http:// ijp.mums.ac.ir
Original Article (Pages: 3293-3298)

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

Joyce Saliba[1], *Manoochehr Karjoo[2], Noha Basouny[3], Afshin Karjoo[4], Mirza Beg[5]

[1]Department of Pediatrics, Golisano Children's Hospital, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, U.S.A. [2]Professor of Pediatrics, Division of Pediatric Gastroenterology, Hepatology and Nutrition, Golisano Children's Hospital, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, U.S.A. [3]Ain Shams University, Khalifa El-Maamon st, Abbasiya sq, Cairo 11566, Egypt. [4]Pharmacy Clinical Coordinator, Venice Regional Bayfront Health, 540 The Rialto, Venice FL 34285, U.S.A. [5]Associate Professor of Pediatrics, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Golisano Children's Hospital, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, U.S.A.

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.

*Please cite this article as: Saliba J, Karjoo M, Basouny N, Karjoo A, Beg M. Single Center Experience with Hydroxyzine in the Treatment of Cyclic Vomiting Syndrome. Int J Pediatr 2016; 4(8): 3293-98.

Corresponding Author:

Manoochehr Karjoo, MD, Professor of Pediatrics, Department of Pediatric Gastroenterology, Hepatology, and Nutrition, Golisano Children's Hospital, SUNY Upstate Medical University 750 East Adams Street, Syracuse, NY 13210, U.S.A.

Email: karjoom@upstate.edu

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

1- 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.

2- MATERIALS AND METHODS

2-1. 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.

2-2. 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.

2-3. Ethics

We have obtained appropriate approval from SUNY Upstate Medical University Institutional Board Review.

3- RESULTS

3-1. Patient population

We identified a total of 48 children diagnosed with CVS at our clinic during the study period of two years and nine months. The average age at diagnosis was 10.4 years. The incidence of CVS in our population was double in females than in males (females n = 32, males n=16). The most frequent personal medical problems

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

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

Patient 11	7	35	10 mg nightly	0.5mg/kg/dose
Patient 12	7	23.3	10 mg nightly	0.5mg/kg/dose
Patient 13	7	23.4	10 mg nightly	0.5mg/kg/dose
Patient 14	12	93.4	50 mg nightly	Adult dose
Patient 15	16	56.2	50 mg nightly	Adult dose

Table-2: Patient's demographics and response to treatment

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

*Legend:*F: female; M: male; Y: years; M: months.

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 H_1-receptors. Positron-emission tomography (PET) with ^{11}C doxepin as the radioactive ligand has shown that the first-generation H_1-antihistamines occupy 50 to 90 percent of the H_1-receptors in the frontal cortex, temporal cortex, hippocampus, and pons. Hydroxyzine was shown to occupy about 68% (6), hence its efficacy on the CNS.

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

1. Li B, Lefevre F, Chelimsky G, Boles R, Nelson S, Lewis D, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Consensus Statement on the Diagnosis and Management of Cyclic Vomiting Syndrome. Journal of Pediatric Gastroenterology and Nutrition 2008; 47(3):379-93.

2. Forbes D. Differential Diagnosis of Cyclic Vomiting Syndrome. Journal of Pediatric Gastroenterology and Nutrition 1995; 21:S11-S14.

3. Tan ML, Liwanag MJ, Quak SH. Cyclical vomiting syndrome: Recognition, assessment and management. World J Clin Pediatr 2014; 3(3):54-8.

4. Simmon FE. Advances in H1-antihistamines. N Engl J Med 2004; 351(21):2203-17.

5. Pagliara A, Testa B, Carrupt PA, Jolliet P, Morin C, Morin D, et al. Molecular properties and pharmacokinetic behavior of cetirizine, a zwitterionic H1-receptor antagonist. J.Med. Chem 1998; 41:853-63.

6. Farré M, Pérez-Mañá C, Papaseit E, Menoyo E, Pérez M, Martin S, et al. Bilastine vs. hydroxyzine: occupation of brain histamine H1-receptors evaluated by positron emission tomography in healthy volunteers. Br J Clin Pharmacol 2014; 78:5 970-80.

7. Lee LY, Abbott L, Mahlangu B, Moodie SJ, Anderson S. The management of cyclic vomiting syndrome: a systematic review. Eur J Gastroenterol Hepatol 2012;24:1001–1006.

8. Vanderhoof JA, Young R, Kaufmann SS, Ernst L. Treatment of cyclic vomiting syndrome in childhood with erythromycin. J Pediatr Gastroenterol Nutr 1993; 17:387–91.

9. Fleisher D, Matar M. The cyclic vomiting syndrome: a report of 71 cases and literature review. J Pediatr Gastroenterol Nutr 1993; 17:361–69.

10. Andersen JM, Sugerman KS, Lockhart JR, Weinberg WA. Effective prophylactic therapy for cyclic vomiting syndrome in children using amitriptyline or cyproheptadine. Pediatrics 1997;100: 977–81.

11. Aanpreung P, Vajaradul C. Cyclic vomiting syndrome in Thai children. J Med Assoc Thai 2002; 85 Suppl 2:S743-8.

12. Abu-Arafeh I, Russell G. Cyclical vomiting syndrome in children: a population-based study. J Pediatr Gastroenterol Nutr 1995; 21:454–58.

13. Goetz DW, Jacobson JM, Apaliski SJ, Repperger DW, Martin ME. Objective antihistamine side effects are mitigated by evening dosing of hydroxyzine. Ann Allergy 1991; 67(4):448-54.

14. Fleisher DR. Cyclic vomiting. In: Hyman PE, DiLorenzo C, editors. Pediatric Gastrointestinal Motility Disorders. New York, NY: Academy Professional Information Services; 1994. p. 89–103.