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Cyclic vomiting syndrome (CVS) responsive to single-dose olanzapine: a case report

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Abstract

Cyclic vomiting syndrome (CVS) is a rare disorder in which stereotypical periods of intermittent nausea and vomiting last between hours and over a week. The disorder overlaps with migraine, and the current treatment recommendations follow those of migraine management. The current patient had experienced vomiting periods lasting up to a week since the age of two. Prophylactic amitriptyline had led to probably slightly longer intervals between CVS periods, while several medications had proven ineffective. At the age of 17, there was an excellent response to peroral olanzapine, which eventually proved sufficient to abort the vomiting periods in a single dose when taken at the beginning of one. In light of these and previously reported cases, early administration of olanzapine is suggested to treat CVS periods.

Keywords

antiemetic, antipsychotic, case report, cyclic vomiting syndrome, dopamine antagonist, migraine, treatment

Introduction

Cyclic vomiting syndrome (CVS) is a rare disorder characterized by stereotypical periods of intermittent nausea and vomiting that last from 1 hour to 10 days [1]. Diagnostic criteria have been provided by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), International Classification of Headache Disorders 3 (ICHD-3), and also in the Rome IV diagnostic criteria. Overlap between CVS and migraine disorders was suggested already in the 19th century and has been consistently observed since. For example, both migraine and CVS episodes can be triggered by various stimuli, such as acute psychological or physiological stress, sleep deprivation, and menses [2]. The overlap between the conditions may obscure the diagnosis and the management of CVS. Current treatment of CVS largely follows the guidelines of migraine management, but there is an unmet treatment need reflected by

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the marked burden of hospital admissions, gastrointestinal procedures, and the estimated annual CVS healthcare costs of $200 million (not including emergency department care, outpatient visits and medications, and time lost from school and work) in the United States [3].

Olanzapine is a dopamine receptor agonist that also binds to serotonin, histaminergic, and muscarinic receptors. It is primarily indicated for psychotic symptoms but also used as an antiemetic in palliative care and investigated for pain relief [4, 5]. There are also previous pediatric and adult case reports suggesting that olanzapine is effective in CVS when combined with other medications [6, 7]. Here we report a case of CVS previously minimally or not responsive to several medications but an excellent response to single-dose peroral olanzapine at the beginning of the episode.

Case report

This female patient had experienced periodic vomiting since the age of two years. These periods lasted usually three to four days but sometimes up to a week. In early childhood, they occurred infrequently. There was no abdominal pain, sensory hypersensitivity, or any other symptoms associated with these episodes, save for a brief feeling of nausea preceding the vomiting. Stress or nervousness often triggers periods. During the periods, the patient had vomiting episodes 5–10 minutes apart at the briefest. Even though the patient was often able to eat and drink between the episodes, the periods were severe enough to repeatedly lead to dehydration and the need for hospital treatment. The symptoms were not responsive to ondansetron, metoclopramide, sumatriptan, zolmitriptan, and magnesium sulphate. Her elder brother had a cluster headache, and her elder sister had severe motion sickness. There were no other diseases (including gastrointestinal or mental disorders) in the family history.

There was a remission of several years in the vomiting periods at an elementary school age. At nine years of age, the disorder recurred but initially manifested only 12–24 months apart. However, they became progressively more frequent until the age of 14, when periods occurred up to three times in a year. The following investigations ordered by a pediatric gastroenterologist yielded normal results: abdominal ultrasound, gastroscopy, magnetic resonance imaging (MRI) of the small intestine, as well as brain MRI. The pediatric gastroenterologist or surgeons found no gastrointestinal disorders, such as congenital malrotation, gastroesophageal reflux disease, (atypical) Crohn's disease, food protein induced enterocolitis syndrome (FPIES), hepatitides, or acute infections. There was no sign of renal dysfunction in laboratory studies, and a pediatric endocrinologist did not observe any signs of metabolic or mitochondrial disease. A pediatric neurologist diagnosed the disorder as abdominal migraine. Amitriptyline 10 mg was initiated as continuous prophylaxis at the age of 14, with initially no apparent effect on vomiting period frequency or severity. When the dose was doubled, the intervals between vomiting periods became perhaps somewhat longer.

At the age of 17, during a hospital admission, based on a consultation of an adult neurologist, peroral olanzapine 5 mg was tried approximately 30 hours after the beginning of a vomiting period. Two doses seven hours apart eased the symptoms considerably, and the vomiting period had ended by the next morning. The patient was discharged 24 hours after the first olanzapine dose. Thereafter, she has taken a single 5 mg dose of olanzapine when a vomiting period has begun, and this has been sufficient to terminate the episodes every time. At the last follow-up, almost 3 years after the initiation of olanzapine, the patient was well and studying, and reported enduring excellent response to olanzapine when needed. Given that the patient has needed olanzapine only 1–2 times annually, no specific side effect monitoring has been arranged.

Discussion

In the current patient, single-dose oral olanzapine proved remarkably effective both as an acute treatment that also instantly terminated the vomiting periods even without short-term continuous prophylactic administration.

The patient fulfilled the pediatric Rome IV criteria for CVS: 1) two or more periods of intense unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-month period; 2) episodes are stereotypical in each patient; 3) episodes separated by weeks to months with return to baseline health between episodes; 4) symptoms not attributed to another medical condition. The most obvious differential diagnostic consideration would be migraine. There were no signs of central sensitization and most importantly, no pain, which rules out both classical and abdominal migraine [8]. Relevant gastrointestinal and endocrine disorders had also been ruled out.

It is well known that acute medications work better in migraine the earlier they are taken after pain onset [9–13]. The situation appeared to be analogous in our patient. The first dose of olanzapine was administered approximately 24 hours after the vomiting period onset, and although it worked well, another dose was needed to quell the resurgence of symptoms the same evening. A couple of months later, the patient took the olanzapine as soon as she recognized that an episode had started, which led to complete remission with a single dose.

Differences in olanzapine administration might explain disparities between the current case and the previous pediatric one, in which olanzapine was initiated over a week after episode onset and took days to work [6]. Indeed, considering that CVS episodes last from an hour to 10 days, it is not entirely clear if the symptoms in that case abated because of the medications given or the natural course of the episode. In the adult case, treatment delay from episode onset was not reported, and olanzapine was administered at a small dose of 1.25 mg (since the patient weighed only 44 kg) and combined with 50 mg of amitriptyline [7]. It is therefore unclear if solitary olanzapine (at a higher dose if needed) would have been effective in that case. Indeed, the remission was attributed to amitriptyline by the authors. In contrast, the dose of amitriptyline was considerably lower (10–20 mg) in our patient, and it had shown only mild/minimal benefit during two years of use. Moreover, solitary olanzapine worked even better in the second period, in which it was used despite the patient having been without amitriptyline or any other medications for months. It therefore appears that in the current case, olanzapine was clearly superior to amitriptyline. Of note, some other antipsychotics such as chlorpromazine and risperidone, have also been reported to have potential in CVS treatment [14, 15].

Serotonin (5HT) regulates mitochondrial biogenesis. It has been shown that lower serotonin levels are related to decreased ATP synthesis and mitochondrial dysfunction, increasing migraine susceptibility [16]. Olanzapine's therapeutic effect on CVS might also come across the mitochondrial pathway: There is a hypothesis that mtDNA polymorphism influences energy metabolism in the cell and can lead to an imbalance between energy supply and need [17]. The advancing field of mitochondrial studies will hopefully clarify CVS etiology and open new opportunities to treat it.

Olanzapine is a second-generation antipsychotic with a structure close to that of clozapine. It acts on many types of dopaminergic (D1, D2, D3, D4, D5) and serotoninergic (5HT2A/2C, 5HT3, 5HT6, and 5HT7) receptors with a higher affinity for 5HT2 receptors (especially 5HT2A) than for dopaminergic receptors. Antagonist of the muscarinic M1, M2, M3, M4, M5 (contributing to reduce the risk of extrapyramidal effects), α1-adrenergic, and histamine H1 receptors. Nearly all of these actions contribute to its antiemetic effects [4]. Its time to peak concentration is 6 hours for oral formulation with a half-life of 21 to 54 hours (average: 30 hours). Similar to other second-generation antipsychotics, olanzapine causes movement disorders less commonly than first-generation dopamine antagonists. However, its main adverse events are metabolic, including weight gain and reduced insulin sensitivity [18]. It is therefore desirable that olanzapine not be used more than strictly necessary. The current case shows that, at least in some patients, CVS can be treated with single doses of olanzapine without any prophylactic medication at all. This would be an optimal treatment regimen, especially for young people, considering the long-term potential of side effects.

Abbreviations

5HT: serotonin

CVS: cyclic vomiting syndrome

MRI: magnetic resonance imaging

Declarations

Author contributions

SS: Investigation, Writing—original draft, Writing—review & editing. KK, VS, and MJ: Investigation, Writing—review & editing. JOTS: Conceptualization, Validation, Writing—original draft, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

Jussi O.T. Sipilä, who is the Editorial Board Member of Exploration of Neuroscience, had no involvement in the decision-making or the review process of this manuscript. The other authors declare no conflicts of interest.

Ethical approval

In Finland, ethical commission permissions are not required for case reports, and ethical commissions do not handle these. This case study was reported in compliance with the Declaration of Helsinki.

Consent to participate

Informed consent to participate was obtained from the patient.

Consent to publication

Informed consent to publication was obtained from the patient.

Availability of data and materials

All datasets analyzed for this study are included in the manuscript.

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