The rational use of drugs in the management of acute diarrhoea in children

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Contents

Introduction

Diarrhoea is associated with an estimated 4 million deaths annually of children under 5 years of age and is thus one of the leading contributors to childhood mortality. In addition, diarrhoea aggravates undernutrition and predisposes to death from other diseases. Correct measures for the prevention and treatment of dehydration, adequate feeding during and after diarrhoea, and the judicious use of antibiotics for cholera and dysentery could substantially reduce this heavy toll. In addition to a solution of oral rehydration salts to treat dehydration,[1] the rational use of drugs in the treatment of acute diarrhoea in children is as follows (*1*):

- Antibiotics should be used *only* for dysentery and suspected cholera. In diarrhoea of any other etiology antibiotics are of no practical value and should not be given.
- Antiparasitic drugs should be used only for:
  - amoebiasis, after antibiotic treatment of bloody diarrhoea for suspected shigella infection has failed or when trophozoites of *Entamoeba histolytica* containing red blood cells are seen in the faeces;
  - giardiasis, when diarrhoea has lasted at least 14 days and cysts or trophozoites of *Giardia intestinalis* are seen in faeces or in the contents of the small intestine.
- Antidiarrhoeal drugs and antiemetics should never be used. None has any proven practical value and some are dangerous.

The recommended antimicrobial agents for use in treating childhood diarrhoea of specific etiology are detailed in Table 1.

Unfortunately, appropriate treatment of diarrhoea often remains the exception rather than the rule. In particular, studies of current patterns of diarrhoea treatment have shown that a large number of pharmaceutical agents of dubious efficacy and potential toxicity are widely used.

Numerous problems are associated with this misuse of medications. Adverse reactions are common, and the extensive use of antimicrobials contributes to widespread antibiotic resistance. The cost of unnecessary medications represents an additional "side-effect", especially in poorer countries. Most importantly, the inappropriate use of drugs often delays or replaces appropriate diarrhoea treatment.

[1] The use of oral rehydration therapy is dealt with comprehensively in *Treatment and prevention of acute diarrhoea. Practical guidelines*. Geneva, WHO, 1989 (new edition in preparation).

Antidiarrhoeal preparations frequently contain combinations of several different antimicrobials, vitamins, or adsorbents. Prescribing guides commonly indicate that these formulations are effective for diarrhoeas of diverse etiology, yet there are few objective data on their efficacy and toxicity.

Drugs commonly used to treat diarrhoea in children can be grouped in three broad categories: oral formulations of drugs without established benefit in any field of paediatric practice; drugs that have no role in the routine treatment of acute diarrhoea but may be useful for the treatment of other specific diseases in children; drugs still being investigated for their potential use in the treatment of acute diarrhoea in children. This review focuses on the first category, reviewing documented pharmacology, mechanism of action, efficacy, adverse effects and drug interactions. The category includes antimotility drugs (diphenoxylate hydrochloride and loperamide), antimicrobial agents (neomycin, streptomycin, hydroxyquinolines and nonabsorbable sulfonamides), and adsorbents (kaolin and pectin, activated charcoal, attapulgite and smectite). Conclusions are presented and recommendations made on the role and use of these in the treatment of acute diarrhoea in infants and young children. This review does not address the rational use of drugs in adults with diarrhoea, the management of chronic or persistent diarrhoea, or the prevention and treatment of traveller's diarrhoea; its purpose is to promote the rational use of drugs in the management of acute diarrhoea in infants and young children.

This information is intended for health policy makers, including managers of national diarrhoeal disease control programmes, health professionals who treat children with acute diarrhoea, and trainers and educators of medical students, nurses, pharmacists and other health workers.

Reference

1. *A manual for the treatment of diarrhoea — for use by physicians and other senior health workers* (WHO document WHO/CDD/SER/80.2, Rev. 2, 1990).

Table 1. **Antimicrobial agents used in the treatment of specific causes of diarrhoea in children**

Cause	Antibiotic(s) of choice[a]	Alternative(s)[a]
Cholera[b,c]	**Tetracycline** 12.5 mg/kg body weight 4 times a day x 3 days	**Furazolidone** 1.25 mg/kg body weight 4 times a day x 3 days *or* **Trimethoprim (TMP)-sulfamethoxazole (SMX)**[d] TMP 5 mg/kg body weight and SMX 25 mg/kg body weight twice a day x 3 days
Shigella dysentery[b]	**Trimethoprim (TMP)-sulfamethoxazole (SMX)** TMP 5 mg/kg body weight and SMX 25 mg/kg body weight twice a day x 5 days	**Nalidixic acid** 15 mg/kg body weight 4 times a day x 5 days *or* **Ampicillin** 25 mg/kg body weight 4 times a day x 5 days
Amoebiasis	**Metronidazole** 10 mg/kg body weight **3 times a day x 5 days** (10 days for severe disease)	In very severe cases: **Dehydroemetine hydrochloride** by deep, intramuscular injection, 1-1.5 mg/kg body weight daily (maximum 90 mg) for up to 5 days, depending on response.
Giardiasis	**Metronidazole**[e] 5 mg/kg body weight 3 times a day x 5 days	**Quinacrine** 2.5 mg/kg body weight 3 times a day x 5 days

[a] All doses shown are for oral administration unless otherwise indicated. If drugs are not available in liquid form for use in young children, it may be necessary to approximate the doses given in this table.

[b] The choice of antibiotic will depend on the frequency of resistance to antibiotics in the area.

[c] Antibiotic therapy is not essential for successful treatment, but it shortens the duration of illness and the period of excretion of organisms in severe cases.

[d] Other alternatives are erythromycin and chloramphenicol.

[e] Tinidazole and ornidazole can also be used in accordance with the manufacturers' recommendations.

PART 1

Antimotility drugs

Diphenoxylate hydrochloride

Abstract

There is no clear evidence that diphenoxylate has a beneficial effect in altering the course of acute diarrhoea. Most importantly, it does not diminish the life-threatening fluid losses that can be associated with diarrhoea. In children, central nervous system toxicity is common and may occur at usual therapeutic dosages, and some evidence exists that diphenoxylate may aggravate bacillary dysentery. Diphenoxylate cannot be recommended for the management of diarrhoea in children, and there is thus no rationale for the production and sale of liquid and syrup formulations for paediatric use.

1. Formulations

Diphenoxylate, a synthetic congener of pethidine developed for use in diarrhoea, is combined with a small amount of atropine to discourage deliberate abuse of the drug (*1*). Typical formulations for oral administration contain 2.5 mg of diphenoxylate and 0.025 mg of atropine per tablet or 5 ml of liquid. The drug is marketed under a variety of trade names and is also sold in formulations combined with antibiotics (*2, 3*).

2. Pharmacology

Diphenoxylate is converted in the liver to a biologically active metabolite, diphenoxylic acid (*1*), which is excreted mainly in the urine and bile. Peak plasma levels occur within 2 hours following an oral dose. The half-lives of diphenoxylate and diphenoxylic acid are approximately 2.5 and 4.5 hours, respectively.

3. Mechanism of action

Diphenoxylate reduces the rate of gastrointestinal propulsion and faecal output in mice and rats (*4*), and significantly decreases the rate of flow of barium in the human small intestine (*5, 6*). This effect has been attributed to a rise in non-propulsive muscle activity in the gut, with an increase in the rhythmic activity of circular smooth muscle and, possibly, an inhibition of the contractility of longitudinal smooth muscle (*7*). It has been postulated that the delay in faecal emptying allows more time for fluid absorption and subsequently reduces fluid losses in the stool, but there is little evidence to support this assertion (*8*).

Numerous studies have also been conducted on the direct effects of opiate derivatives on intestinal fluid absorption and secretion. Morphine and some synthetic opiates have been shown to decrease the intestinal secretion stimulated by a number of intestinal secretagogues (*9, 10*), including prostaglandins (*11*) and cholera toxin (*12*). The role of diphenoxylate as an antisecretory agent, however, has not been established, nor is there any clear evidence that diphenoxylate can promote intestinal fluid absorption.

4. Efficacy

Adults

Most of the early studies on the efficacy of diphenoxylate were performed in adults with chronic diarrhoea (*6, 13–19*). These studies, though largely uncontrolled, suggested that diphenoxylate could decrease stool frequency in irritable colon and ulcerative colitis. A randomized clinical trial confirmed this effect in both irritable colon and mild ulcerative colitis, but no benefit was observed in more severe cases of ulcerative colitis (*20*).

Several non-blind studies performed in adults with acute diarrhoea have compared diphenoxylate (*21*) and diphenoxylate/neomycin (*22*) with a preparation containing neomycin and sulfaguanidine. Results suggested that diphenoxylate decreases stool frequency and improves stool consistency in the first 12–24 hours after the initiation of therapy. Another trial, however, which looked at stool frequency throughout the course of diarrhoea, was unable to detect any effect of diphenoxylate (*23*).

In the late 1960s, the General Practitioner Research Group in the United Kingdom decided that the role of diphenoxylate in the management of acute diarrhoea needed to be clarified. Two double-blind trials were conducted, in which diphenoxylate was compared with clioquinol; efficacy results were based on diaries kept by patients (*24, 25*). Neither of these trials was able to attribute any significant benefit to diphenoxylate therapy. In another double-blind trial in adults with acute diarrhoea, a single 5-mg dose of diphenoxylate was observed to have no effect on the subsequent passage of unformed stools (*26*).

A mean decrease of one stool per 24 hours was reported in a further double-blind trial in which adults with acute diarrhoea were treated with diphenoxylate (*27*). Of the patients receiving diphenoxylate, 80% stated that the medication "helped a lot", but 75% of those receiving a placebo reported the same effect. (This difference was not statistically significant.)

Another trial examined the use of diphenoxylate in the prevention of traveller's diarrhoea (*28*). Although the trial was hampered by a significant loss of subjects to follow-up, the results suggested that diphenoxylate might actually increase the risk of subsequent diarrhoea.

Diphenoxylate has been shown to be significantly less effective than tetracycline in the treatment of cholera (*29*), and provides no advantage when added to tetracycline therapy.

Children

In many trials of diphenoxylate efficacy, the "outcome variables" have been highly subjective, which is a particular problem when evaluators are not blind to the treatment assignment. The author of one controlled trial considered that he had confirmed the efficacy of diphenoxylate simply because the majority of children treated with the drug recovered within five days.

To be truly effective, an antidiarrhoeal agent should reduce stool water and electrolyte losses. In one of the few studies to consider this outcome, diphenoxylate was ineffective in reducing stool water losses (*31*). Moreover, neither of two blind trials was able to demonstrate a significant effect of diphenoxylate in reducing stool frequency in children (*31, 32*).

Among the double-blind trials considered, the only one to show any effect of diphenoxylate in children with diarrhoea was a small study that demonstrated a significantly shorter duration of hospitalization for malnourished infants with acute diarrhoea treated with diphenoxylate (*33*). However, there was no effect in children with chronic diarrhoea, and the criteria used to decide when a child was ready for discharge were not clearly explained. In another, larger, double-blind trial in which discharge criteria were more clearly stated, diphenoxylate had no effect on the duration of hospitalization (*32*).

The trials of the efficacy of diphenoxylate therapy in children which have been considered here (*31–40*) are summarized in Table 2.

5. Adverse effects

Reported side-effects of diphenoxylate therapy include anorexia, nausea and vomiting, swelling of the gums, abdominal distension, paralytic ileus, toxic megacolon, headache, drowsiness, confusion, insomnia, dizziness, restlessness, euphoria, depression, and skin reactions (*1, 2*). In addition, the atropine component of treatment may be associated with hyperthermia, tachycardia, urinary retention, flushing, and dryness of the skin and mucous membranes. Several of these adverse reactions deserve further comment.

Effects on the central nervous system

In a study in which most participants were under 1 year of age, drowsiness was observed in 17% of infants treated with diphenoxylate compared with

Table 2. **Efficacy of diphenoxylate in acute diarrhoea of children**

Ref.	Double-blind	No. of patients	Treatment groups	Outcome variables	Results
31	Observer-blinded	80	Diphenoxylate Placebo Kaolin/pectin Pectin	Stool frequency Stool water content Stool weight	No significant differences between the treatment groups
32	Yes	50	Diphenoxylate Placebo	Variations in hydration Stool frequency at 12, 24 and 36 hours Duration of hospitalization	No significant differences between the treatment groups
33	Yes	15	Diphenoxylate Placebo	Duration of hospitalization	Infants treated with diphenoxylate were ready for discharge from the hospital significantly sooner than those treated with placebo. All patients with infective diarrhoea were excluded from this study. In view of the small numbers, an analysis of the comparability of the two groups at the outset of treatment would have been useful.
34	No	128	Diphenoxylate No therapy	Positive response to treatment defined as <3 stools/12 hours after 3 days of therapy	78% responded to diphenoxylate whereas 88% responded to no therapy. Dehydration was more severe in the control group. Five deaths occurred in the control group, none in the diphenoxylate group. Four of these deaths occurred within 10 hours of admission and are unlikely to have been related to the presence or absence of diphenoxylate treatment.

35	No	714	Diphenoxylate Loperamide No therapy	Time until change in stool consistency was noted	Stool frequency and consistency improved faster in the loperamide-treated group than in the diphenoxylate group. Both treatment groups appeared to improve faster than the untreated group, but timing in the treatment groups began only when vomiting stopped and the child was able to take the medicine, whereas the time for the control group began at the time of admission.
36	No	120	Diphenoxylate Neomycin Diphenoxylate/neomycin Diphenoxylate/gentamicin	Response defined as improvement in stool frequency and consistency at 24 hours	Response rates ranged from 56% to 63% in all groups except those treated with gentamicin. Response in the diphenoxylate/gentamicin group was significantly higher at 81%. Coincidentally, this was the only group that was not randomly assigned at admission.
37	?	80	Diphenoxylate plus furazolidone Kaolin	"Responders" "Nonresponders"	80% in the diphenoxylate group "responded" to therapy compared with 58% in the kaolin group.
38	No	300	Diphenoxylate Diphenoxylate/neomycin Kaolin	"Improvement" within: 24 h (excellent) 48 h (good) 96 h (fair) >96 h (poor)	The two diphenoxylate-treated groups had a significantly higher proportion of "excellent" and "good" responses.
39	No	100	Diphenoxylate Pectokab (both groups received furazolidone)	"Response" within: 24 h (excellent) 48 h (good) 72 h (fair)	96% treated with diphenoxylate had an excellent or good response compared with only 56% of those treated with Pectokab.
40	No	202	No control	Responders defined as those who returned to normal within 72 hours.	The response rate was 100% in children with mild diarrhoea and 69% in children with moderate diarrhoea.

6% of controls (*34*). Other studies have reported a similar rate of sedation in children (*35*). Several cases of severe central nervous system toxicity with normal therapeutic doses have been reported in the literature (*41–43*). In addition, overdose is common when repeated doses are taken for severe diarrhoea (*44–49*). Partly because initial responses are poor, excessive doses are often administered, reportedly resulting in coma or even death. Diphenoxylate is also a common source of accidental poisoning in toddlers (*41, 44, 50*).

Gastrointestinal side-effects

Abdominal distension has been reported in 7–12% of infants receiving diphenoxylate therapy, but it is also common in untreated children with acute diarrhoea (*34, 40*). A number of other problems related to the slowing of gastrointestinal motility have been identified, including that of delay in clearance of pathogens from the stool following the use of antimotility drugs. In shigella infections in experimental animals, opiates have actually been shown to enhance the pathogenicity of the infecting organism (*50*). Similar results were demonstrated in 25 volunteers with experimental shigellosis, in whom diphenoxylate prolonged fever and reduced the efficacy of antibiotics (*51*).

Moreover, drugs that lower intestinal motility may actually increase the risk of diarrhoea in travellers (*29*). A study of 200 healthy people given lincomycin in conjunction with diphenoxylate, codeine, or placebo revealed an increased risk of diarrhoea in those who received codeine or diphenoxylate, which might call into question the use of either drug to treat lincomycin-associated diarrhoea (*52*).

There is some concern that, if antimotility agents are effective in reducing gastrointestinal motility, water and electrolytes may simply be sequestered in distended loops of the bowel (*8*). The subsequent masking of fluid losses could lead to delays in seeking appropriate care and hinder efforts to achieve accurate fluid replacement.

6. Conclusions

Diphenoxylate appears to have some effect in relieving symptoms of mild chronic diarrhoeas in adults, but there is no clear evidence of a beneficial effect in acute diarrhoea in either children or adults.

Diphenoxylate does not diminish the fluid losses associated with diarrhoea and may in fact interfere with fluid replacement. There is some evidence that the antimotility effects of diphenoxylate may actually worsen bacillary dysentery. Potentially fatal side-effects of diphenoxylate on the central nervous system are not uncommon and may occur at usual therapeutic dosages.