Proton pump inhibitors for irritable infants

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Abstract

Question Crying is common in infants; however, caring for infants with inconsolable crying, previously also known as *colic* or *reflux*, is often extremely distressing for parents. Is there a benefit to using gastric acid suppression (eg, proton pump inhibitors [PPIs]) in these infants?

Answer The use of PPIs in infants and children has increased in recent years. The efficacy of proton pump inhibitors has not been demonstrated in the treatment of irritability and excessive crying in otherwise healthy infants younger than 3 months of age. Conversely, while PPIs are generally well tolerated, there is some evidence to link the use of PPIs with increased susceptibility to acute gastroenteritis, community-acquired pneumonia, and disorders of nutrient absorption and utilization. Irrespective of treatment, crying and irritability in infancy generally improve with time. Proton pump inhibitors do not improve symptoms in the interim.

In the western world, excessive crying in the first months of life is the most common reason parents seek medical attention for their infants.[1] Up to 40% of infants are reported to have excessive crying, previously also referred to as *infantile colic* or *reflux*.[2] Biocultural factors implicit in early development and infant care, as well as different definitions for what constitutes *excessive crying*, might explain the wide variation in the report of crying in the world literature, especially given the global diversity in cultures and nationalities.[1,3] *Excessive crying* has been defined in many ways to reflect the duration of crying, the infant's inconsolability, or the distress caused by the crying on the caretaker. Wessel et al described *colic* as paroxysms of crying for 3 or more hours per day for 3 days or more per week in otherwise healthy, well-fed infants.[4] Other definitions include severe crying for several hours per day[5] or crying to a point at which parents think they are no longer able to cope.[6] Crying is a normal developmental phenomenon in healthy infants, which peaks between 6 weeks and 3 months of age.[7] While excessive crying in infancy might be seen as a common and sometimes trivial problem, it has been associated with serious issues of child abuse, maternal depression, attachment issues, and family breakdown.[8-10]

Gastroesophageal reflux in infancy

Gastroesophageal reflux (GER) is the retrograde passage of gastric contents into the esophagus, often manifested as vomiting or regurgitation.[11] In a study of 948 healthy infants (0 to 13 months old), 50% of those 0 to 3 months old, 67% of those 4 months old, and 21% of those 6 to 7 months old regurgitated at least once a day. For infants aged 10 to 12 months, only 5% regurgitated at least once a day.[12] Similarly, a prospective cohort study of 693 children followed from birth reported that 41% of infants between 3 and 4 months of age had regurgitation with most feeds, while the incidence declined to less than 5% between 13 and 14 months of age.[13] Thus, GER is a common physiologic phenomenon in infancy that is age related, with most infants having complete resolution by the time they are walking. In contrast, gastroesophageal reflux disease (GERD) is defined as GER that is associated with persistent symptoms or complications, such as esophagitis, failure to thrive, or respiratory disorders.[14] Some physicians have considered GERD in the differential diagnosis of infants with excessive crying and irritability.

In recent decades there has been an exponential increase in the diagnosis and treatment of GERD in infants.[12] A retrospective study of 2469 infants in the United States between 1999 and 2004 reported a greater than 7-fold increase in proton pump inhibitor (PPI) use, with the liquid PPI formulation having a 16-fold increase during the study period. More important, 50% of infants had initiated PPI treatment by the age of 4 months.

Efficacy of PPIs in infancy

When reviewing clinical trials that assess the efficacy of PPIs in infants with recurrent regurgitation or excessive crying, it is important to recognize that symptom reduction (eg, irritability or regurgitation) or changes in gastric acidity are usually among the study outcome measures. This poses a challenge to study interpretation because these symptom parameters are inherently expected to

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diminish as infants age. It is also worth considering that studies that examine outcomes of infant behaviour (eg, crying) are encumbered by a heterogeneous population that is broadly aged (3 to 12 months) with a wide spectrum of developmental maturity.

A recent systematic review including 5 placebo-controlled studies in infants (34 weeks postmenstrual age to 12 months old) concluded that PPIs were not effective in reducing GERD symptoms of feeding-related crying or infant irritability.[15] Of 64 healthy but irritable infants recruited for a placebo-controlled, randomized, double-blind study to assess the efficacy of omeprazole for irritable infants with GERD (abnormal pH probe results or endoscopic biopsy findings or both), 30 infants (3 to 12 months of age) had met inclusion criteria with proven GERD. There was a significant reduction in reflux index (the percentage of time pH was less than 4 during 24-hour esophageal pH monitoring) in infants taking omeprazole compared with placebo (change in reflux index -8.9%, -1.9%, respectively; $P<.001$).[16] However, no significant difference in crying or irritability scores was observed between the omeprazole or placebo groups (cry score 191 min/d, 201 min/d, respectively; $P=.4$). Moreover, there was a substantial improvement in irritability over a 4-week period in both the treatment and control groups, supporting the concept that infant irritability improves with age.[16]

The recently published pediatric gastroesophageal reflux clinical practice guidelines jointly sponsored by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition state that GERD is an uncommon cause of unexplained crying or distress in otherwise healthy infants and that empiric use of acid suppression therapy in these infants is not recommended.[14]

Safety of PPIs for infants

While many have long considered PPIs to be well tolerated and of low risk, several recent adult studies have challenged the safety profile of PPIs.[17] However, there are few data on the dosage or safety of PPIs in infants younger than 1 year of age. A study with 186 children aged 4 to 36 months who were followed for 4 months demonstrated a significant increase in episodes of acute gastroenteritis (19% control, 47% gastric acid inhibitors; $P=.001$) and pneumonia (2% control, 12% gastric acid inhibitors; $P=.03$).[18]

Further theoretical concerns for infants such as the potential risks of reduced absorption of nutrients including vitamin B12 and iron due to reduced gastric acidity, while not adequately studied in children, is not reported in adult studies.[19,20] In addition PPIs might have an effect on calcium absorption or regulation as evidenced by recent reports of an increased risk of hip fractures among adults using PPIs, but the pathophysiology of this is as yet unclear.[21]

Conclusion

The use of PPIs in the management of infants with excessive crying, based on a presumptive diagnosis of GERD, remains a common practice among pediatric caregivers despite the lack of any evidence-based treatment efficacy or utility in these patients. Indeed the recent North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition practice guidelines for gastroesophageal reflux specifically assert that PPIs are not generally indicated in these

cases. When GERD or other gastrointestinal pathology is considered the most likely cause of excessive crying, definitive investigation might be warranted, and only in selected infants might a short trial of acid suppression therapy be indicated.

Competing interests
None declared

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