Parkinsonism and Related Disorders 20 (2014) 1171–1176

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Randomized, placebo-controlled trial of trimethobenzamide to control nausea and vomiting during initiation and continued treatment with subcutaneous apomorphine injection

Robert A. Hauser [a, *], Stuart Isaacson [b], Thomas Clinch [c], The Tigan/Apokyn Study Investigators[1]

[a] University of South Florida, Tampa, FL, USA
[b] Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL, USA
[c] US WorldMeds, LLC, Louisville, KY, USA

ARTICLE INFO

Article history:
Received 27 February 2014
Received in revised form
5 August 2014
Accepted 16 August 2014

Keywords:
Trimethobenzamide
Apomorphine
Nausea
Vomiting
Treatment
Clinical trial

ABSTRACT

Background: Nausea and vomiting can occur in Parkinson's disease (PD) patients initiated on apomorphine subcutaneous injections and antiemetic prophylaxis is recommended per product labeling. Data suggest long-term antiemetic prophylaxis may not be needed, although this has not been systematically studied.

Methods: We evaluated coadministered trimethobenzamide with apomorphine in 182 PD subjects using a randomized, double-blind, placebo-controlled design, with phased withdrawal of subjects from trimethobenzamide to placebo. Evaluations included presence/absence of nausea and vomiting; Index of Nausea, Vomiting, and Retching (INVR); subject evaluation of medication; Unified Parkinson's Disease Rating Scale (UPDRS) motor score; "on" response post-injection; and safety assessments.

Results: Incidence of nausea and/or vomiting on Day 1 of apomorphine initiation (primary endpoint) was not significantly different between trimethobenzamide and placebo. Over a longer period, a significantly lower incidence was found for trimethobenzamide during Period 1 (Days 1–28, $p = 0.025$) and Period 2 (Days 29–56, $p = 0.005$), with no difference during Period 3 (Days 57–84). INVR results were generally more favorable with trimethobenzamide than placebo in Period 1 and significantly more favorable in Period 2. The majority of subjects in both groups achieved an "on" response after apomorphine injection at all assessments. No significant differences were found between groups for UPDRS motor scores. No added safety risk with concomitant use of trimethobenzamide and apomorphine was found.

Conclusion: Our data suggest that trimethobenzamide helps reduce nausea/vomiting during the first 8 weeks of apomorphine therapy, but is generally not needed thereafter. Trimethobenzamide did not worsen parkinsonism nor affect "on" response after apomorphine injection.

1. Introduction

Subcutaneous injection of apomorphine hydrochloride is used for the acute, intermittent treatment of "off" episodes associated with advancing Parkinson's disease (PD). At recommended doses, nausea and vomiting can occur [1–8] and, per product labeling, antiemetic prophylaxis is recommended [9]. However, data from a long-term, open-label study suggest that some apomorphine treated patients may not require prophylaxis with an antiemetic [10]. No systematic studies have evaluated this or the duration that antiemetic treatment is needed.

In the United States, trimethobenzamide (Tigan®) is the only recommended anti-emetic for use in PD because it does not have central dopamine antagonistic effects (the peripheral dopamine receptor antagonist domperidone is not approved by the FDA [11]). The mechanism of trimethobenzamide action is unclear but may involve the chemoreceptor trigger zone in the medulla oblongata [12]. The primary objective of our study was to assess the efficacy of trimethobenzamide in preventing nausea and vomiting when

* Corresponding author. University of South Florida, Parkinson's Disease and Movement Disorders Center, National Parkinson Foundation Center of Excellence, 4001 E. Fletcher Ave, 6th Floor, Tampa, FL 33613, USA. Tel.: +1 813 396 0765; fax: +1 813 905 9829.
E-mail address: rhauser@health.usf.edu (R.A. Hauser).
[1] See acknowledgments for list of investigators.

http://dx.doi.org/10.1016/j.parkreldis.2014.08.010
1353-8020/

initiating intermittent subcutaneous apomorphine injection therapy in PD patients. In addition, we examined the optimal duration for continued trimethobenzamide after apomorphine initiation as well as the safety of the two drugs in combination.

2. Methods

2.1. Study design and participants

This was a phase 4, randomized, double-blind, placebo-controlled study of trimethobenzamide when coadministered with apomorphine, with phased withdrawal from trimethobenzamide to placebo. The study was conducted at 24 sites in the United States from May 9, 2007 through March 28, 2012 and is registered at ClinicalTrials.gov (identifier number NCT00489255). The study protocol and its 6 amendments were approved by appropriate institutional review boards, and all subjects gave written informed consent.

Subjects with advanced PD (≥18 years) and disabling "off" episodes who were to be initiated on intermittent subcutaneous apomorphine injections were eligible for inclusion. Key exclusion criteria included previous treatment with subcutaneous apomorphine or contraindication to apomorphine or trimethobenzamide.

Subjects were randomized (3:1 ratio; Supplemental Fig. 1) to receive trimethobenzamide 300 mg 3 times daily or matching placebo beginning 3 days before initiation of subcutaneous apomorphine injections on Day 1, which was titrated to clinical response in accordance with prescribing information (unit dose range 0.2–0.6 mL [2–6 mg]). Subjects then continued on trimethobenzamide or placebo TID during Period 1 (Days 1–28), along with apomorphine at the established dose. After 4 weeks (28 days), subjects assigned to trimethobenzamide were re-randomized (2:1 ratio; Fig. 1) to continue trimethobenzamide or switch to placebo, to achieve a total theoretical 1:1 allocation of trimethobenzamide: placebo during Period 2 (Days 29 ± 3 days to Day 56 ± 3 days). On Day 56 (±3 days), subjects still assigned to trimethobenzamide were re-randomized (1:1 ratio) to continue trimethobenzamide or switch to placebo, to achieve a total theoretical 1:3 allocation of trimethobenzamide: placebo during Period 3 (Day 57 ± 3 days to Day 84 ± 3 days).

2.2. Study treatments

Trimethobenzamide hydrochloride (Tigan®) 300-mg capsules (King Pharmaceuticals, Inc., Bristol, TN) and placebo capsules (Almac Clinical Services, Audubon, PA) were over-encapsulated in identically-appearing capsules and orally administered. Apomorphine hydrochloride (10 mg/mL) solution was used as supplied in 3-mL glass cartridges (Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany). After withholding PD medications overnight, subjects were initiated on 0.2 mL subcutaneous apomorphine in the clinic on Day 1, receiving up to 3 titrated doses (maximum of 0.6 mL) as needed to determine the subject's optimal dose, defined as the dose providing an "on" response as confirmed by improvement in Unified Parkinson's Disease Rating Scale (UPDRS) Part III Motor Score without intolerable side effects. If after the first injection, the subject did not achieve an "on" response and had no tolerability issues, the dose was increased to 0.4 mL at the next observed "off" period, but not sooner than 2 h after the initial injection. If optimal dose was not determined after the second injection, this procedure was repeated at 0.6 mL. After Day 1, subjects (or caregivers) self-injected apomorphine at their defined optimal dose for the treatment of "off" episodes as an outpatient. To document clinical response to apomorphine, subjects received an injection at their defined optimal dose in the clinic on Days 28, 56, and 84, after withholding PD medications overnight.

2.3. Efficacy measures

Presence or absence of nausea and vomiting was recorded after each injection in a subject diary. Subjects also completed an Index of Nausea, Vomiting, and Retching (INVR) every evening to cover the prior 12 h period. Additionally, subjects underwent UPDRS Motor ratings within 60 min before apomorphine injection (all visits) and 10 min after injection on Days 28, 56, and 84, and the percent of subjects achieving an "on" response (as judged by the investigator) was determined at all visits. Subjects completed a global evaluation of how the medication controlled their nausea/vomiting (responses ranging from excellent to poor) on Days 28, 56, and 84.

2.4. Safety measures

Subjects recorded any unusual signs or symptoms in the subject diary. Nausea and vomiting reported in the subject diary were not considered an adverse event unless it met criteria for a serious adverse event or resulted in subject discontinuation. At each visit, the investigator questioned subjects about adverse events and reviewed the diary-recorded unusual signs/symptoms to determine if any should be reported as an adverse event. Blood pressure and pulse rate were recorded supine (after 5 min) and standing (after 1 min sitting and 2 min standing).

2.5. Statistical analysis

The primary endpoint was the incidence of nausea *and/or* vomiting during initial dose titration of apomorphine on Day 1 (revised from percentage of injections with

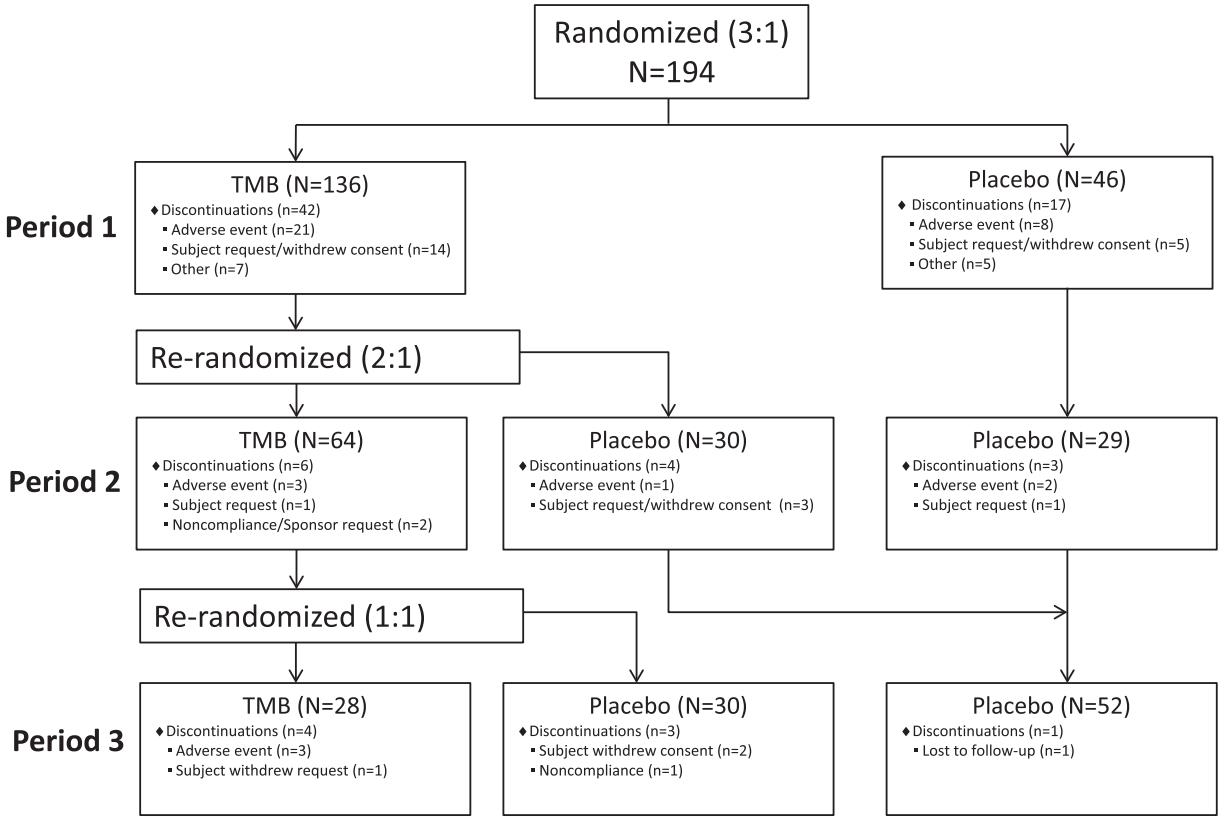

Fig. 1. Patient disposition. TMB — trimethobenzamide.