Complementary Feeding: Keeping the Message Simple

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See ''Effect of Sequencing of Complementary Feeding in Relation to Breast-Feeding on Total Intake in Infants'' by Shah et al on page 339.

During the first 6 months of life, the dietary advice given to mothers is simple and boils down to ''start breast-feeding within one hour from birth'' and ''exclusively breast-feed up to the age of 6 months.'' During the complementary feeding period, the message is more complex. In 2003, the Pan American Health Organization (PAHO) and the World Health Organization (WHO) published a short document with 10 guiding principles to advise mothers during the complementary feeding period (1). Despite the remarkable efforts to coin simple messages in this document, they remain difficult to deliver in the context of a typically overcrowded poor country under-5 clinic or by overworked community health workers. This is a problem because diets are often inadequate during this period and/or they lacked some key nutrients.

The maintenance of breast-feeding beyond 6 months is one of the key PAHO-WHO guiding principles. To preserve this principle, some programmes also advise ''always'' breast-feeding before each meal of complementary food. This makes the message more complex, but this advice was not included in the PAHO-WHO guiding principles. A review of the literature carried out during the preparation of the PAHO-WHO guiding principles did not find any evidence in favour of the advice (2). One study from the United Kingdom (published in a journal not referenced in the usual bibliographic medical databases) suggested that breast-feeding before or after complementary food did not have an effect on total breast milk or energy intake (3). Because of the weak evidence base, no message about the order of breast and complementary feeds was included in the PAHO-WHO guiding principles.

An article from India published in an upcoming issue of the *Journal of Pediatric Gastroenterology and Nutrition* helps to fill this evidence gap (4). This well-designed crossover study confirms the lack of effect of the timing of complementary feeds in relation to breast-feeding on daytime energy intake and breast milk volume. Although the study had limitations and examined this effect only in the short term, current evidence does not support the advice, that is, to always breast-feed before each complementary feeding.

The practical difficulties of preparing adequate complementary feeds in the context of poverty should not be underestimated. Asking the mother to breast-feed before giving complementary foods makes the process more complicated, especially if she is trying to juggle feeding both an infant and other family members. Thus, this new evidence from India is a welcome addition to the evidence base on complementary feeding.

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Lubiprostone in Pediatric Functional Constipation

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See ''Lubiprostone for the Treatment of Functional Constipation in Children'' by Hyman et al on page 283.

Intestinal fluid secretion is driven by an osmotic gradient that is dependent on chloride transport at the apical plasma membrane of epithelial cells. Three different channels have been identified through which chloride can be secreted into the intestinal lumen: the cystic fibrosis transmembrane conductance regulator (CFTR), the calcium-activated chloride channels, and the chloride channel type-2 (ClC-2) (1).

CFTR is a cyclic adenosine monophosphate (cAMP)–activated chloride channel that is mainly expressed in the crypt of the intestinal epithelium. Mutations in the *CFTR* gene are responsible for the autosomal recessive cystic fibrosis (2). ClC-2 channels are located close to the tight junctions on the lateral membrane of the murine villus enterocyte and in a supranuclear compartment in humans (3). The definitive role of ClC-2 in intestinal chloride secretion is not yet fully elucidated, but the cross-talk between ClC-2 and CFTR has been demonstrated

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because the ClC-2 agonist lubiprostone was shown to be dependent on an intact CFTR (4).

Intestinal secretion is finely controlled by a variety of endocrine, paracrine, neuronal, and immunological modulators. The well-characterized intracellular second messengers are cAMP, cyclic guanosine monophosphate, and free cytosolic calcium. The abnormal regulation of the intestinal secretion such as activation of cAMP production by cholera toxin may lead to an acute life-threatening diarrhea. Accordingly, chloride secretagogues have been developed to enhance intraluminal water secretion. Linaclotide, a guanylate cyclase 2C agonist, increases intracellular cyclic guanosine monophosphate content and activates chloride secretion (5). Another chloride secretagogue is lubiprostone. This is a fatty acid derived from prostaglandin E1, which is a ClC-2 agonist. The mode of action of lubiprostone is thought to promote chloride secretion via activation of the EP4-type prostanoin receptor/cAMP/protein kinase A/CFTR through stimulation of intestinal and colonic secretion of chloride-rich fluid into the intestinal lumen (6). The increased fluid level is expected to soften the stools, promoting spontaneous bowel movements and reducing abdominal discomfort and pain.

In adults, lubiprostone has been shown to accelerate intestinal and colonic transit in healthy subjects without significantly affecting colonic motility or sensitivity assessed by barostat (7,8). Randomized controlled trials have demonstrated that lubiprostone is efficacious and safe in adult patients with chronic constipation and irritable bowel syndrome with constipation. In adults, lubiprostone is marketed at a dose of 24 μg twice per day (9–13). Some publications report a sustained effect and good long-term safety on a 48- to 52-week period (14,15). Lubiprostone is reported to cause nausea in approximately 30% of patients, with higher doses of lubiprostone associated with more gastrointestinal adverse events.

In this issue of the *Journal of Pediatric Gastroenterology and Nutrition*, Hyman et al (16) reported the results of an open-label, multicenter study on safety and effectiveness of lubiprostone for the treatment of functional constipation in children. In this 4-week study in 124 children ages 3 to 17 years with chronic constipation, according to the Rome III criteria, lubiprostone was administered to them after a 2-week period of observation. According to age and weight, the mean daily dose of lubiprostone ranged between 0.6 (in the younger children who received 12 μg every day) and 0.8 μg/kg (in the oldest children who received 24 μg twice per day). Symptoms were adequately monitored using personal electronic diaries. A total of 109 of 127 (86%) patients successfully completed the study protocol. The majority of patients (61.8%, 76/123) experienced a spontaneous bowel movement within 48 hours of the first dose of lubiprostone, but the first stool was achieved earlier in the children taking 24 μg twice per day. Statistically significant improvements from baseline were reported at each treatment week and overall for stool frequency, straining, and pain for bowel movements and stool consistency. There was no effect on abdominal discomfort and bloating and a poor effect on fecal incontinence. The tolerability was overall good with a low discontinuation rate because of adverse events. There was no relation between the dose of lubiprostone and any adverse events, with the exception of nausea, which occurred in 31.3% (10/32) of patients taking lubiprostone 24 μg twice per day compared with 18.5% (12/65) taking lubiprostone 12 μg twice per day and 3.7% (1/27) taking lubiprostone 12 μg every day.

Overall, the present study shows that lubiprostone is able to increase the stool frequency in constipated children. These findings also suggest that the onset of lubiprostone effect follows similar pattern in pediatric and adult patients and could be dose dependent. The short-term safety profile in children resembles the adults' profile, with nausea being the most reported adverse effect. Although these data are important for the proof of concept and the dose finding of lubiprostone in pediatric constipation, the main limitation of this study, as acknowledged by the authors, is the lack of a placebo group or of a comparator. Before drawing any definitive conclusion on the routine use of lubiprostone in constipated children, a randomized controlled trial is warranted.

WHAT WILL ADD LUBIPROSTONE TO TREATMENT CHOICES IN PEDIATRIC CONSTIPATION?

As proposed by Hyman et al, it is tempting to suggest that lubiprostone, whose mechanism of action is original, may be appropriate when standard therapies fail to resolve symptoms of functional constipation in children. The present guidelines recommend the use of osmotic laxatives such as polyethylene glycol (PEG) or lactulose as the first-line treatment for disimpaction and maintenance therapy in constipated children. PEG and lactulose have been both demonstrated to be effective and are inexpensive, with excellent safety and tolerance (17). In this context, one could ask whether lubiprostone, which is expensive, could really bring any additional value in the treatment of constipated children, although adverse events appear benign and self-limited. Data in adult patients comparing lubiprostone and PEG or any other therapy are presently lacking. The efficacy of lubiprostone on fecal incontinence should also be specifically addressed. Moreover, given that lubiprostone has no effect on visceral sensitivity and in view of the results presented by Hyman et al, it is critical to ask to what extent this treatment will help children with irritable bowel syndrome with constipation? Finally, the long-term safety in children must certainly be studied before the long-term administration of lubiprostone in children.

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