Single Center Experience with Hydroxyzine in the Treatment of Cyclic Vomiting Syndrome

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Abstract

Background
To this date, there has been no specific therapy proven to be effective for cyclic vomiting syndrome (CVS) in controlled trials. Multiple regimens have been proposed including: cyproheptadine, propranolol, amitriptyline, and phenobarbital. These medications are not without major side effects. The aim of this study was to describe the authors’ experience with hydroxyzine in children with CVS.

Materials and Methods
This was a systematic retrospective review of charts from March 1st 2012 till December 31st 2014. Patients diagnosed with CVS and treated with hydroxyzine were included in this study. Demographic criteria as well as response to therapy were reviewed.

Results
48 patients were diagnosed with CVS during the period of two years and nine months. Female to male ratio was 2:1. The average age at diagnosis was 10.4 years. Fifteen patients were treated with hydroxyzine. Overall success rate was 86.7%. The rates of complete and partial remission were respectively 61.5% and 38.4%. Only 2 patients failed to respond.

Conclusion
Hydroxyzine seems to be a safe and effective alternative prophylactic treatment in children with CVS. Further randomized controlled studies are needed to support this specific indication for prescribing hydroxyzine.

Key Words: Cyclic vomiting syndrome, Hydroxyzine, Pediatric, Gastroenterology, Prophylaxis.


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Received date Jun20, 2016; Accepted date: Jul 22, 2016
INTRODUCTION

Cyclic vomiting syndrome (CVS) affects about 2% of school-aged children (1). Patients with CVS experience a recurrent typical pattern of vomiting and nausea characterized by a stereotypy of onset, symptoms and duration (2, 3). Other associated symptoms with CVS include anorexia, abdominal pain, headache, pallor and photophobia (3). Despite our medical and scientific advances, it’s etiology and pathogenesis remains unclear. The diagnosis is made by a combination of fulfillment of clinical criteria and investigations to rule out other possible etiologies (1). Although, several different therapeutic regimens have been suggested for CVS, there is no standard and curative regimen. In 2008, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, published a clinical report recommending preventive therapy based on case series and expert opinion. These prophylactic drugs have included amitriptyline, cyproheptadine, propranolol and phenobarbital (1).

However, these medications are not without major side effects; this triggered the search for a safe and effective alternative. To our knowledge, there has been no published literature regarding Hydroxyzine use in CVS in children. The aim of this study was to assess the effectiveness of Hydroxyzine as a prophylactic treatment for CVS in the pediatric age group.

MATERIALS AND METHODS

Population

Eligible patients were children aged two to eighteen years, diagnosed with cyclic vomiting syndrome and treated at the Pediatric Gastroenterology Clinic at SUNY Upstate Medical Center, USA.

Methods

This study was a systematic retrospective review of charts from March 1st 2012 till December 31st 2014. Charts with the diagnosis of ICD-9-CM 536.2 were selected for review. Patients that fulfilled the NASPGHAN criteria for diagnosis of CVS were included in the study population (1). The diagnostic work up that led to the diagnosis with CVS was also, noted and patients that were found to have secondary causes for vomiting were excluded from the study.

Patients treated with Hydroxyzine and that had records for at least two follow up visits after starting the medication were included in the study. The following data was collected: age, gender, personal medical and family history and the characteristics of vomiting episodes (frequency, duration, number of hospitalization and emergency department visits related to emesis, missed school days). The dose of Hydroxyzine prescribed with relation to the current weight was recorded. Charts were screened for any side effects reported by the patient/caregivers or discontinuation of the medication due to undesirable effects. The response to therapy was measured by the number of episodes of emesis reported at these three incidences: prior to treatment, at the first and second follow up visits post treatment.

Ethics

We have obtained appropriate approval from SUNY Upstate Medical University Institutional Board Review.
recorded were anxiety/depression in 31.3% and constipation in 25%. Other medical problems included attention deficit disorder in 12.5%, migraine in 8.3% and irritable bowel syndrome in 4.2%. Of note, one patient had chromosome 18q syndrome and another had tetrasomy 18p. As for the family history, 33% of patients had a family history of migraines, 18.8% irritable bowel syndrome, 2% anxiety and 6.3% other mental illnesses (including depression, bipolar disorder or anorexia nervosa).

3-2. Clinical outcome

Our population of interest consisted of 15 patients who were treated with hydroxyzine (Table.1) and had at least two follow-up evaluations post treatment. 18 patients were managed with other prophylactic agents such as amitriptyline or cyproheptadine; and 15 patients were lost to follow up.

The therapeutic response of the patients treated with hydroxyzine is outlined in Table.2. At the first follow up visit ranging from 1 to 6 months, 8 patients achieved resolution of vomiting episodes and 5 patients had a partial response with decreased number of episodes compared to the pre-treatment period. At the second follow up visit, which ranged from 7 to 24 months post initiation of therapy, 10 patients achieved complete resolution of symptoms and 3 had significant reduction of symptoms with episodes occurring once per year on average. Therefore, 86.7% achieved either a complete or a partial resolution of symptoms. Two patients failed to respond. Patient 7 had a strong personal and family history of migraines. Hydroxyzine was discontinued after 2 months and topiramate was trialed, to which the patient responded well. Hydroxyzine was the second line of therapy for patient 15 after she failed to improve with amitriptyline. Subsequently, 3 months of hydroxyzine then phenobarbital then metoprolol were trialed, all with no improvement. Multiple factors played in the resilience of her disease including severe symptoms requiring multiple emergency visits and hospitalizations, daily cannabinoids abuse and non-compliance to daily prophylactic therapy.

3-3. Dose and adverse events

Patients treated with hydroxyzine were aged 7 through 17 years. Patients that weighed less than thirty kilograms were given a dose of 0.5 to 1 mg/kg/dose. Those greater than thirty kilograms followed the adult dosing of 25-50 mg/dose. Avoidance of sedation, which is the major side effect of the medication, was managed by giving a single dose at bedtime. There were no reported side effects by the patients or their caregivers.

Table-1: Dosing of Hydroxyzine used per patient

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age at diagnosis in years</th>
<th>Weight at diagnosis in Kg</th>
<th>Dose of hydroxyzine used</th>
<th>Unit dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>15</td>
<td>71.9</td>
<td>50 mg nightly</td>
<td>Adult dose</td>
</tr>
<tr>
<td>Patient 2</td>
<td>17</td>
<td>76.9</td>
<td>25 mg nightly</td>
<td>Adult dose</td>
</tr>
<tr>
<td>Patient 3</td>
<td>16</td>
<td>68.7</td>
<td>50 mg nightly</td>
<td>Adult dose</td>
</tr>
<tr>
<td>Patient 4</td>
<td>16</td>
<td>55.1</td>
<td>25 mg nightly</td>
<td>Adult dose</td>
</tr>
<tr>
<td>Patient 5</td>
<td>12</td>
<td>27</td>
<td>25 mg nightly</td>
<td>1mg/kg/dose</td>
</tr>
<tr>
<td>Patient 6</td>
<td>12</td>
<td>30</td>
<td>25 mg nightly</td>
<td>1mg/kg/dose</td>
</tr>
<tr>
<td>Patient 7</td>
<td>12</td>
<td>62.4</td>
<td>50 mg nightly</td>
<td>Adult dose</td>
</tr>
<tr>
<td>Patient 8</td>
<td>11</td>
<td>37.4</td>
<td>25 mg nightly</td>
<td>1mg/kg/dose</td>
</tr>
<tr>
<td>Patient 9</td>
<td>9</td>
<td>32</td>
<td>10 mg nightly</td>
<td>0.5mg/kg/dose</td>
</tr>
<tr>
<td>Patient 10</td>
<td>10</td>
<td>25.6</td>
<td>10 mg nightly</td>
<td>0.5mg/kg/dose</td>
</tr>
</tbody>
</table>
### 4- DISCUSSION

CVS can be a debilitating condition for the patients and their families. Frustrations arise from the recurrent unpredictable episodes, the frequent emergency department or doctors’ visits and school and/or work absences. Alongside the lifestyle changes, preventive prophylactic pharmacotherapy can be a tool to help families cope with this diagnosis. The current recommendations for prophylactic management are based on expert opinion as the published pharmacologic data consist of retrospective or uncontrolled studies (1). Furthermore, the recommended therapies including amitriptyline, cyproheptadine, propranolol and phenobarbital are not without side effects and should be used with caution in children (1, 3). Our study hopes to shine the light on hydroxyzine as a possible safer alternative therapy. Pharmacologically, hydroxyzine is a first-generation antihistamine. It acts as a central nervous system (CNS) depressant and exhibits sedative antihistaminic, anticholinergic, antiemetic, antispasmodic, and local anesthetic properties (4). Hydroxyzine is of the piperazine antihistamine therapeutic class and is thus a highly lipophilic drug (5). The effects of these chemical properties on the central nervous system are determined by their ability to cross the blood brain barrier and bind to their respective H1-receptors. Positron-emission tomography (PET) with 11C doxepin as the radioactive ligand has shown that the first-generation H1-antihistamines occupy 50 to 90 percent of the H1-receptors in the frontal cortex, temporal cortex, hippocampus, and pons. Hydroxyzine was shown to occupy about 68% (6), hence its efficacy on the CNS.

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**Table 2: Patient’s demographics and response to treatment**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at diagnosis</th>
<th>Vomiting Frequency</th>
<th>First follow up</th>
<th>Response</th>
<th>Second follow up</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>15 y</td>
<td>2-3 weeks</td>
<td>4 m</td>
<td>Occasional nausea</td>
<td>10 m</td>
<td>No episodes</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>17 y</td>
<td>2-3 weeks</td>
<td>3 m</td>
<td>No episodes</td>
<td>10 m</td>
<td>No episodes</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>16 y</td>
<td>Daily for 4 weeks</td>
<td>5 m</td>
<td>Episodic nausea, no emesis</td>
<td>7 m</td>
<td>No episodes</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>16 y</td>
<td>2 months</td>
<td>4 m</td>
<td>No episodes</td>
<td>9 m</td>
<td>No episodes</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>12 y</td>
<td>2-4 weeks</td>
<td>2 m</td>
<td>Decreased frequency</td>
<td>8 m</td>
<td>Once in 8 m</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>12 y</td>
<td>2-4 weeks</td>
<td>2 m</td>
<td>Decreased frequency</td>
<td>8 m</td>
<td>No episodes</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>12 y</td>
<td>1 month</td>
<td>2 m</td>
<td>No improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>12 y</td>
<td>2-3 weeks</td>
<td>4 m</td>
<td>No episodes</td>
<td>9 m</td>
<td>No episodes</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>11 y</td>
<td>1 month</td>
<td>5 m</td>
<td>No episodes</td>
<td>11 m</td>
<td>No episodes</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>9 y</td>
<td>2-4 weeks</td>
<td>3 m</td>
<td>No episodes</td>
<td>24 m</td>
<td>1-2 episodes per year</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>10 y</td>
<td>2 weeks</td>
<td>2 m</td>
<td>Decreased frequency (1 episode in 2 months)</td>
<td>12 m</td>
<td>No episodes</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>7 y</td>
<td>1 month</td>
<td>3 m</td>
<td>No episodes</td>
<td>9 m</td>
<td>No episodes</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>7 y</td>
<td>1 week</td>
<td>4 m</td>
<td>1 episode in 4 months</td>
<td>9 m</td>
<td>2 episodes in 9 m</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>7 y</td>
<td>4-6 weeks</td>
<td>6 m</td>
<td>2 episodes in 6 months</td>
<td>12 m</td>
<td>No episodes</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>16 y</td>
<td>2-4 weeks</td>
<td>3 m</td>
<td>No improvement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Legend:* F: female; M: male; Y: years; M: months.
Although the exact mechanism in CVS is unknown, the choice behind this molecule emanated from its combined anxiolytic and antiemetic properties. Anxiety has been noted to be prevalent among our population of patients, so using a molecule that could appease anxiety symptoms while acting as an antiemetic appeared as a promising drug option.

Our study population reflects the demographics of patients in previous reports. Lee et al. performed a systematic review of the literature pertaining to CVS between 1948 and 2011. They described clinical characteristics of CVS in adults and children. Comparably, our population has an increased female to male ratio, history of anxiety/depression and family history of migraines (8, 9). Our mean age at diagnosis was 10.4 whereas other writers described a range from 6.7 to 9.6 (10-13). The NASPghan consensus statement recommends cyproheptadine as the first line of prophylactic therapy for children less than five years of age and amitriptyline for children above five years. Propranolol is the second drug of choice for all ages (1). The review of the literature showed that amitriptyline had a variable success rate based on combined partial and complete remission with 61%, 72% and 91% (2, 10, 11). Anderson et al. found a success rate of 83% with cyproheptadine. Propranolol was less effective with reported rates of 61 and 67% (2, 11). In our study, hydroxyzine appears to be as effective as the first line regimens with a success rate of 86.7%.

Furthermore, the safety of a medication is as valuable as its efficacy. Increased precaution should be observed while managing CVS with the usual drugs. Cyproheptadine can increase appetite and lead to weight gain, amitriptyline can increase the corrected QT interval increasing the risk of ventricular arrhythmias, propranolol can cause bradycardia and needs to be tapered before discontinuation and finally phenobarbital has a potential of cognitive impairment (1). However, the adverse reactions profile of the long used hydroxyzine, well described in the literature, is limited, with sedation being the most prominent (13).

In our experience, hydroxyzine was used effectively as a single nighttime dose to reduce the effect of sedation on the daytime activities. The review of the charts did not reveal any reported side effects by caregivers or patients. There were no incidences of medication discontinuation related to undesired side effects.

4-1. Limitations of the study

Finally, the limitations of this study are adherent to its retrospective nature. Also, the outcomes measured relied on a subjective report from patients and their caregivers with no structured interview or symptoms scoring questionnaire. In addition, Fleisher described a placebo effect of 70% from consultation alone prior to instituting therapy (14). Our patient population was mostly treatment naïve and was not compared with a control group; therefore a placebo effect could not be excluded. However, extended chronological chart review on patients 4 and 5 revealed that they were weaned at 17 and 8 months post therapy respectively. Both experienced recurrence of their vomiting episodes. When patients were placed back on hydroxyzine, these episodes subsided. Patients 6 and 7, who were identical twins, were weaned successfully after 4 years of therapy with no recurrences. These incidences pledge towards a therapeutic role of hydroxyzine in CVS prophylaxis. Lastly and unfortunately, the small population size prevents generalization of our

5- CONCLUSION

In summary, we found in our population that hydroxyzine was an effective prophylaxis agent for CVS with
comparable success rates to cyproheptadine and amitriptyline. Thus, hydroxyzine may represent a safer alternative for the treatment of children with CVS. Further randomized controlled studies comparing this medication to the standard of care and placebo are needed to support this specific indication for prescribing hydroxyzine.

6- STATEMENT OF AUTHORSHIP

All authors were involved the conceptualization of the study, the acquisition and interpretation of the data, the writing and revising of the manuscript. All approve of the final version submitted and are accountable for all aspects of the work.

7- CONFLICTS OF INTEREST AND SOURCE OF FUNDING

We have none to declare.

8- REFERENCES


