Treatment of diarrheal disease

Canadian Paediatric Society

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A review of the last five to 10 years of literature regarding oral rehydration recommendations and the treatment of diarrhea have yielded the following information.

There is no change in the indications and recommendations for the use of oral rehydration solutions in diarrheal disease in children outlined in the original Canadian Paediatric Society statement (1). However, there have been a number of studies that amplify the recommendations made in this paper and new evidence is presented on the composition of oral rehydration solutions (ORS) and therapy with antidiarrheal compounds. These compounds have a variety of mechanisms of action: alteration of intestinal motility, alteration of secretion, absorption of toxins or fluid and alteration of intestinal flora. They have the potential to modify the amount of fluid loss and the duration of diarrhea, but some are of no proven benefit and may have the potential for toxicity. It is worth considering the latest evidence about these compounds.

It is also worthwhile to re-emphasize some of the basic strategies in dealing with diarrheal disease.

ORAL REHYDRATION

The compositions of fluids that are used for oral rehydration have not changed much. There are two main types of oral rehydration salts in use. The first is the standard World Health Organization (WHO)/United Nations International Children's Fund (UNICEF) (see <http://www.unicef.org/ffl/07/5.htm>) solution which has an osmolality of 310 and contains 90 mmol/L of Na compared with ORS in use in Canada, which have osmolalities of 250 to 270 and contain 45 mmol/L to 60 mmol/L of Na. Use of the high Na WHO/UNICEF solution has the potential of inducing hypernatremia, but there have been few studies confirming this.

There is evidence from a recent collaborative study (evidence level I [see Table 1 for a description of the levels of evidence]) (2), suggesting that hypo-osmolar ORS may decrease the amount and duration of diarrhea in children compared with standard WHO/UNICEF ORS. WHO is planning to make changes in the WHO/UNICEF standard solution based on these research findings.

Complex carbohydrates, especially modified starches, appear to be useful adjuncts to standard ORS to promote fluid and electrolyte absorption and may add additional energy without increasing the osmotic load. However, results are variable. In a survey of randomized studies comparing standard WHO/UNICEF ORS with ORS in which the glucose (20 g/L) was replaced with 50 g/L to 80 g/L of rice powder, stool output was decreased in cholera but not in noncholera diarrhea (evidence level I) (3). However, in another study, uncooked rice powder was found to be an

Table 1
Levels of evidence

Level of evidence	Description
I	Evidence obtained from at least one properly randomized trial
II-1	Evidence obtained from well-designed controlled trial without randomization
II-2	Evidence obtained from well designed cohort or case-controlled analytic studies, preferably from more than one center of research group
II-3	Evidence obtained from comparisons between time and places, with or without the intervention. Dramatic results in uncontrolled experiments could also be included in this category
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports from expert committees
	Recommendations for preventive measures
A	There is good evidence to support this recommendation
B	There is fair evidence to support this recommendation
C	There is poor evidence to support this recommendation, but a recommendation could be made on other grounds
D	There is fair evidence to support the recommendation of exclusion
E	There is good evidence to support the recommendation of exclusion

Data from reference 32

Correspondence: Canadian Paediatric Society, 2204 Walkley Road, Suite 100, Ottawa, Ontario K1G 4G8. Telephone 613-526-9397, fax 613-526-3332, Web sites www.cps.ca, www.caringforkids.cps.ca

effective alternative to glucose or cooked rice in home based ORS (4).

Other starches have been added to ORS regimens with good effect. Modified tapioca starch (5), and plantain flour (6) have been found to be useful adjuncts to ORS by shortening the recovery period from diarrheal disease.

REFEEDING

Food (both milk and solids) should not be withheld during diarrheal disease (7) so that gut nutrition can be maintained. Breastfeeding should be continued along with the administration of ORS throughout the course of the diarrhea. It is not necessary to dilute milk or to give nonlactose milk in refeeding nonbreastfed babies, except in certain children younger than one year of age who may show a temporary intolerance to lactose. Early refeeding has been shown to reduce the abnormal increase in intestinal permeability that occurs in acute gastroenteritis. It may also enhance enterocyte regeneration and promote recovery of disaccharides in the brush border membrane.

THERAPY WITH ANTIDIARRHEAL COMPOUNDS

Alteration of intestinal motility

Loperamide: Loperamide, chemically related to meperidine, may decrease transit velocity and increase the ability of the gut to retain fluid. It can reduce stools and shorten the course of diarrhea in infants and children with gastroenteritis (8). However, because of the possibility of hidden fluid loss in the gut associated with the ileus, dehydration may occur without external evidence of severe diarrhea and treatment with ORS may be delayed. Loperamide also has a high incidence of severe side effects besides fluid loss in the ileus, including lethargy, respiratory depression and coma, which outweigh its limited benefits in reducing stool frequency (9,10).

Opiates and opiate-antispasmotic combinations: These drugs are contraindicated in children because of potentially severe side effects (11,12).

Alteration of secretion

Bismuth: Bismuth subsalicylate has been used effectively for many years for the prophylaxis and treatment of traveler's diarrhea. There are also a number of papers that suggest that bismuth compounds, which decrease secretions from the gut, are safe for infants and children and are effective in decreasing both the quantity of stools and the duration of diarrhea (13-15). Figueroa-Quintanilla et al (evidence level I) (13) used a dosage of 100 mg/kg to 150 mg/kg of bismuth subsalicylate for up to five days.

Concerns of toxicity from either bismuth or salicylate absorption have been expressed, but these are unlikely with administration for a short duration (15). Absorption of bismuth across the gut is minimal, less than 1%, while that of salicylate may be up to 80%. The administration of salicylate should be avoided in children with chicken pox or influenza because of the possible risk of Reye's Syndrome. Bismuth is also contraindicated in patients with renal impairment (16,17).

Racecadotril: Racecadotril (acetorphan), an enkephalinase inhibitor, represents a promising new approach to the treatment of diarrhea. It enhances the antisecretory role of the neurotransmitter, enkephalin, and is a safe and effective treatment for acute diarrhea in adults and children (evidence level I) (18-20), helping to control diarrhea within 24 h to 48 h. Data suggest that antisecretory agents should be routinely used in acute watery diarrhea in addition to ORS (21). Racecadotril is not yet available in Canada.

Adsorption of toxins or fluid

Kaolin-pectin, fibre and activated charcoal have no place in the treatment of diarrhea and dehydration in infants and children. There is no conclusive evidence that they reduce stool losses, duration of diarrhea or stool frequency (22). Although nontoxic, disadvantages may include adsorption of nutrients, enzymes and antibiotics in the intestine as well as masking the severity of fluid loss into the intestine.

Alteration of intestinal microflora

Lactobacillus: Early administration of *Lactobacillus casei sps rhamnosis* (*Lactobacillus* GG) associated with the administration of ORS significantly decreases the amount and duration of diarrhea and increases weight gain compared with ORS plus placebo (evidence level I) (23). Although yogurt has been advocated in the treatment of diarrhea, Bhatnagar et al (24) found that routine substitution of yogurt, as an addition to solids in malnourished children with acute diarrhea, does not achieve any clinical benefit versus cow's milk.

Immunization

Active: Rotavirus immunization was found to be as effective as natural infection in preventing subsequent rotavirus diarrhea (25). However, because of the high prevalence of intussusception within two weeks of its administration, it was withdrawn from the market in 1999.

Passive: Oral ingestion of immunoglobulins extracted from immunized bovine colostrum (evidence level II, B, C) is effective in the management of children with acute rotavirus diarrhea (evidence level I) (26).

Other adjuncts

Folic acid administration has also been found to be of little use in treating diarrhea (27) and there is little evidence for routine administration of Vitamin A to influence the course of diarrhea (evidence level D) (28).

On the other hand, zinc therapy decreases the duration and severity of diarrhea when given during the course of gastroenteritis in children (evidence level I) (29). Furthermore, in an analysis of pooled controlled trials in developing countries, zinc supplementation reduced the incidence of diarrhea in children by 18% and pneumonia by 41% (evidence level I) (30).

Antibiotics

Routine empirical use of antibiotics for infectious diarrhea should be avoided because of the self-limited nature of most cases, the cost of antibiotics and the potential of worsening the already significant problem of antibiotic resistance of enteric pathogens. For patients with severe invasive or prolonged diarrhea or who are at high risk of complications, empirical treatment with a quinolone antibiotic for three to five days can be considered. Antibiotic treatment can be highly effective for *Shigella*, *Escherichia coli*, and *Vibrio cholerae* infections, and metronidazole is indicated for *Clostridium difficile* colitis. The impact of antibiotics for other specific pathogens is modest, and antibiotic therapy in these cases (ie, *salmonella*, *campylobacter*, etc) should be reserved for the same group of patients who would be considered for empirical treatment (evidence level II-2, B) (31).

CONCLUSIONS

Though there is very little to add to previous recommendations on the diagnosis and treatment of dehydration with ORS, the disadvantage of its use is that total fluid loss is not diminished. There are a number of effective, safe treatments that can modify the amount of fluid loss. There may therefore be some justification for the use of antidiarrheal drugs such as enkephalinase inhibitors and bismuth, modifying intestinal flora by the use of lactobacillus or providing zinc supplements in the treatment of diarrhea.

RECOMMENDATIONS

- ORS should be used routinely in the treatment of watery diarrhea and dehydration as outlined in the previous CPS statement (evidence level I, A) (1).
- Feeding should be continued throughout rehydration to help maintain gut nutrition (evidence level II-2, A).
- Loperamide and Lomotil, (Pharmacia Canada Inc, Canada) antimotility drugs, should not be used in children because of safety considerations (evidence level III, E).
- Racecadotril (acetorphan), an antisecretory drug, is safe and effective and can be used routinely in children for treatment of watery diarrhea (not yet available in Canada) (evidence level I, B).
- Bismuth subsalicylate, an antisecretory drug, is effective and generally safe but should not be given in the presence of chicken pox or influenza because of the danger of Reye's Syndrome (evidence level I, B).
- Kaolin-pectin, fibre and activated charcoal have no place in the treatment of diarrhea and dehydration in infants and children (evidence level III, A).
- The administration of some *Lactobacillus* species to modify intestinal flora in diarrhea treatment is safe and may be effective (evidence level I, A).
- The administration of yogurt is of doubtful effectiveness (evidence level B).
- Zinc therapy can modify diarrhea, and may prevent diarrhea and pneumonia in malnourished groups of children (evidence level I, A).
- There is little indication for the use of folic acid or vitamin A in the treatment of acute diarrhea in the absence of overt deficiency (evidence level A).
- Antibiotics should be used sparingly, except in selected cases of severe bacterial diarrhea (evidence level B).

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