Clonidine in Cyclic Vomiting

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A 6-year-old boy of Asian descent presented with repeated vomiting, which was preceded by a runny nose and cough. He had no fever or diarrhoea, but he did have associated nausea with abdominal pain. He had not responded to sublingual ondansetron and failed oral rehydration at home. He was clinically dehydrated and was admitted and given intravenous (IV) rehydration. He had similar episodes since he was 4 years old; however, the intensity of the attacks was worsening, requiring prolonged admission. He had a diagnosis of cyclic vomiting syndrome (CVS) made after ruling out gastroenterological, metabolic, neurological, and urological causes. Abdominal ultrasound, upper gastrointestinal contrast study, magnetic resonance imaging of the brain, and urine metabolic screen failed to reveal any underlying abnormality. Because his mother had a history of migraines, an empiric trial of cyproheptadine/pizotifen and sumatriptan was initiated but failed as a part of his prophylactic and abortive treatment, respectively.

During this admission, he was on continuous rehydration along with IV ondansetron infusion, IV chlorpromazine, benztropine, and IV omeprazole, but he did not respond. Full blood cell count, electrolytes, blood sugar, serum lipase, and liver and renal functions were normal. Urine dipstick had 4+ ketones. He was started on 10% dextrose normal saline infusion, with no improvement. He was pale with a heart rate between 100 and 120 bpm. His blood pressure (BP) was normal on admission, but after 48 hours, it was persistently high, with systolic pressure 130 to 147 mmHg and diastolic 80 to 90 mmHg. He had been noted to be hypertensive at times during his previous admissions. Urinary catecholamines were normal. His requests for hot-water baths rapidly became compulsive. His abdominal pain was concerning enough to warrant a surgical opinion to rule out surgical causes. A trial of dexamethasone failed. Clonidine was tried on day 5, initially at a low dose of 25 μg IV (1 μg/kg), which was later stepped up to 50 μg IV (2 μg/kg). Clonidine was given as an infusion for 30 minutes, with his heart rate and BP monitored every 5 minutes. Symptom control was obtained within 1 hour along with normalisation of BP. Vomiting recurred after 6 hours along with an increase in BP. He was anxious, pale, and miserable. A repeat dose resolved his symptoms and normalised his BP. The association between his symptoms and BP was marked. He was discharged on day 7. He had an episode 3 months later, wherein a trial of routine care was initiated but with no response and an elevated BP; IV clonidine was introduced on day 3, initially at 25 μg with minimal response and increased to 50 μg with good effect. He was discharged on day 5. Oral clonidine 25 μg was tried during 1 of the episodes and was commenced on day 1, even in the absence of hypertension with good effect. He was discharged on day 3. On a later admission, he did not tolerate oral clonidine because of his ongoing emesis and required IV administration. Interestingly, he responded to a low dose of 25 μg and was discharged in 36 hours; however, a dose of 25 μg IV did not work during the subsequent admissions. We have been successful with an IV dose of 2 μg/kg in our patient even in the later admissions (Table 1). We currently use 2 μg/kg IV clonidine early in the course of his illness along with ondansetron infusion and IV proton pump inhibitors to help curtail the episode and repeat clonidine every 6 to 8 hours as required. He is also receiving amitriptyline as a part of his prophylactic treatment, which has remarkably reduced the frequency of his episodes.

DISCUSSION

Cyclic vomiting is an idiopathic gastrointestinal disorder occurring in approximately 2% of children (1). Although initially thought to be a paediatric disorder, it is increasingly recognised in adults (2). It is characterised by recurrent, stereotypic episodes of nausea and vomiting, with episodes of well-being in the interval between attacks. Although vomiting is the hallmark, other symptoms include nausea, headache, abdominal pain, and photophobia. Autonomic dysfunction is evidenced by tachycardia, high BP, pallor, fever, and, occasionally, diarrhoea.

CVS is believed to be a variant of migraine, although several theories prevail including mitochondrial/genetic factors, autonomic dysregulation, neuromuscular disorders, and a tendency to anxiety (1,2). A heightened sympathetic response may also play a role. Evidence of activation of the hypothalamo-pituitary-adrenal axis was first provided by Wolfe and Adler (3) and Sato et al (4). Elevated levels of adrenocorticotropic hormone, antidiuretic hormone cortisol, prostaglandin E2, and serum and urinary catecholamines during episodes of CVS were demonstrated by Sato et al (5). Blunting of the accentuated hypothalamo-pituitary-adrenal axis with symptom reduction has been shown through the use of clonidine (5) and high-dose dexamethasone (3). The present theory is that CVS is a functional brain–gut disorder involving central neuroendocrine mediation and peripheral gastrointestinal manifestations (2).

There are no controlled therapeutic trials; however, a North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement has outlined management based on paediatric case series (6). Recommendations include lifestyle changes, prophylactic therapy (cyproheptadine in $\leq$5 years, amitriptyline for >5 years) and acute therapy (5-HT receptor antagonists as abortive therapy), and 10% dextrose and ondansetron for those requiring IV hydration. The standard hospital management involves restoring and maintaining hydration and aborting the attack with ondansetron and/or chlorpromazine, the rationale being to induce sleep and stop vomiting. H2 blockers or proton pump inhibitors are used to counter the associated oesophagitis and gastritis. Ten percent glucose infusions are tried because of the possibility of an underlying metabolic disorder. In children in whom anxiety appears to be the trigger, cognitive behavioural therapy and anxiolytics may be helpful. The role of family support

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TABLE 1. Use of clonidine during admissions

Presentation	Day of commencement of clonidine	Initial dose of clonidine, μg/kg	Route	Dose increased in view of no response, μg/kg	Day of discharge
1	5	1	IV	2	7
2	3	1	IV	2	5
3	On admission	1	PO	—	3
4	On admission	1	PO failed→IV	—	$1^1/_2$
5	On admission	1	IV	2	2
6	On admission	2	IV	—	$2^1/_2$

Repeat doses given every 6 to 8 hours according to symptoms. IV = intravenous; PO = per oral.

cannot be underestimated during these enduring and frustrating times (7).

Intractable cases require a longer duration of stay with the associated morbidity of the condition. There have been reports of use of dexmedetomidine and clonidine (8,9). Dexmedetomidine is an alpha$_2$-adrenergic agonist with an increased specificity for alpha$_2$ versus alpha$_1$ receptors when compared with clonidine. It was successfully used in 3 children with CVS (8).

Clonidine is a presynaptic CNS alpha$_2$-agonist, stimulating receptors in the nucleus tractus solitarii of the medulla. It inhibits sympathetic outflow, which reduces vasoconstriction, inotropy, and chronotropy; therefore, it is used primarily as an antihypertensive. Particularly in the last couple of decades, clonidine has been tried in various conditions (10).

Clonidine is a useful preanaesthetic medication in children because of its sedative and analgesic properties (11,12). The sedative effect is possibly the result of its inhibitory effect on locus coeruleus, a noradrenergic pontine structure involved in the control of the sleep/wake cycle. Clonidine has also reduced the need for intra- and postoperative analgesia (13,14). Clonidine was thought to induce vomiting in humans and animals by its action on the chemoreceptor trigger zone (15). In a study designed to demonstrate whether there was an increase in postoperative vomiting in patients with clonidine, it was shown that, on the contrary, premedication with oral clonidine reduces postoperative vomiting after paediatric strabismus surgery (16). It was thought to be unique to this group. A similar observation was made, again substantiating the above finding (17). Recently, there has been an interest in the antiemetic effect of clonidine as documented by its use with general anaesthesia to reduce postoperative nausea and vomiting (18,19).

Clonidine has also been evaluated for childhood migraine prevention. In a study of 54 children, clonidine was no more effective than placebo (20). A subsequent study of 50 children found benefit for clonidine in an open-label phase, but not in a double-blind, placebo-controlled phase (21). The American Academy of Neurology practice parameter concluded that clonidine is not effective and is not recommended (22).

There have been limited data on the use of clonidine in cyclic vomiting (5,9). Clonidine $2\ \mu g \cdot kg^{-1} \cdot dose^{-1}$ was tried in a child with intractable CVS along with IV midazolam infusion leading to resolution of symptoms, and was repeated on subsequent presentations with good response and early discharge (9). Clonidine was effective in this child, although the BP was normal.

A dose of 2 μg/kg consistently produced the desired effect, but concern about hypotension led us to try a lower dose of 1 μg/kg, which interestingly provided a partial/inconsistent response. Heart rate and BP were closely monitored during the infusion with no concerns. Dry mouth and sedation, which are the usual adverse effects of clonidine, are beneficial for a child with CVS. Hypotension, bradycardia, and disturbance of atrioventricular conduction are the possible untoward adverse effects of clonidine, but doses of 2 to 4 μg/kg were found to be relatively safe in most studies wherein clonidine was used as a preanaesthetic agent (10,16,17). BP typically decreases more in hypertensive than in normotensive patients after systemic clonidine administration. We used clonidine in our patient even when he was normotensive with good response and no concern about hypotension. Palmer and Cameron (9) also used clonidine in a child with normal hemodynamic parameters with good effect.

The sedative action of clonidine along with its analgesic, sympatholytic, and possible antiemetic effect possibly explains its role in CVS. The increased salivation in CVS is also reduced by clonidine, which decreases secretions. It would be reasonable to try clonidine in a child who does not respond to conventional management. Because children with CVS have stereotypical presentation, early introduction of clonidine would be beneficial in subsequent attacks. This would abort the episode faster and help in earlier discharge.

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