Ramosetron as a Treatment for Cyclic Vomiting Syndrome: A Small-Scale Patient Trial

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Introduction

Cyclic vomiting syndrome (CVS), a disorder involving recurrent episodes of nausea, vomiting, and lethargy, is observed most frequently in children, and occasionally in teenagers or adults. Episodes may occur regularly, randomly, or as a result of triggering factors such as emotional excitement or infections. CVS is classified within migraine subgroup 1.6 (“Episodic syndromes that may be associated with migraine”) in the Third Edition of the International Headache Classification (ICHD-3).¹ Sumatriptan, a serotonin 1B/1D receptor agonist, was reportedly effective in acute treatment of migraine, and of some (but not all) CVS cases.²-⁵ Ondansetron, a serotonin 5-HT3 receptor antagonist, has been suggested as a therapeutic agent for CVS treatment,⁶-⁸ but there has been no clinical trial of its efficacy. Ramosetron, another selective serotonin 5-HT3 receptor antagonist,⁹-¹¹ has been applied clinically for treatment of irritable bowel syndrome (IBS) in Japan.¹²,¹³ Typical IBS symptoms (abdominal pain and/or diarrhea) are often observed in CVS cases. In this small-scale patient trial, we examined the effects of ramosetron applied for CVS treatment.

Methods

Five patients referred to Hikita Pediatric Clinic or Teikyo University Hospital and diagnosed with CVS were enrolled in this trial after informed consent was obtained. For each patient, we obtained detailed family history of migraine and detailed medical history, including results of previous physical examinations and neurological examinations. We performed additional diagnostic tests to rule out possible organic causes of CVS, including gastrointestinal, neurological, or metabolic diseases.

Patients were diagnosed with CVS on the basis of ICHD-3 criteria.¹ Treatment consisted of oral administration of 2.5 to 10 μg ramosetron (dosage based on body weight). Patients filled out a “headache diary” for monitoring of vomiting time and duration. For patients who experienced daily abdominal pain, ramosetron was administered once per day. For patients who experienced prodrome symptoms of CVS (abdominal pain, diarrhea, nausea, appetite loss, headache, and/or menstruation-associated headache or vomiting), ramosetron was administered during the prodrome period. Ramosetron was administered during vomiting attacks if the patient was capable of keeping down the tablet. Patient responses to treatment for each attack were classified as: (i) complete (no vomiting following treatment), (ii) effective (frequency of vomiting after treatment reduced by ≥50% relative to previous attack prior to initiation of treatment), or (iii) noneffective (frequency of vomiting reduced by <50% by treatment).

Results

Responses of the 5 patients to ramosetron treatment are summarized in Table 1. All patients reported a family history of migraine in a first-degree relative. Three patients (cases 1-3) showed no response of CVS symptoms to sumatriptan treatment, and 1 patient (case 4) showed response to sumatriptan treatment in 30% of CVS attacks. One patient (case 5) reported an adverse effect (body stiffness) to sumatriptan treatment of migraine headache. None of these patients had received ondansetron previously. Prior to this study, patient 1 received valproic acid and phenobarbital, patient 3 received amitriptyline, and patient 4 received phenobarbital. However, none of these patients responded to these attempted prophylactic treatments.

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Table 1. Data for 5 CVS Patients in This Study, and Their Responses to Ramosetron Treatment.

| Case # | Gender | Migraine | Family history of migraine | Age at CVS onset (years) | Age at initiation of ramosetron trial (years) | Ramosetron dosages (μg) | Timing of ramosetron administration |
|--------|--------|----------|---------------------------|-------------------------|---------------------------------------------|------------------------|-------------------------------------|
|        |        |          |                           |                          |                                             |                        | Prodrome period                      | During vomiting                     |
|        |        |          |                           |                          |                                             |                        | Complete    | Effective | Noneffective | Complete | Effective | Noneffective |
| 1      | F      | −        | Father                    | <1                      | 15                                          | 2.5, 5                 | 14          | 6         | 7           |          |           |              |
| 2      | F      | −        | Mother                    | 4                       | 10                                          | 2.5, 5                 | 1           | 1         | 1           |          |           |              |
| 3      | M      | +        | Mother                    | 5                       | 11½                                         | 5, 10                  | 9           | 8         | 4           |          |           |              |
| 4      | F      | +        | Father, mother            | 6                       | 19½                                         | 2.5                    | 1           | 1         | 1           |          |           |              |
| 5      | F      | +        | Father                    | 8                       | 41¼                                         | 2.5, 5                 | 4           |           |             |          |           |              |
All 5 patients experienced prodrome symptoms (see Methods). Following ramosetron treatment during prodrome period, 3 of the patients showed essentially “complete” response (out of 40 attacks, there were 24 complete, 1 effective, and 15 noneffective responses), and 1 showed effective response (for 1 attack). Overall, 24 of the 45 responses (53.3%) were classified as complete or effective.

For 3 of the patients, ramosetron treatment was initiated after vomiting had started, in a total of 12 attacks. One of these 3 patients showed effective response (in 1 attack), while the other 2 showed noneffective responses (in 11 attacks).

In 2 of the 5 patients (40%; cases 1, 4), ramosetron treatment resulted in constipation as an adverse effect. Such constipation was not severe, and resolved rapidly following termination of ramosetron treatment.

Discussion

Ramosetron, a specific serotonin 5-HT3 receptor blocker developed in Japan, has been shown to reduce frequency of nausea, vomiting, and anorexia in cancer patients undergoing chemotherapy. Dosages used to obtain anti-emetic effect are 0.1 mg (oral) or 0.3 mg (intravenous), while dosages used for IBS treatment are much smaller, ranging from 2.5 to 10 μg (oral). CVS and IBS are both classified as functional gastrointestinal disorders, and may belong to the same disease group. The major symptom of CVS is vomiting, whereas those of IBS are abdominal pain and diarrhea. Many CVS patients experience abdominal pain and diarrhea during vomiting attacks, and some develop other functional disorders, including IBS.

Ondansetron, another specific serotonin 5-HT3 receptor blocker, has also been reported to reduce frequency of nausea, vomiting, and anorexia in cancer patients undergoing chemotherapy. Application of ondansetron for CVS treatment has been described in some review articles, but no clinical trial of its efficacy has been performed. Dosages of ondansetron used for CVS treatment have been similar to those used for anti-emetic effect. The present report is the first to describe a patient trial of a specific serotonin 5-HT3 receptor blocker for CVS treatment.

In this study, 4 patients with CVS were responsive to ramosetron treatment. Ramosetron may act on IBS symptoms or exert an anti-emetic effect. Ramosetron was not effective in the 3 cases when it was administered during a vomiting attack, but was effective in the 4 cases when it was administered during the prodrome period. However, the majority of CVS patients do not experience prodrome, and oral administration of ramosetron is difficult in such cases. Possible alternative treatments are i.v. administration of a specific serotonin 5-HT3 receptor blocker, i.v. administration of fluids, or i.c. administration of a serotonin 1B/1D receptor agonist. We presume that suppression of gastrointestinal movement by ramosetron had the effect of reducing nausea and vomiting in our cases.

An obvious limitation of the present study is the small sample size. Placebo effects are often observed in clinical studies of migraine patients, and ramosetron may have exerted a placebo effect for CVS treatment in the present study. Confirmation of our preliminary findings will require randomized, placebo-controlled studies of ramosetron efficacy in CVS treatment.

Conclusion

Our findings suggest that ramosetron is potentially effective for treatment of patients with CVS. Placebo-controlled studies with larger sample sizes are necessary to confirm this interesting possibility.

Abstract Presentation

The findings of this study were presented as an abstract at the 19th Congress of the International Headache Society (“IHC 2019”) (Sep 2019, Dublin).

Author Contributions

TH and HH: conceptualised the study, responsible for literature search, supervised and participated in data collection, data analysis and prepared the manuscript under the guidance and supervision of MM.

MM: reviewed the literature and manuscript. All authors contributed to critical revisions of the manuscript and approved the final submitted version.

Declaration of Conflicting Interests

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