ± 0.33	0.17	1.05 ± 0.30	0.04
# Vomiting Episodes/Day	0.56 ± 0.17	0.64 ± 0.30	0.7	0.66 ± 0.28	0.61
Overall Gastroparesis Symptoms	2.26 ± 0.15	1.81 ± 0.23	0.02	1.49 ± 0.24	<0.01
GCSI-DD Composite	1.89 ± 0.15	1.57 ± 0.20	0.01	1.34 ± 0.21	<0.01

Figure 1: Mean daily symptom scores during initial baseline and two weeks of GTS treatment.

change in GCSI-DD composite score with the change in overall gastroparesis symptom severity ($r=0.75$; $p < 0.001$). Nausea, early satiety, postprandial fullness, GCSI-DD composite score, and overall symptom severity significantly improved ($p < 0.05$) during the first week of treatment compared to the baseline week. Abdominal pain significantly improved during the second week of

treatment. Episodes of vomiting did not significantly change.

Patients completed the CPGAS question regarding nausea and vomiting on GTS treatment compared to their baseline symptoms. The mean CPGAS score was 3.7 ± 0.6 ($p < 0.01$ compared to no change; $n=10$).

Side Effects

No serious adverse events were reported, and mild adverse effects included pruritus (2 patients) and redness (1) at the patch site, headache (1), and constipation (1). In addition, poor patch adherence was reported by 5 patients.

Discussion

We evaluated the efficacy of GTS in patients with nausea and gastroparesis using the GCSI-DD, which records individual symptoms on a daily basis over time. Nausea and early satiety showed significant improvement by day five of treatment that was maintained throughout the treatment period, whereas postprandial fullness and abdominal pain also improved but showed a more variable response. When symptoms scores during the first week of treatment were compared with baseline symptom scores; nausea, early satiety, postprandial fullness, and overall symptom score experienced significant improvement. Abdominal pain showed significant improvement during the second week of treatment.

Prior recent studies have shown that use of GTS improved nausea and vomiting in 50-76% of patients with gastroparesis [6,7]. Additionally, patients reported improvement in other gastroparesis symptoms such as early satiety, loss of appetite, abdominal pain, and postprandial fullness [7]. This present study also shows improvement of nausea as well as some other gastroparesis symptoms including early satiety, postprandial fullness, and abdominal pain. Perhaps the improvement in nausea allows improvement in other symptoms such as early satiety since there is less nausea with eating. Alternatively, 5-HT₃ antagonists may have an effect on neural pathways mediating these symptoms. 5-HT₃ antagonists do not appear to alter gastric emptying [16]. Other serotonergic receptors, particularly 5-HT₄ receptors, may be involved in gastric accommodation response [17]. Another 5-HT₃ receptor antagonist, ondansetron, has been suggested in case reports to decrease nausea and vomiting in gastroparesis [18,19]. Ondansetron may have effects on vagal afferent nerves [20].

It is of interest that GTS improved nausea, but did not significantly improve vomiting. Although nausea and vomiting are thought to be mediated through similar pathways; perhaps, there are alternate neural pathways mediating these two symptoms. Vomiting can have different characteristics in patients with gastroparesis.

In a prior study of ours, we described the characteristics of nausea and vomiting in patients with gastroparesis [21]. The characteristics of nausea (severity, timing) were similar in diabetic and idiopathic patients. Vomiting was present in approximately half the patients but was considered the predominant symptoms in only a small percentage (4%) of the patients. In contrast to nausea, vomiting was more prevalent and severe in diabetic than in idiopathic gastroparesis.

Side effects with the GTS included pruritus (2 patients) and redness (1) at the patch site, headache (1), constipation (1). Some patients experienced difficulty with patch adherence to the skin (5). These have been seen in other studies evaluating the GTS in patients with gastroparesis [6,7] as well as chemotherapy-induced nausea and vomiting. Application site reactions have been reported in a previous clinical trial which were generally mild in intensity and did not lead to discontinuation of use [22].

Most of the symptoms that improved did so significantly on day five of GTS treatment. This is of interest as therapeutic levels of granisetron have been shown to reach maximum level at 48 hours [23]. It is not known why there is a delay in symptom relief compared to the therapeutic levels. Based on our data, it is reasonable to counsel patients that therapeutic effects of GTS are likely to occur towards the end of the first week of treatment and that results may continue to improve with longer treatment.

We acknowledge certain limitations in this study. As an open label study, we are unable to assess any placebo effect that might be occurring with the GTS treatment.

However, the patients in this study had refractory symptoms and we monitored their symptoms for a baseline run-in period in the study. Randomized, placebo controlled trials will be needed to gain FDA approval for GTS for treatment in gastroparesis patients. This study was a relatively short duration, 2 weeks in duration. Clinically, we have seen patients maintain the clinical improvement with GTS over several months. We did not look at subjective measurements on quality of life or objective measurements such as gastric emptying. Lastly, patients were permitted to continue other therapeutic agents (antiemetics, opioid analgesics, etc.) during the treatment period. We are unable to determine if these agents impacted on the results of our study.

In summary, this study evaluated the use of GTS in patients with nausea from gastroparesis and suggests that GTS may be effective for treating refractory nausea and vomiting in some patients with gastroparesis. Symptoms improved with treatment, particularly nausea. There were also improvements in other gastroparesis symptoms such as early satiety, postprandial fullness, and abdominal pain. Nausea improved by day five of treatment. Nausea and early satiety showed significant improvement that was maintained throughout the treatment period, whereas postprandial fullness and abdominal pain showed a more variable response. Thus, it is reasonable to counsel patients that the therapeutic effects of GTS may help their nausea and possibly other symptoms of gastroparesis and are likely to occur within the first week of treatment.

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