

Drugs for diarrhoea?

After the large-scale introduction of oral rehydration therapy (ORT) in the early 1980s, it was hoped that we now had a simple, cost-effective management strategy that was implementable in primary care as well as at home and that would also solve the forbidding mortality rate from childhood diarrhoea in the developing world. This was premised on the fact that severe acute diarrhoea causes dehydration that can kill unless adequately managed, and the demonstration that providing extra water with sugar and salt can prevent and treat dehydration. ORT was therefore strongly promoted, and occasionally it was forgotten that oral rehydration solution (ORS) treats the water and electrolyte loss but not the diarrhoea, and that ORT certainly does not lessen the predisposition to and incidence of diarrhoea.

So it was a disappointment but not really a surprise that while appropriate hydration therapy has indeed lessened case fatality rates from diarrhoeal dehydration,¹ diarrhoea has remained one of the two biggest post-neonatal killers of young children worldwide, together with acute respiratory infections. According to the World Health Organization (WHO), diarrhoea still accounts for 16% of child deaths, up to 1.8 million annually.

To the mother, it is the child's diarrhoea that matters even when she has fully understood the importance of and method of fluid replacement by ORT. Accordingly, many mothers seek therapy that can stop the diarrhoea, either at home or by consulting the whole range of available health practitioners. Such treatment may range from traditional cures to medicines obtained over the counter or on prescription.

The article by Uchendu *et al.*² in the previous issue of *SAJCH* illustrates this fact well. The authors studied the use of pre-hospital drugs and oral rehydration therapy by caregivers. It was found that a majority of caregivers had administered antibacterial agents or other medicines to their children before coming to hospital. Children who had received antibacterial medication were also brought to hospital later than those who had not received any drugs. Importantly, the patients who had home treatment with antibacterial and antidiarrhoeal drugs presented with higher degrees of dehydration in comparison with those who had not been managed with these agents.

Home drug treatment of diarrhoea by parents and caregivers, before or in addition to health worker advice, is not restricted to the developing world. In their study of children presenting to a paediatric casualty service, Li *et al.*³ found that only 53% of mothers had given appropriate fluids, but 14% had treated their children with antidiarrhoeal medication or inappropriate fluids, and 13% had used functional foods such as yoghurt and probiotics.

Drug choices

Given the frequency, potential severity and distressing nature of infantile diarrhoea, a 'drug for diarrhoea' would indeed be an appealing option. This is recognised by the pharmaceutical companies, which offer numerous drug choices for diarrhoeal disease, ranging from antibiotics, antidiarrhoeal medicines and combinations, anti-emetics and antispasmodics to functional foods, probiotics, trace elements, minerals and vitamins.

However, there is no single drug for diarrhoea. The symptom of loose or watery stools reflects disturbance of gut function (digestion, absorption) caused by the interaction between the disease (e.g. gut infection) and the body's defence system (mucosal integrity and nutritional state).

Antibiotics cannot be expected to improve the symptom of diarrhoea. In bacterial infection diarrhoea is frequently mediated by toxins that have already been elaborated by the time the patient becomes ill. Unless given early in the disease, antibiotic therapy does not significantly shorten the duration of diarrhoea in most cases, even in sensitive infections. Antibiotic therapy is therefore indicated for the treatment of evident parenteral infection accompanying diarrhoea, or to limit further bacterial spread to contacts (e.g. when given early in cholera or dysentery).

Antidiarrhoeal drugs are intended to have antimotility, antisecretory or adsorbent effects. In paediatric diarrhoea, more than one mechanism is operative at the same time in most cases, and these drugs do not have proven efficacy. In addition, side-effects (drowsiness, arrhythmia) are more common in children than in adults. Adsorbents (e.g. kaolin mixtures) may hide the true extent of water losses by intraluminal adsorption and impede clinical assessment, without influencing the actual disease. Apart from some specific exceptions, antidiarrhoeal drugs are therefore not indicated in children.

Anti-emetic drugs and antispasmodics are frequently prescribed for the vomiting and cramp-like abdominal pain that often accompany acute gastro-enteritis. Insofar as the vomiting of acute gastro-enteritis is mainly due to local gastric factors such as disturbed gastric emptying, anti-emetics are not indicated. Similarly, antispasmodics should be used with caution as their use in dysentery has been associated with an increased risk of the haemolytic uraemic syndrome.

The 'zinc breakthrough'

In an article entitled 'The great zinc breakthrough', *Time* magazine of 17 August 2009 implied that zinc was potentially the 'drug for diarrhoea'. Zinc is known to have a key role in gut mucosal integrity. Zinc deficiency was shown to have effects on intestinal permeability, intestinal water and electrolyte transport, brush border enzymatic function and intestinal repair.^{4,6} Zinc absorption is most prominent in the proximal small gut, and zinc levels are known to decline during diarrhoea. Not coincidentally, the proximal small gut is precisely where mucosal injury associated with infection or immune-mediated disease such as coeliac disease has its most prominent effect on the nutritional state. In addition, zinc has an important role in both cell-mediated and humoral immune function and is a co-factor in carrier proteins (such as retinol-binding protein) and enzyme systems (e.g. alkaline phosphatase).

Studies in developing countries have shown that zinc given in doses of 10 - 20 mg elemental zinc per day for 10 - 14 days as the water-soluble acetate, sulphate or gluconate salt has an effect in reducing severity and duration of both acute and persisting diarrhoea. This effect is moderate but significant: in acute diarrhoea studies the pooled analysis suggested

a summary effect size of 16% for reduced mean duration of diarrhoea as well as a 15% lower probability of developing persisting diarrhoea. The effect tends to be more pronounced in patients who are malnourished and in those with lower baseline zinc concentrations.⁵

In a recent multi-site study in several developing countries,⁷ zinc tablets given in addition to standard ORS were found to be well accepted, to improve compliance with ORS, and even to reduce self-decided use of additional medicines such as antibiotics. It was speculated that the provision of tablets might have fulfilled the caregivers' wish for a 'medicine' for diarrhoea, but the authors also considered that the detailed patient care instructions given to the mothers were critical in the study's success.

So far, there have been no studies of the effect of zinc on diarrhoea in children or adults in developed countries, where zinc deficiency is unlikely to be of major public health significance. Nevertheless, on the basis of meta-analyses of available trials the WHO⁸ has recommended that all children with diarrhoea be given zinc supplements. Zinc is, indeed, becoming a 'drug for diarrhoea'.⁹

The role of zinc in diarrhoea management therefore extends beyond correction of a nutrient deficiency. It stands to reason that where deficiencies of vitamin A or folate are likely to exist, these should be corrected and that would contribute to recovery and a decreased incidence of diarrhoea, but they have not been shown to have independent effects.¹⁰

In view of the complex interaction between intestinal bacterial flora and epithelium, the role of probiotics remains controversial. A number of strains have been shown to have a beneficial effect, particularly when the intestinal bacterial flora are disrupted, such as in antibiotic-treated patients, traveller's diarrhoea¹¹ or persisting diarrhoea. The use of functional foods (yoghurt and other fermented foods) likewise has a strong cultural basis in many areas, but not a uniformly defined role.

The bottom line in childhood diarrhoea is the need for communication with mothers and caregivers. Prevention must be the aim, by improvement in home circumstances and safe water supply, education on hygiene, vaccination

against rotavirus and a healthy nutritional state, but treatment demands attention to fluid balance and to judicious feeding while awaiting recovery. Zinc and other drugs may aid this process, but drugs alone do not treat diarrhoea.

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