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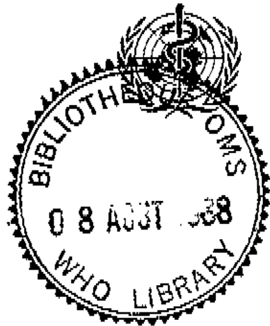

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DRUGS IN THE MANAGEMENT OF ACUTE DIARRHOEA IN INFANTS AND YOUNG CHILDREN

This article, rather than providing a discursive analysis of the literature, presents an overview of current therapeutic practice as recommended by the WHO Diarrhoeal Diseases Control Programme.

The recommendations apply solely to acute diarrhoeal disease in infants and children. They should not be extrapolated to the management of travellers' diarrhoea.

Diarrhoea is a major cause of death and malnutrition among children in developing countries. Each child experiences on the average 3 episodes per year during the first 2 years of life (in some areas the incidence is much higher), and an estimated 4 to 5 million diarrhoea-associated deaths occur annually in the world (1). There are three important forms of diarrhoea: acute watery diarrhoea (stools are soft or liquid, but are not bloody), dysentery (stools contain blood and mucus), and persistent diarrhoea (diarrhoea that begins acutely but lasts more than 14 days). The main complications of diarrhoea are dehydration and tissue catabolism; the latter contributes to malnutrition, which is further aggravated when food is withheld as part of the treatment.

Current views on the use of drugs to treat acute watery diarrhoea and dysentery in infants and young children are summarized here. Therapy is primarily concerned with the prevention or correction of dehydration, the maintenance of nutrition and the treatment of dysentery. Watery diarrhoea, and accompanying vomiting and fever, cause losses of body water and electrolytes which can lead to clinically evident dehydration. A small proportion of diarrhoeal episodes (approximately 2 to 5%) result in detectable (usually moderate) dehydration; while less than 1% lead to severe dehydration, which may be lethal if not vigorously treated. At least 90% of all episodes of watery diarrhoea that are sufficiently serious to present for treatment at a health facility can be managed by oral rehydration therapy alone. Of all the cases occurring at home, an even higher proportion can be treated effectively in this way. Only patients with serious dehydration, such as may be caused by cholera, require initial rehydration intravenously. In all instances dietary intake, including breast milk, should continue without interruption.

Antiobiotics are primarily of value in cholera and dysentery. Antiparasitic agents are used for symptomatic infection with G. lamblia and E. histolytica. Many other treatments are available, most of which are intended to diminish stool volume and shorten illness, but none has proven both safe and sufficiently effective to be used routinely in infants and young children.

The various approaches to treatment are considered in greater detail below.

Oral rehydration

Oral rehydration therapy (ORT) is the keystone of all national diarrhoeal disease control programmes because it is simple, highly effective, inexpensive and technologically appropriate. A solution prepared from Oral Rehydration Salts (ORS) is used both to treat clinically evident dehydration (i.e. to replace deficits of fluid and electrolytes) and to prevent dehydration by replacing losses early in the course of diarrhoea or when diarrhoea continues after rehydration (2). The ORS solution recommended by the World Health Organization and UNICEF contains in g/l: NaCl 3.5; KCl 1.5; trisodium citrate 2.9 (or

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$NaHCO_3$ 2.5); glucose 20. It is effective because some active absorption of glucose by the small intestine continues during the course of intestinal infection, allowing glucose-coupled sodium transport and absorption of water; the process thus provides a way to replace water and electrolytes lost in the stool. Home-based therapy given at the onset of diarrhoea can also be used to prevent dehydration. Suitable fluids may be prepared from commonly available household ingredients such as sugar/salt mixtures, lightly salted soups or diluted gruels (2, 3).

Although ORT is highly effective for combating dehydration and its serious consequences, it does not diminish the amount or duration of diarrhoea. It is generally agreed that a drug that could diminish diarrhoea would be a useful adjunct to ORT. To be of practical value, such a drug would also need to be inexpensive and safe, especially in small children. The categories of adjunct drugs currently available include antimotility agents, antisecretory agents, bacterial flora intended to inhibit growth of pathogens and adsorbents.

Antimotility drugs

Opiates and their derivatives are widely used "antidiarrhoeal" drugs which act primarily through their antimotility properties. They include codeine, paregoric, deodorized tincture of opium (all alkaloids) and diphenoxylate and loperamide (both synthetic opiate derivatives). None is recommended for routine use in infants and children because the benefits are modest and they may cause serious side effects. All can cause nausea, vomiting, drowsiness, paralytic ileus and even cardiopulmonary arrest. They may also worsen the clinical course of infectious diarrhoeas. For example, treatment with diphenoxylate has caused prolongation of both fever and excretion of the pathogen in volunteers infected with *Shigella* (4); and antimotility agents may cause fluid to pool within the bowel in severe diarrhoea, such as that caused by *V. cholerae* or enterotoxigenic *E. coli*, so that fluid losses are both underestimated and under-replaced.

The clinical value of these agents is moderate, at best. In controlled trials diphenoxylate did not significantly decrease the number or volume of diarrhoeal stools or the intravenous fluid requirements of infants with acute diarrhoea (5, 6). Similar trials with loperamide (0.24 mg/kg/day) failed to demonstrate any clinically significant effect on the daily stool volume or the rehydration fluid requirement, although the duration of diarrhoea was moderately shortened (7, 8). A larger daily dose (0.48 mg/kg) also caused a modest, but statistically significant, shortening of the duration of diarrhoea; however, before diarrhoea stopped the rate of stool loss was not affected (9, 10), indicating that this drug does not have antisecretory properties of clinical benefit in acute diarrhoea.

Antisecretory drugs

While several drugs have shown an antisecretory effect in experimental studies, only a few have been properly studied in clinical trials, and virtually all of them have had important side effects, a low therapeutic index, and/or only modest efficacy. Consequently, none can at present be recommended for the treatment of acute infectious diarrhoea in infants and children. Chlorpromazine, a tranquilizer with antisecretory effects, has been carefully studied in cholera (11, 12). Although it caused a statistically significant reduction in stool volume, the required dose also caused sedation, which interfered with the patients' ability to drink the ORS solution.

Bismuth subsalicylate in liquid formulation significantly diminished the number of unformed stools and subjective complaints in young adults with travellers' diarrhoea (13), but had no effect on stool water or total weight of stool passed, implying that it did not have an antisecretory effect. Moreover, a large volume needed to be given (240 to 480 ml in less than 4 hours), and the total dose of salicylate was too great to be practical or safe in children (13, 14). A placebo-controlled, double-blind trial of the effect of a tablet formulation of bismuth subsalicylate in volunteers with diarrhoea caused by enterotoxigenic *E. coli* also showed no effect upon stool frequency or stool weight (15).

Aspirin (25 mg/kg/day) was studied as an antisecretory agent in a double-blind, placebo-controlled trial in malnourished children with acute diarrhoea after initial

intravenous rehydration. The reduction in daily stool volume was statistically significant but the mean change was only 100 ml per child, which was not considered clinically important (16). Berberine, an alkaloid used in some traditional remedies for diarrhoea, has been shown to have an antisecretory effect in animal studies. However, in two controlled clinical trials among adults with cholera or cholera-like diarrhoea, it had either no effect upon the rate of stool output or reduced the rate to a degree not considered clinically important (17, 18).

Aciduric bacteria

For decades it has been recognized that normal aciduric bacteria in the human intestine inhibit the growth of certain bacterial pathogens, such as *Salmonella* and *Shigella*. Thus it has been suggested that intestinal infections might be treated or prevented by the feeding of normal flora (19), *Lactobacillus acidophilus*, *Bifidobacterium*, and *Streptococcus faecium* being the species most frequently mentioned. Double-blind trials of *Streptococcus faecium* in adults and children with acute diarrhoea in Italy have reported a shortening of the duration of illness and of pathogen excretion (19, 20). However, a recently completed double-blind, placebo-controlled study in Bangladesh did not show any effect of *Streptococcus faecium* upon stool volume and duration of diarrhoea in children and adults with acute watery diarrhoea. Controlled trials of the therapeutic or prophylactic value of *Lactobacilli* have also demonstrated no benefit (21, 22, 23).

Adsorbents

Kaolin, charcoal and other adsorbents have been proposed as antidiarrhoeal agents in view of their ability to bind and inactivate bacterial toxins, but the results of clinical studies have been disappointing. Kaolin showed no efficacy in cholera (24); in non-cholera infantile diarrhoea it increased the consistency of stools, but stool weight and water content were not affected (5). Charcoal was also ineffective in cholera (25); moreover, it also interfered with the beneficial effect of tetracycline (26). An experimental charcoal-GM_1 ganglioside preparation (which binds cholera toxin and *E. coli* heat-labile toxin) caused a modest reduction in rate of stool loss in cholera patients but only for a short period early in the illness (25). However, aside from cholera and some enterotoxigenic *E. coli* diarrhoeal infections, this therapy would have little use.

Cholestyramine is a nonabsorbable quaternary exchange resin that avidly binds bile acids and bacterial endotoxin. Several uncontrolled clinical studies suggest that it may be useful in treating persistent diarrhoea in some children. Although one placebo-controlled, double-blind trial of the drug used for the therapy of diarrhoea in adults (mostly persistent diarrhoea) demonstrated no beneficial effect (27), two others showed that cholestyramine substantially shortened the duration of illness (and hospitalization) for infants with acute diarrhoea (28, 29). In the highest dosage studied, cholestyramine also caused prolonged acidosis when the base deficit was not fully corrected. Studies to further evaluate the antidiarrhoeal properties of cholestyramine are under way.

Improved ORS

The most effective and safest "antidiarrhoeal" drug may turn out to be an improved ORS solution containing organic carriers other than, or in addition to, glucose, such as certain amino acids or cereal powders (3, 30, 31). It is possible that these organic components may promote sodium and water absorption more effectively than glucose and thus actually reduce the volume of stool passed; this effect has already been demonstrated using an ORS containing cooked rice powder (31). Although one study suggested that the addition of glycine to glucose ORS caused improved fluid absorption and reduced stool volume during acute diarrhoea (30), results from several recently completed studies have shown that the addition of glycine (and in some cases glycyl-glycine) to glucose ORS has no consistent beneficial effect on stool volume, ORS consumption or duration of diarrhoea in children under 3 years. Research is under way on other "improved oral rehydration solutions", including ones containing other amino acids, or maltodextrins rather than glucose, and on cereal-based solutions. The objective is to define a formulation that will maximally (and safely) diminish the severity and duration of diarrhoea while providing the required water and electrolytes.

Antibiotics and Antiparasitic Drugs

For a few infectious diarrhoeas, antibiotics can significantly diminish the severity and duration of diarrhoea and shorten the duration of excretion of the pathogen (32). In proven or suspected cholera, tetracycline should be given because it diminishes by nearly 50% the total stool volume and the required volume of oral and intravenous fluids. Although tetracycline is generally not used in children under 12 years of age to avoid possible tooth discolouration, the two-day course required to treat cholera does not carry this risk (33). In those relatively uncommon instances where V. cholerae 01 strains are resistant to tetracycline, trimethoprim-sulfamethoxazole, furazolidone, chloramphenicol, or erythromycin may be used. The duration of diarrhoea caused by Campylobacter jejuni can be significantly shortened by treatment with erythromycin, but only when this is begun on the first day of illness (34); unless a simple method for rapid diagnosis of this infection is available, antibiotic treatment is not recommended.

Moderate to severe dysentery (characterized by fever and grossly bloody stool) is often caused by Shigella, and these patients should be given antibiotics, whether or not coprocultures are available to identify the cause. Ampicillin and trimethoprim-sulfamethoxazole are widely used, but Shigella may be resistant to these. If possible, antibiotic selection should be based on knowledge of the antibiotic susceptibility of Shigella recently isolated from the same area. In young infants, especially those less than 1-2 months of age, diarrhoea may be accompanied by bacteraemia; when signs of systemic infection are present and persist after rehydration, parenteral broad spectrum antibiotics should be seriously considered.

Amoebic dysentery, diagnosed by identification of E. histolytica trophozoites in the stool, should be treated with metronidazole, often combined with diloxanide furoate. The diagnosis of diarrhoea caused by Giardia lamblia requires the identification of trophozoites or giardial antigen in the stool or intestinal fluid; treatment can be with metronidazole, tinidazole, quinacrine or furazolidone.

No antibiotic or chemotherapeutic agent (including sulfaguanidine, other poorly absorbed sulfonamides, neomycin and halogenated oxyquinolines) has proven value for the routine treatment of acute diarrhoea; their use is inappropriate and possibly dangerous.

Conclusion

In summary, approximately 90% of children with watery diarrhoea who visit a health care facility can be successfully and optimally treated solely with oral rehydation therapy and continued feeding. Antibiotic or antiparasitic therapy should be reserved for patients with dysentery, proven or presumed cholera, or proven infection with E. histolytica or G. lamblia. Currently available adjunct agents, including antimotility and antisecretory agents, exogenous aciduric flora and adsorbents have no practical value and increase both the cost of treatment and the risk of adverse reactions. The practice encountered in many countries of routinely treating episodes of diarrhoea with multiple adjunct agents and antibiotics, sometimes available as combination drugs, is to be deplored (34). Oral rehydration therapy is the only proven cost-effective method of treating diarrhoea and the economic savings from treating the disease in this way can be considerable (35).

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