Clinical Practice: Clinical Vignettes

Use of a Once-Daily NSAID in Treatment of Cyclic Vomiting Syndrome

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Cyclic vomiting syndrome (CVS) is a rare disorder characterized by episodes of intense vomiting and nausea separated by symptom-free periods. We report the case of a 71-year-old man who presented with a long history of poorly controlled CVS whose symptoms resolved with the addition of a once-daily dose of meloxicam, a semi-selective non-steroidal anti-inflammatory drug (NSAID). This is the first report of symptom alleviation in a CVS patient using a once-daily NSAID, as well as one with selectivity to COX-2 inhibition. This is important due to both the increased compliance seen with once-daily medications, as well as the decreased gastrointestinal effects seen with selective COX-2 inhibitors compared to nonselective NSAIDs.

KEY WORDS: clinical vignette; disease management; gastroenterology.

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INTRODUCTION

We present a case of a 71-year-old man with long history of cyclic vomiting syndrome (CVS), in which recurrence of vomiting episodes was prevented by treatment with a once-daily non-steroidal anti-inflammatory drug (NSAID). CVS is a rare disorder characterized by bouts of intense vomiting and nausea interspersed between periods of normal health. Other associated symptoms include abdominal pain, anorexia, lethargy, pallor, sweating, and photophobia.¹ Acute vomiting attacks may be triggered by psychological and physical stressors such as exhaustion, emotional distress, infection, menstruation, and certain foods.² CVS most often affects children, but can present at any age and is increasingly being diagnosed in adults.

CASE REPORT

A 71-year-old Caucasian man with a past medical history of hypertension, hyperlipidemia, benign prostatic hypertrophy, and essential tremor presented to our clinic with a long history of recurrent episodes of nausea, vomiting, and often headaches, separated by asymptomatic intervals. He began having these symptoms in 1991, with attacks occurring every 1–4 weeks, usually lasting less than a day. The diagnosis of CVS was finally made at the Mayo Clinic in February of 1999, based upon a negative gastrointestinal and neurologic evaluation coupled with the three classic clinical criteria of CVS: stereotypical episodes of vomiting with acute onset and duration of less than 1 week, three or more discrete episodes in the prior year, and periods between episodes absent of nausea and vomiting.³

At the time of his diagnosis in 1999, his only medication was metoprolol tartrate (50 mg) for mild hypertension. Between 1999 and 2007, the patient sought medical advice from various CVS experts and tried a number of therapies, including a variety of anti-emetics, triptans, and tricyclic anti-depressants (TCAs), but none fully alleviated his symptoms. Eventually, the patient found that high dose nortriptyline hydrochloride (150 mg, every night) was a partially effective agent for prophylactic management of his symptoms. His new baseline symptoms included weekly headaches and monthly nausea and vomiting. He continued to take metoprolol tartrate for his hypertension and was started on atorvastatin (20 mg) in 2005 for management of his hyperlipidemia.

In May of 2007, the patient started experiencing worsening symptoms, including episodes of nausea and vomiting occurring weekly. At this time, he changed to a new internal medicine physician at Northwestern Memorial Hospital in Chicago (one of the authors, LLB). Since his hypertension was also mildly worse and there was some evidence that CVS symptoms might represent a migraine equivalent, his dose of metoprolol tartrate was increased from 50 to 100 mg in an attempt to address both concerns. This treatment was ineffective and was changed to diltiazem hydrochloride 180 mg daily, which was subsequently increased to 360 mg daily. This resulted in fewer headaches and a reduction of his blood pressure, but no improvement of his nausea and vomiting.

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Later in 2007, a new regimen of medications was prescribed for acute symptoms, including both eletriptan hydrobromide and tramadol hydrochloride/acetaminophen for headaches, as well as bethanechol chloride for gastric emptying during nausea; these treatments were ineffective. Topiramate was tried as a migraine abortive agent, but doses up to 100 mg twice a day failed to alleviate the patient's symptoms. He noted he could avert the full onset of his symptoms if he could sleep, and thus diazepam was provided for as-needed use. He later found he preferred alprazolam (1 mg) for these scenarios, because it made him less fatigued upon waking. In 2008, the patient was prescribed gradually increasing doses of valproic acid/divalproex sodium, which helped decrease symptoms; however, the medication caused the patient's baseline essential tremor to worsen and was therefore discontinued in 2009. Lamotrigine was then started and tapered up to 150 mg twice daily, but only resulted in a slight improvement. In 2010, he decreased his nortriptyline from 150 mg to 75 mg nightly without any change in his symptoms.

In March of 2011, the patient was still vomiting weekly while taking his usual routine of atorvastatin, diltiazem hydrochloride, lamotrigine, and nortriptyline with alprazolam as needed. He reported lower back pain and radicular leg pain for which he was prescribed meloxicam, a once-daily NSAID. While using the meloxicam daily for his back pain, he noticed that he had no episodes of headaches, nausea, or vomiting for a full month, the first such instance of complete alleviation of symptoms since he was originally diagnosed. He continued the daily meloxicam and noted that his symptoms returned about once a month for 6 months, and then completely resolved by August of 2011.

The patient was then required to discontinue meloxicam a few weeks before undergoing back surgery in November of 2011, but was able to continue his other medications. He noted that his CVS symptoms resurfaced within several days of stopping the meloxicam, and persisted weekly while off the meloxicam. Meloxicam was restarted a few days after surgery and his CVS symptoms once again resolved quickly.

The patient fully weaned off his lamotrigine by July of 2012, and then weaned his nortriptyline dosage from 75 to

50 mg in August, 2012. However, when he tried to decrease his nortriptyline further to 25 mg, his CVS symptoms began to return. The patient continued taking the full dose of meloxicam 15 mg along with the relatively small dose of nortriptyline 50 mg, with full resolution of all CVS symptoms.

DISCUSSION

The clinical course of CVS may be divided into four phases: the inter-episodic, between attacks; the prodrome, when the patient first senses an oncoming episode; the emetic, characterized by intense vomiting and nausea; and the recovery, once vomiting begins to subside.¹ Avoidance of triggers, lifestyle changes, and prophylactic medications can be used to deter attacks during the inter-episodic phase.² Prophylactic medications include tricyclic antidepressants and anti-migraine medications since patients often have a history of anxiety, depression, or migraines.^{2,4,5} Abortive medications are used to terminate an emetic episode in the prodromal and emetic phases, and include anti-emetics, 5-HT receptor antagonists, and sedatives such as benzodiazepines.^{4,6,7} Supportive therapies are employed in the emetic and recovery phases, and include rehydration and sedatives.⁴⁻⁷ The clinical course and treatments utilized in each phase are summarized in Fig. 1.^{2,4-7} Controlled clinical trials are still needed to determine efficacies of many of these therapies, but retrospective studies have demonstrated partial efficacy of tricyclic antidepressants as prophylactic agents in adults.^{5,8}

Nonselective NSAIDs have been reported to abort and prevent episodes of CVS. A report by Pankaj et al. in 1996 described an adult case of CVS where episodes were aborted and prevented by a twice-daily dose of ketorolac, a nonselective NSAID.⁹ NSAIDs may prevent episodes of CVS by inhibiting the synthesis of prostaglandins. In the case report by Pankaj et al., the authors noted that their patient's serum adrenocorticotrophic hormone (ACTH), serum cortisol, and urinary cortisol levels were elevated prior to a vomiting episode and during the episode.⁹ This finding was consistent with a prior study by Sato et al., which reported elevated ACTH levels in children with CVS prior to their vomiting episodes.⁹ Since prostaglandins can stimulate ACTH release and are known to cause vomiting, Pankaj et al. proposed that ketorolac, as well as other nonselective NSAIDs, may prevent CVS episodes by inhibiting prostaglandins synthesis.⁹ Nonselective NSAIDs have since been considered as a treatment option for both children and adults with CVS.^{7,10,11} Tricyclic antidepressants are also important in alleviating the symptoms of CVS, and it has been proposed that they do so by regulating the activity of the splanchnic sympathetic nervous system, and the neurotransmission in the medulla and nucleus tractus solitarius.⁸

Figure 1. Clinical course of cyclic vomiting syndrome and categories of current treatments.^{2,4-7}

While meloxicam is traditionally categorized as a nonselective NSAID, in vitro pharmacological testing has shown it to be more selective towards COX-2 than other nonselective NSAIDs such as naproxen and ibuprofen, which inhibit both COX-1 and COX-2 equally.¹² However, meloxicam is not as COX-2 selective as well-known highly selective COX-2 inhibitors, such as etoricoxib and rofecoxib.¹² Risks and side effects of meloxicam include cardiovascular thrombotic events, gastrointestinal ulcers and bleeding, and diarrhea, although the Meloxicam Large-scale International Study Safety Assessment (MELISSA) trial found that it significantly improved gastrointestinal (GI) tolerability in comparison with other nonselective NSAIDs in patients with osteoarthritis over the course of 28 days.^{13,14} This is consistent with many other studies, including the Celecoxib Long-term Arthritis Safety Study (CLASS), which have shown that selective COX-2 inhibitors such as celecoxib, rofecoxib, and etoricoxib result in fewer upper gastrointestinal complications than nonselective NSAIDs.^{15–17} However, additional studies are required to confirm the long-term GI benefits of selective COX-2 inhibitors, as the CLASS trial noted significantly fewer adverse upper GI effects over 6 months; but it was unclear that this benefit was maintained over 12–15 months.^{16,18}

And of course clinicians must balance the cardiovascular risks with the GI benefits when prescribing COX-2 selective NSAIDs to CVS patients. Studies evaluating the long-term effects of selective COX-2 inhibitors are critical for determining appropriate management of CVS patients, who may require long-term usage of these medications.

The patient in this case experienced rapid reduction of symptoms upon adding meloxicam to his tricyclic antidepressant prophylaxis regimen of nortriptyline nightly. Furthermore, he was able to decrease his nortriptyline dose three-fold, implying that the most significant effect was from the meloxicam. However, it should be noted that he has not been able to fully eliminate the nortriptyline, thus suggesting an interesting synergy. Similarly, in the prevention of migraines, the combination of sumatriptan with an NSAID was found to be more effective than either one alone, likely because each drug class affects a different pathway of migraine pathophysiology, nociceptor activation and central sensitization, respectively.¹⁹ One possible explanation for our observation is that NSAIDs modulate the patient's pain threshold, thereby allowing a lower dose of the TCA to have a greater therapeutic effect on CVS symptoms. Alternatively, both TCAs and NSAIDs have separately been shown to reduce nitric oxide (NO) levels.^{20,21} Thus, their combined use may lead to a summative decrease in NO, yielding a greater anti-inflammatory effect, and providing better CVS prophylaxis than either medication alone.

CONCLUSION

This is the first report in which an NSAID with semi-selective COX-2 inhibition was found to have a significant effect on alleviating symptoms in a CVS patient, possibly by inhibiting prostaglandin synthesis through its more preferential COX-2 inhibitory activity.²² Additionally, this is the first report of using a once-daily NSAID for CVS management, which has clinical significance since treatment compliance, and subsequent effectiveness, increases with less frequent dosing regimens.²³ Finally, this is the first report of the possible synergistic effect of combining an NSAID with a tricyclic antidepressant to effectively treat CVS. Our report thus supports the idea that once-daily COX-2 selective NSAIDs may be considered as a viable treatment option, or at least an important adjuvant, for some patients with CVS. Further research on the use of COX-2 selective NSAIDs, perhaps in combination with tricyclic antidepressants, should be considered for this difficult-to-control disease.

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Conflict of Interest: The authors declare that they do not have a conflict of interest.

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REFERENCES

1. **Fleisher DR, Gornowicz B, Adams K, Burch R, Feldman EJ.** Cyclic Vomiting Syndrome in 41 adults: the illness, the patients, and problems of management. *BMC Med.* 2005;3:20.
2. **Abell TL, Adams KA, Boles RG, et al.** Cyclic vomiting syndrome in adults. *Neurogastroenterol Motil.* 2008;20:269–284.
3. **Tack J, Talley NJ, Camilleri M, et al.** Functional gastroduodenal disorders. *Gastroenterology.* 2006;130:1466–1479.
4. **Hejazi RA, McCallum RW.** Review article: cyclic vomiting syndrome in adults — rediscovering and redefining an old entity. *Aliment Pharmacol Ther.* 2011;34:263–273.
5. **Lee LYW, 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.
6. **Pareek N, Fleisher DR, Abell T.** Cyclic vomiting syndrome: what a gastroenterologist needs to know. *Am J Gastroenterol.* 2007;102:2832–2840.
7. **Olden KW, Chepyala P.** Functional nausea and vomiting. *Nat Clin Pract Gastroenterol Hepatol.* 2008;5:202–208.
8. **Hejazi RA, Reddymasu SC, Namin F, Lavenbarg T, Foran P, McCallum RW.** Efficacy of tricyclic antidepressant therapy in adults with cyclic vomiting syndrome: a 2-year follow-up study. *J Clin Gastroenterol.* 2010;44:18–21.
9. **Pasricha PJ, Schuster MM, Saudek CD, Wand G, Ravich WJ.** Cyclic vomiting: association with multiple homeostatic abnormalities and response to ketorolac. *Am J Gastroenterol.* 1996;91:2228–2232.

10. **Sunku B.** Cyclic vomiting syndrome: a disorder of all ages. *Gastroenterol Hepatol.* 2009;5:507–515.
11. **Li BU, Lefevre F, Chelimsky GG, et al.** North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr.* 2008;47:379–393.
12. **Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P.** Pharmacodynamic of cyclooxygenase inhibitors in humans. *Prostaglandins Other Lipid Mediat.* 2007;82:85–94.
13. National Institutes of Health. Meloxicam. Available at: <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601242.html>. Accessed April 11, 2012.
14. **Hawkey C, Kahan A, Steinbrück K, et al.** Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. *Br J Rheumatol.* 1998;37:937–945.
15. **Engelhardt G.** Pharmacology of meloxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibition of COX-2. *Br J Rheumatol.* 1996;35:4–12.
16. **Chaiamnuay S, Allison JJ, Curtis JR.** Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs. *Am J Health Syst Pharm.* 2006;63:1837–1851.
17. **Silverstein FE, Faich G, Goldstein JL, et al.** Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *JAMA.* 2000;284:1247–1255.
18. **McCormack JP, Rangno R.** Digging for data from the COX-2 trials. *CMAJ.* 2002;166:1649–1650.
19. **Edwards KR, Rosenthal BL, Farmer KU, et al.** Evaluation of sumatriptan-naproxen in the treatment of acute migraine: a placebo-controlled, double-blind, cross-over study assessing cognitive function. *Headache.* 2013;53:656–664.
20. **Vismari L, Alves GJ, Muscará MN, et al.** A possible role to nitric oxide in the anti-inflammatory effects of amitriptyline. *Immunopharmacol Immunotoxicol.* 2012;24:578–585.
21. **Dave M, Amin AR.** Yin-yang regulation of prostaglandin and nitric oxide by PGD2 in human arthritis: reversal by celecoxib. *Immunol Lett.* 2013;152:47–54.
22. **Bombardier C, Laine L, Reicin A, et al.** Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med.* 2000;343:1520–1528.
23. **Claxton AJ, Cramer J, Pierce C.** A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001;23:1296–1310.