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REVIEW

Clinical Practice: Nausea and vomiting in acute gastroenteritis: physiopathology and management

Beatrice C. Canziani[1] · Peter Uestuener[1] · Emilio F. Fossali[1] · Sebastiano A. G. Lava[2,3,4] · Mario G. Bianchetti[5,6] · Carlo Agostoni[1] · Gregorio P. Milani[1,7]

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Abstract Currently recommended management of acute gastroenteritis is supportive. Although the affected children habitually have vomiting, recommendations do not focus on the correction of this symptom. In this condition, elevated ketone bodies and stimuli initiated by gut mucosa damage produced by the enteral pathogen likely underlay nausea and vomiting. As compared to 0.9% saline, intravenous administration of a dextrose-containing bolus of 0.9% saline is associated with a greater reduction of circulating ketones and a shorter duration of nausea and vomiting. Nonetheless, this treatment strategy is not followed by a lower rate of hospitalization.

Conclusion: Well-designed investigations suggest that antagonists of the type 3 serotonin receptor, most frequently oral ondansetron, reduce the rate of vomiting, improve the tolerance of oral rehydration, and reduce the need for intravenous rehydration.

What is Known:
- *Although children with gastroenteritis habitually have vomiting, current recommendations do not focus on the correction of this symptom.*

What is New:
- *Recently acquired evidence supports the prescription of ondansetron, an antagonist of the type 3 serotonin receptor, to increase the success rate of oral rehydration therapy.*

Keywords Acute gastroenteritis · Antagonists of the type 3 serotonin receptor · Ketosis · Ondansetron · Vomiting

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✉ Gregorio P. Milani
milani.gregoriop@gmail.com

Beatrice C. Canziani
bccanziani@gmail.com

Peter Uestuener
peter.uestuener@gmail.com

Emilio F. Fossali
emilio.fossali@unimi.it

Sebastiano A. G. Lava
sebastiano.lava@bluewin.ch

Mario G. Bianchetti
mario.bianchetti@usi.ch

Carlo Agostoni
agostoc2@gmail.com

[1] Pediatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy

[2] University Children's Hospital, Inselspital, Bern, Switzerland

[3] University of Bern, Bern, Switzerland

[4] Division of Clinical Pharmacology and Toxicology, Ente Ospedaliero Cantonale, Institute of Pharmacological Sciences of Southern Switzerland, Lugano, Switzerland

[5] Pediatric Department of Southern Switzerland, 6500 Bellinzona, Switzerland

[6] Università della Svizzera Italiana, 6900 Lugano, Switzerland

[7] Pediatric unit, Foundation IRCCS Ca' Granda, Ospedale Maggiore Policlinico, via della Commenda 9, 20122 Milan, Italy

Introduction

Acute childhood gastroenteritis is an infectious syndrome characterized by three or more loose stools per day (or a number of bowel movements exceeding the child's usual number of daily bowel movements by two or more) with or without associated fever and vomiting. It usually lasts less than 1 week and no longer than 2 weeks [20]. Currently recommended management is supportive and includes repletion and maintenance of ongoing fluid losses and the resumption of an age-appropriate diet as soon as rehydration is complete (breastfeeding can continue during diarrhea). Since both viral and bacterial gastroenteritides mostly resolve spontaneously, therapy with antidiarrheal agents, antimotility drugs, antisecretory drugs, absorbents, or antimicrobials is not advised. Finally, except in cases with bloody diarrhea or very high fever and in patients immunocompromised or with relevant comorbidities, identifying the pathogen is not warranted [20].

Although children with acute gastroenteritis habitually have vomiting, current practice recommendations exclusively promote hydration with oral solution given in fractionated, small portions but do not focus on the correction of this symptom [20]. Nonetheless, more and more observations indicate that vomiting is the main cause of failure of oral rehydration therapy. This brief article aims to review the mechanisms underlying vomiting and focus on new treatment strategies such as control of gastroenteritis-associated ketosis and agents prescribed for chemotherapy-induced emesis such as ondansetron, an antagonist of the type 3 serotonin receptor.

Physiology of vomiting

Vomiting is usually preceded by nausea, i.e., an unpleasant sensation centered in the epigastrium and retching, i.e., a contraction of the abdominal muscles and diaphragm. Vomiting itself is characterized by a violent coordinated contraction of the diaphragm and abdominal muscles accompanied by pyloric constriction and gastroesophageal relaxation [18].

The vomiting center (Fig. 1), which is located in the medulla oblongata, can be activated from the cerebral cortex (anticipation, fear, memory), from sensory organs (disturbing sights, smells, pain), and from the vestibular apparatus, by the gastrointestinal tract or by stimuli that activate the chemoreceptor trigger zone [18]. This zone is located within the floor of the fourth ventricle, is outside of the blood-brain barrier, and in intimate contact with the blood [18].

Two mechanisms likely underlay vomiting in gastroenteritis [18, 20]. First, similar to diabetic ketoacidosis, in children with moderate to severe acute gastroenteritis, elevated ketone bodies contribute to ongoing symptoms of nausea and vomiting. Second, the major pathways, through which vomiting is induced, are afferent stimuli initiated by gut mucosa damage produced by the pathogen. Repair of ketosis and antiemetic drugs that modulate the visceral afferent stimuli have been investigated over the past decade to manage vomiting in acute childhood gastroenteritis.

Ketosis

In gastroenteritis, poor dietary intake, vomiting, and malabsorption result in an energy deprivation with transition from a phase in which carbohydrates are the primary cellular energy source to a phase in which proteins and fats supply energy [4, 11]. The initial response to energy deprivation is to switch off insulin production, which is followed by a release of glucagon and subsequently cortisol and epinephrine. This in turn enhances glycogen and protein breakdown [4, 11]. Finally, lipolysis occurs and releases glycerol, which is converted to glucose and free fatty acids, which are oxidized to ketone bodies. Infants and young children have higher energy requirements than adults. Furthermore, they have limited glycogen stores that last for a maximum of 4 hours in infants and of 8–(12) hours in young children [4, 11]. Consequently, in these age groups, ketosis occurs a few hours after energy deprivation. Whilst ketones allow withstanding periods of starvation, they cause nausea and vomiting [4, 11].

Fasting or food reduction is no more advocated in acute childhood gastroenteritis. Currently recommended resumption of an age-appropriate diet not only stimulates repair of the intestinal mucosa and sustains breastfeeding [20] but also prevents, at least in part, the development of ketosis.

It has been hypothesized that moderately to severely dehydrated children given a dextrose-containing intravenous bolus would have a greater reduction in ketone levels (through increased endogenous insulin release), a shorter duration of vomiting, and subsequently a lower rate of hospitalization [4, 11]. Available data point out that, as compared to 0.9% saline, administration of a dextrose-containing intravenous bolus of 0.9% saline is associated with a greater reduction of ketones and a shorter duration of nausea and vomiting. Nonetheless, this treatment was not followed by a lower rate of hospitalization [9, 12, 13, 16]. A 5%-dextrose-containing 0.9% saline solution is currently advised for standard intravenous maintenance fluid prescription in children [14, 15]. In this solution,

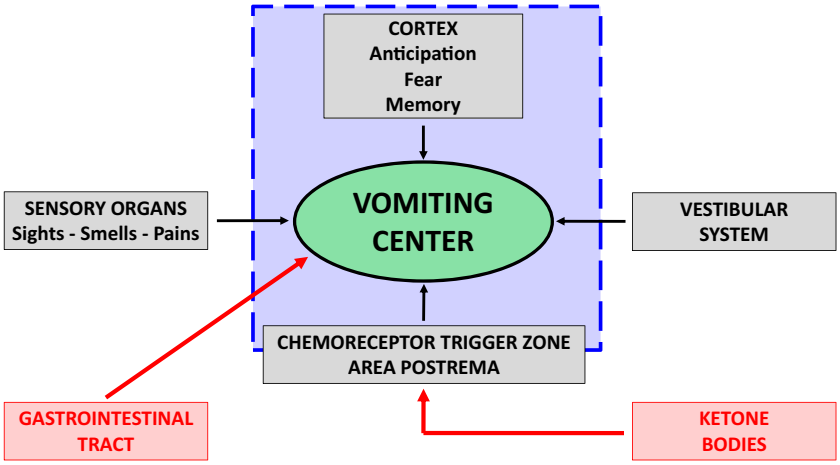

Fig. 1 Pathophysiology of vomiting. Noxious stimulations of the vomiting center via one or more of four sites may cause vomiting: the gastrointestinal tract, the vestibular system, the chemoreceptor trigger zone, which it is outside the blood-brain barrier (blue color) and higher centers in the cortex. Ketone bodies-mediated activation of the chemoreceptor trigger zone and especially afferent stimuli from the gastrointestinal (red color) tract are presumed to play a major role in the development of vomiting associated with acute gastroenteritis

dextrose, which is rapidly metabolized on entering the bloodstream, is provided to prevent hypoglycemia and ketosis, although it does not provide complete nutritional support. This recommendation appears valuable also for severe acute childhood gastroenteritis [16].

Antiemetic drugs

Acetylcholine, histamine, dopamine, and serotonin are of primary importance in the vomiting reflex. Several classes of antiemetic drugs have been made available that antagonize receptors of these neurotransmitters [7, 8, 18].

1. *Anticholinergic drugs* like scopolamine and *antagonists of the type 1 histamine receptor* such as meclizine and dimenhydrinate act on the vestibular system. They are prescribed for motion sickness and inner ear disorders [7, 8].
2. *Antagonists of the type 2 dopamine receptor* include phenotiazines such as prochlorperazine or chlorpromazine, which also have anticholinergic and antihistamine blocking effects; butyrophenones such as droperidol or haloperidol and benzamides, such as metoclopramide, which also has some effect on the type 3 serotonin receptor. Domperidone, a further antagonist of the type 2 dopamine receptor, does not cross the blood-brain barrier and therefore lacks the neurologic side effects of the remaining drugs with this mode of action. These drugs act on the chemoreceptor trigger zone and are prescribed for mild chemotherapy-induced emesis and postoperative vomiting [7, 8].
3. *Antagonists of the type 3 serotonin receptor* such as ondansetron, granisetron, dolasetron, and palonosetron are the most prescribed class of antiemetics for chemotherapy-induced emesis and postoperative vomiting. The oral formulation of these drugs has similar efficacy to intravenous dosing [7, 8].

Antiemetics in acute gastroenteritis

Approximately 80% of Italian pediatricians routinely administer antiemetics to children with an acute gastroenteritis. The type 1 antihistamine meclizine and the antagonists of the type 2 dopamine receptor metoclopramide and domperidone have been widely prescribed [1, 21]. Nonetheless, few and inconclusive data support the use of these agents in this setting [3].

Well-designed investigations and recent literature overviews suggest that antagonists of the type 3 serotonin receptor, most frequently oral disintegrating tablets of ondansetron, reduce the rate of vomiting, improve the tolerance of oral rehydration, and reduce the need for intravenous rehydration and the length of hospital stay [3, 17, 19]. Ondansetron prolongs the electrocardiographic QT interval and subsequently has a potential to cause cardiac arrhythmias. However, the administration of a single ondansetron dose in a previously healthy child with gastroenteritis is safe and does not require electrocardiogram or electrolyte screening [3, 17, 19].

More and more data indicate that in childhood gastroenteritis, ondansetron use dramatically increases [5]. Nonetheless, intravenous rehydration decreases only minimally thereby not confirming the efficacy observed in clinical trials [5]. At least three causes may explain these apparently surprising data [5, 6, 10]. First, administering ondansetron to a child with gastroenteritis having minimal to no vomiting is not likely to change the outcome. Second, ondansetron is probably not being

Table 1 Management of vomiting with a single dose of ondansetron in acute childhood gastroenteritis

- Not advised in children without vomiting whose exclusive symptom is moderate to severe diarrhea (because the most common side effect of ondansetron is diarrhea)
- Warranted uniquely in otherwise healthy infants > 6 months of age and children with mild to moderate dehydration who have failed oral rehydration therapy
- Weight-based oral dosing regimen (oral rehydration therapy should be initiated 15 min after administration of ondansetron):
  - 7–15 kg: 2 mg
  - 16–30 kg: 4 mg
  - >30 kg: 8 mg
- Begin oral rehydration 15 min after ondansetron is given

properly incorporated into a bundle of care delivered in the emergency unit. More specifically, it may be that the sequencing or timing of its delivery with respect to the evaluation and decision making for these children is not appropriate. For example, ondansetron may not be given early enough to have the anticipated effect, and so oral rehydration therapy is abandoned for intravenous rehydration. Finally, ondansetron is given but its effect is never used to make a decision about whether a trial of oral rehydration therapy should be attempted or continued (e.g., the patient arrives in the emergency unit, is given ondansetron, and immediately is given intravenous rehydration). The discrepancy between the results from well-conducted trials and lack of effectiveness in the real world makes a strong case for research looking at why and how clinicians take decisions on treatments, and how these can be improved [6, 10]. In the meantime, many institutions (including our own) currently prescribe ondansetron as detailed in Table 1 [2].

Conclusions

In children with moderate to severe dehydration, management with 5%-dextrose-containing 0.9% saline is associated with a reduction of circulating ketones and a shorter duration of nausea and vomiting.

Available data do not support the management of gastroenteritis-associated vomiting with an antagonist of the type 1 histamine receptor or an antagonist of the type 2 dopamine receptor. Current evidence supports administration of a single dose of ondansetron to increase the success rate of oral rehydration therapy, and this intervention may be endorsed in the management of acute childhood gastroenteritis in emergency departments. Nonetheless, research is required to test out the best practices in deciding how to maximize the benefits of this agent in everyday pediatric practice.

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Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals Not applicable (review study).

Informed consent Not applicable (review study).

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