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

World Health Organization
Geneva
The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of some 165 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of health manpower, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a wide variety of activities, such as developing systems of primary health care that reach the whole population of Member countries; promoting the health of mothers and children; combating malnutrition; controlling malaria and other communicable diseases, including tuberculosis and leprosy; having achieved the eradication of smallpox, promoting mass immunization against a number of other preventable diseases; improving mental health; providing safe water supplies; and training health personnel of all categories.

Progress towards better health throughout the world also demands international cooperation in such matters as establishing international standards for biological substances, pesticides and pharmaceuticals, formulating environmental health criteria; recommending international non-proprietary names for drugs; administering the International Health Regulations; revising the International Classification of Diseases, Injuries, and Causes of Death; and collecting and disseminating health statistical information.

Further information on many aspects of WHO's work is presented in the Organization's publications.
The rational use of drugs in the management of acute diarrhoea in children

World Health Organization
Geneva
1990
WHO Library Cataloguing in Publication Data

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


ISBN 92 4 156142 4

© World Health Organization 1990

Publications of the World Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. For rights of reproduction or translation of WHO publications, in part or in toto, application should be made to the Office of Publications, World Health Organization, Geneva, Switzerland. The World Health Organization welcomes such applications.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

Printed in Switzerland
90/6621 — Strategic — 8000
# Contents

Acknowledgements

Introduction

## Part 1. Antimotility drugs
- Diphenoxylate hydrochloride
- Loperamide

## Part 2. Antimicrobial agents
- Streptomycin and dihydrostreptomycin
- Neomycin
- Hydroxyquinolines
- Nonabsorbable sulfonamides: sulfaguanadine, succinylsulfathiazole, phthalylsulfathiazole

## Part 3. Adsorbents
- Kaolin and pectin
- Activated charcoal
- Attapulgite and smectite
Acknowledgements

The contribution made by the following people in reviewing these articles, is gratefully acknowledged:

Dr M.K. Bhan, All India Institute of Medical Sciences, New Delhi, India.
Dr M. Couper, Pharmaceuticals, World Health Organization, Geneva, Switzerland.
Dr J.F. Dunne, Pharmaceuticals, World Health Organization, Geneva, Switzerland.
Dr H.L. Dupont, University of Texas Health Science Center at Houston, TX, USA.
Dr A. Herxheimer, Department of Clinical Pharmacology and Therapeutics, Charing Cross Hospital, London, England.
Dr C.M. Kunin, Department of Internal Medicine, Ohio State University, Colombus, OH, USA.
Dr D. M. Mahalanabis, International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh.
Dr D.W. Powell, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA.
Dr B. Sack, International Health and Medicine, Geographic Medicine, Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD, USA.
Dr E. Salazar-Lindo, Department of Pediatrics, Universidad Peruana Cayetano Heredia, Lima, Peru.
Dr P.D. Santos Ocampo, Department of Pediatrics, University of the Philippines, Manila, Philippines.
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, 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.

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

<table>
<thead>
<tr>
<th>Cause</th>
<th>Antibiotic(s) of choice&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Alternative(s)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| Cholera<sup>b,c</sup>        | 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)<sup>d</sup>  
TMP 5 mg/kg body weight and SMX 25 mg/kg body weight twice a day x 3 days |
| Shigella dysentery<sup>b</sup> | 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 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                                   |

<sup>a</sup> 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.

<sup>b</sup> The choice of antibiotic will depend on the frequency of resistance to antibiotics in the area.

<sup>c</sup> 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.

<sup>d</sup> Other alternatives are erythromycin and chloramphenicol.

<sup>e</sup> 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, diphenoxylate 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 diphenoxylate 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>
<thead>
<tr>
<th>Ref.</th>
<th>Double-blind</th>
<th>No. of patients</th>
<th>Treatment groups</th>
<th>Outcome variables</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Observer-blinded</td>
<td>80</td>
<td>Diphenoxylate Placebo Kaolin/pectin Pectin</td>
<td>Stool frequency Stool water content Stool weight</td>
<td>No significant differences between the treatment groups</td>
</tr>
<tr>
<td>32</td>
<td>Yes</td>
<td>50</td>
<td>Diphenoxylate Placebo</td>
<td>Variations in hydration Stool frequency at 12, 24 and 36 hours Duration of hospitalization</td>
<td>No significant differences between the treatment groups</td>
</tr>
<tr>
<td>33</td>
<td>Yes</td>
<td>15</td>
<td>Diphenoxylate Placebo</td>
<td>Duration of hospitalization</td>
<td>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.</td>
</tr>
<tr>
<td>34</td>
<td>No</td>
<td>128</td>
<td>Diphenoxylate No therapy</td>
<td>Positive response to treatment defined as &lt;3 stools/12 hours after 3 days of therapy</td>
<td>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.</td>
</tr>
<tr>
<td>No.</td>
<td>Treatment</td>
<td>No.</td>
<td>Patients</td>
<td>Reporting Time</td>
<td>Outcome Description</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>-----</td>
<td>----------</td>
<td>----------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>35</td>
<td>Loperamide</td>
<td>714</td>
<td>Diphenoxylate</td>
<td>Time until change in stool consistency was noted</td>
<td>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.</td>
</tr>
<tr>
<td>36</td>
<td>Neomycin</td>
<td>120</td>
<td>Diphenoxylate/neomycin</td>
<td>Response defined as improvement in stool frequency and consistency at 24 hours</td>
<td>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.</td>
</tr>
<tr>
<td>37</td>
<td>Furazolidone</td>
<td>80</td>
<td>Diphenoxylate plus furazolidone</td>
<td>“Responders” “Nonresponders”</td>
<td>80% in the diphenoxylate group “responded” to therapy compared with 58% in the kaolin group.</td>
</tr>
<tr>
<td>38</td>
<td>Kaolin</td>
<td>300</td>
<td>Diphenoxylate/neomycin</td>
<td>“Improvement” within: 24 h (excellent) 48 h (good) 96 h (fair) &gt;96 h (poor)</td>
<td>The two diphenoxylate-treated groups had a significantly higher proportion of “excellent” and “good” responses.</td>
</tr>
<tr>
<td>39</td>
<td>Kaolin</td>
<td>100</td>
<td>Diphenoxylate Pectokab</td>
<td>“Response” within: 24 h (excellent) 48 h (good) 72 h (fair)</td>
<td>96% treated with diphenoxylate had an excellent or good response compared with only 56% of those treated with Pectokab.</td>
</tr>
<tr>
<td>40</td>
<td>No control</td>
<td>202</td>
<td>No control</td>
<td>Responders defined as those who returned to normal within 72 hours.</td>
<td>The response rate was 100% in children with mild diarrhoea and 69% in children with moderate diarrhoea.</td>
</tr>
</tbody>
</table>
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.
There is no role for diphenoxylate in the treatment of childhood diarrhoeas and thus no rationale for the production and sale of liquid and syrup preparations for paediatric use.

References


Loperamide

Abstract

There is no good evidence that conventional doses of loperamide can reduce the losses of fluids and electrolytes in children with diarrhoea. Following reports of association with fatal episodes of paralytic ileus in infants and young children, the major manufacturer of loperamide has withdrawn the drop formulation from the market throughout the world and has restricted the sale of the syrup formulation. Adverse effects on the central nervous system are most commonly observed in infants under 6 months. For these reasons, loperamide 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

Loperamide is a synthetic opiate analogue developed specifically for use in diarrhoea. It is available in tablet and syrup form under a variety of brand names.

*Note:* In the United Kingdom, loperamide is not recommended for use in children under 4 years of age (1).

2. Pharmacology

Systemic absorption of loperamide is poor. Approximately 10% of the administered dose is recovered in the urine, and about 40% is excreted unchanged in the faeces. Mean biological half-life is about 11 hours, with a range of 8-14 hours (2).

3. Mechanism of action

All opiate agonists have effects on intestinal smooth muscle. Loperamide inhibits propulsive motor activity, predominantly in the jejunum, and this effect is partially inhibited by opiate antagonists (3). Other effects on intestinal motility may be mediated through inhibition of prostaglandin stimulation of gut motility (4) and/or through calcium antagonist actions (5).

Two investigations of the effect of loperamide on fluid absorption in healthy adult volunteers were unable to demonstrate any action that might be of benefit in the treatment of diarrhoea (3, 6).

Some studies of the action of loperamide in people and animals have demonstrated a reduction in the intestinal fluid secretion stimulated by
prostaglandins and cholera toxin (7–10). Other investigations, however, have been unable to demonstrate any effect of loperamide in blocking secretion induced by vasoactive intestinal polypeptide (6).

4. Efficacy

A number of studies assessing the efficacy of loperamide in the treatment of diarrhoea in children have been inadequately randomized, or not blind, or have failed to define outcome measures clearly (11–14). The better-designed studies can be classified on the basis of their outcome measurements: those assessing changes in stool fluid losses, those examining changes in intestinal motility, and those looking at outcomes other than these.

Fluid losses

Two randomized, double-blind, placebo-controlled clinical trials have failed to show an effect of loperamide on stool output of infants and young children with acute diarrhoea (16); loperamide was used in one study at the recommended daily dose of 0.24 mg/kg of body weight, and in the second at 0.48 mg/kg of body weight. In contrast, loperamide has been reported to cause marked reductions in stool output of infants with chronic diarrhoea unresponsive to other therapies (15). However, only six infants were studied, the observations were uncontrolled, and the authors noted that the drug was not effective in all cases; ileus requiring discontinuation of drug therapy occurred in some infants, and the average daily dose (1.26 mg/kg of body weight) far exceeded the usual recommendation.

At first glance, measurement of the duration of diarrhoea as an outcome variable would appear to be a useful indicator of stool fluid losses. However, duration of diarrhoea may well be a reflection of the antimotility effects of the drug and not necessarily correlated with changes in fluid loss (16). This outcome is therefore discussed below in the section on gastrointestinal motility.

Gastrointestinal motility

Loperamide has been shown to decrease stool frequency by an average of less than one stool per day in children with mild, chronic diarrhoea (17). It has also been shown to modify stool frequency in children with acute diarrhoea (11, 18), but the effects are clearly dose-dependent (16, 19) and are often minimal or nonexistent at usual therapeutic dosages.

Assessing the efficacy of loperamide on the basis of changes in the duration of diarrhoea is complicated by the difficulty of defining precisely when
an episode of diarrhoea has terminated. Nevertheless, this has been the outcome measurement used in the majority of studies on loperamide. Two of these studies were unable to demonstrate any effect of loperamide on the duration of diarrhoea when children were given conventional dosages (20, 21).

Some larger studies suggested that loperamide may shorten the duration of diarrhoea by up to 24 hours (16, 18). Again, these effects appear to be dose-dependent, the most significant occurring in children given four times the usual dosage (22, 23).

Miscellaneous outcomes

A number of studies used weight gain as an outcome measurement and have reported mixed results with loperamide therapy (16, 20–23). This measure is inappropriate, however, as weight gain is determined by the adequacy of fluid replacement, and minor differences in weight may also reflect pooling of fluids in the intestine induced by an antimotility agent.

The time required to achieve rehydration has been assessed in two different studies, with conflicting results (16, 18). Again, it is difficult to discern what is actually measured in assessing this outcome.

5. Adverse effects

Gastrointestinal side-effects

Transient ileus or abdominal distension has been observed in some children treated with loperamide for acute diarrhoea (22–24), and two cases of necrotizing enterocolitis have been observed in children with loperamide-induced ileus (25). One case of toxic megacolon has been reported in a 24-year-old man with underlying ulcerative colitis (26).

A matter of great concern is the development of paralytic ileus, a complication with a high mortality rate, in some infants who received loperamide. Following published reports (27–29) of a number of deaths of infants with severe abdominal distension and ileus after ingestion of loperamide drops, the major manufacturer of loperamide agreed to halt worldwide sales of the drops, withdraw existing stocks from developing countries, and restrict the sale of loperamide syrup (30).

Effects on the central nervous system

Loperamide causes fewer adverse effects on the central nervous system (CNS) than comparable doses of diphenoxylate (11). Early reports stated
that loperamide was essentially devoid of CNS activity (31); however, drowsiness has been recognized in controlled clinical trials at daily dosages of 0.8 mg/kg of body weight (22) and CNS depression has been demonstrated at daily dosages as low as 0.1 mg/kg of body weight (21, 32). Coma has occurred after daily doses of 0.5 mg/kg and after a single dose of 0.125 mg/kg (33, 34). In a study of 151 infants suffering drug intoxications in Mexico, 10 cases were related to loperamide (35). In only two of these cases had the manufacturer’s recommended dose been exceeded (by more than twofold); six infants required naloxone therapy and nine were less than 6 months of age.

Other side-effects

Other complaints reported by patients treated with loperamide for acute diarrhoea include nausea, vomiting, drowsiness, dizziness, depression, blurred vision, abdominal pain, and headache. However, the relative frequency of these complaints in children taking loperamide or placebo has not been reported, and many of the symptoms may have been caused by the underlying disease. Adverse effects have been noted less frequently with loperamide than with diphenoxylate (36). Overall, side-effects in controlled clinical trials have been rare, but more frequent at higher dosages (22).

6. Conclusions

Loperamide has not been shown to reduce losses of fluid and electrolytes in acute diarrhoea. While the drug may have a modest effect on the duration of diarrhoea, probably as a result of reduced gastrointestinal motility, this effect is dose-dependent and of questionable clinical importance.

Abdominal distension and potentially fatal paralytic ileus have been reported in infants and young children treated with loperamide. As a result, the drug’s leading manufacturer has halted the sale of loperamide drops and restricted the distribution of loperamide syrup in developing countries.

Toxic effects on the central nervous system have been most commonly observed in children under 6 months of age. Although these adverse effects are less common than with other opiate antidiarrhoeals, they may be severe when therapy is poorly supervised.

Loperamide has no place in the routine management of diarrhoea in children, and there is thus no rationale for the production and sale of liquid or syrup formulations for paediatric use.
References


PART 2

Antimicrobial agents
Streptomycin and dihydrostreptomycin

Abstract
Streptomycin has no proven value in the treatment of diarrhoea. Indeed, there is some evidence that it may actually increase the severity or prolong the duration of some cases of diarrhoea. In addition, the widespread use of streptomycin promotes resistance to antimicrobial agents. Oral preparations containing streptomycin or dihydrostreptomycin should not be used in the treatment of diarrhoea, and the production and sale of these “antidiarrhoeals” therefore cannot be justified.

1. Formulations
Streptomycin is an aminoglycoside antibiotic which can serve as an important adjunct to tuberculosis therapy when given parenterally, but is widely marketed as an oral preparation for the treatment of diarrhoea. It is often combined with a variety of adsorbents, vitamins, or other antibiotics (1, 2). Dihydrostreptomycin is a related aminoglycoside with similar properties but greater toxicity. Despite the lack of studies on its use in diarrhoea, dihydrostreptomycin is also widely available for diarrhoea treatment.

Note: Because of the paucity of information about dihydrostreptomycin, the subsequent discussion focuses on streptomycin.

2. Pharmacology
In general, streptomycin is not absorbed from the gastrointestinal tract, though absorption may occur through damaged gastrointestinal mucosa (3). The greater part of an orally administered dose is excreted unchanged in the stool.

3. Mechanism of action
Like other aminoglycosides, streptomycin is rapidly bactericidal (4). It binds to one specific protein on the bacterial ribosome, inhibiting protein synthesis and causing the production of “nonsense” proteins.

4. In vitro spectrum and bacterial resistance
Streptomycin is active against a large number of aerobic Gram-negative bacteria, some strains of *Staphylococcus aureus*, and *Mycobacterium tuber-*
culosis (3). Extensive use of streptomycin, however, has been associated with the development of widespread antimicrobial resistance: current reports of streptomycin resistance range from 36% for Escherichia coli and 67% for Shigella spp. in Boston, USA (4) to almost 100% for enteropathogenic E. coli in Delhi, India (5).

Resistance to the aminoglycosides can occur through one of three different mechanisms: alteration of the permeability of the bacterial cell wall, enzymatic inactivation of the aminoglycoside, and alteration of aminoglycoside binding sites on the bacterial ribosome (4). Unlike resistance to other aminoglycosides, which bind to multiple sites on the bacterial ribosome, resistance to streptomycin and dihydrostreptomycin can occur through a change in only a single ribosomal protein.

Resistance is usually conferred by transferrable plasmids, which often carry resistance to other antibiotics as well (3). In some instances these plasmids also encode the production of bacterial enterotoxins (6). This suggests that widespread use of streptomycin may select for organisms with enhanced pathogenicity in addition to increasing the frequency of resistant microorganisms.

5. Efficacy

Most trials purporting to assess the efficacy of oral streptomycin in the treatment of acute diarrhoea have been non-blind, have not utilized placebo controls, and/or have not incorporated clear definitions of outcome measures (7). Since diarrhoea is a self-limiting disease, these uncontrolled trials lack significance. In the one trial that did incorporate appropriate randomization, blinding, and placebo controls, streptomycin therapy was associated with increased severity and duration of diarrhoea (8).

*Escherichia coli*

Streptomycin was widely used in the 1950s in the treatment of diarrhoea, despite the fact that its efficacy had not been demonstrated in controlled clinical trials. With the emergence of widespread resistance, however, it was largely replaced by other antibiotics for the treatment of E. coli infections (4), and controlled clinical trials of its efficacy have never been performed.

*Shigella* spp.

Early uncontrolled trials suggested that streptomycin might be effective in the treatment of shigellosis (9, 10), but other reports showed high failure rates or detected no difference between streptomycin treatment and sup-
portive therapy alone (11, 12). Some of these treatment failures have been attributed to the high rates of resistance to streptomycin but failure rates of 60% in the treatment of shigella dysentery have been noted despite in vitro sensitivity of the causative organism to streptomycin (13). Trials comparing ampicillin and neomycin (14) have led to the conclusion that non-absorbable antibiotics, such as neomycin and streptomycin, do not exert a significant effect on organisms that invade the intestinal mucosa and hence have little effect on the clinical or bacteriological outcome of shigella infections.

_Salmonella_ spp.

High failure rates have been reported with streptomycin, as with other antibiotics, in the treatment of salmonella gastroenteritis (13). Subsequent reports have suggested that antibiotic therapy can actually prolong the carrier state in acute gastroenteritis caused by salmonellae (15, 16). Placebo-controlled trials of neomycin (16), ampicillin (17), and amoxicillin (17) have confirmed the lack of efficacy of antibiotic therapy in this disease and have suggested that clinical relapse may be more frequent in patients treated with antibiotics.

6. **Adverse effects**

It is well known that streptomycin, administered parenterally, causes ototoxicity and nephrotoxicity. Since it is poorly absorbed in the intestine, orally administered streptomycin should rarely produce these complications; however, the extent of absorption and the toxicity of the drug in children with acute diarrhoea have not been fully evaluated.

A related aminoglycoside antibiotic, neomycin, can induce steatorrhoea, decrease disaccharidase activity, and induce malabsorption of lactose, sucrose, xylose, and calcium (18–20). Eosinophilic invasion of the lamina propria and destruction of the microvilli of the small intestine may be seen, with significant changes occurring after as little as three days of therapy. There have been no analogous studies with streptomycin but, in view of the clinical evidence that this drug worsens acute diarrhoea (8), there is concern that it might have similar effects.

7. **Formulations and drug interactions**

Streptomycin is seldom marketed as a single agent for the treatment of diarrhoea; it is commonly combined with kaolin, pectin, hydroxyquinolines, sulfonamides, or chloramphenicol. The efficacy of these combination products has not been established, and the multiple agents found
in them may lead to additional side-effects or to undesirable drug interactions. For instance, the neurotoxicity of hydroxyquinolines has resulted in their removal from the market in many countries (21): the kaolin and pectin contained in some of these “antidiarrhoeal” products may decrease the bioavailability of particular drugs, including certain essential antibiotics or antimalarials (22–26).

8. Conclusions

There is no evidence that streptomycin is effective in the treatment of diarrhoea, whatever the etiology of the condition. Existing data on the potential toxicity of orally administered streptomycin are inadequate, but there is evidence that the drug may exacerbate diarrhoea in some cases. Moreover, the widespread use of streptomycin promotes resistance to antimicrobial agents.

Streptomycin and dihydrostreptomycin preparations for oral administration are produced solely for the purpose of treating diarrhoea. Lacking any beneficial effect, however, they simply divert attention and resources from more important aspects of diarrhoea treatment, such as rehydration, proper nutrition, and appropriate antibiotics for the treatment of dysentery. “Antidiarrhoeal” agents containing streptomycin or dihydrostreptomycin should not be used in the treatment of diarrhoea, and the production and sale of these products cannot be justified.

References


21. Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments. New York, United Nations, 1987.


Neomycin

Abstract
Neomycin, an antibiotic contained in a large variety of oral antidiarrhoeal preparations, has no proven efficacy in the treatment of acute diarrhoea. Orally administered neomycin is clearly associated with gastrointestinal toxicity and may exacerbate or prolong a diarrhoeal episode. In addition, the widespread use of neomycin can promote antimicrobial resistance. Oral preparations containing neomycin should not be used in the treatment of diarrhoea, and the production and sale of these "antidiarrhoeals" cannot be justified.

1. Formulations
Neomycin is an aminoglycoside antibiotic that has been used extensively either alone or in combination with intestinal adsorbents, antimotility agents, or other antibiotics.

2. Pharmacology
Neomycin is generally classified as nonabsorbable, and most of an orally administered dose is excreted unchanged in the stool (1). Some neomycin is absorbed from the gastrointestinal tract (2), however, and is excreted primarily in the urine.

3. Mechanism of action
Like other aminoglycosides, neomycin is rapidly bactericidal (1). It binds to specific bacterial ribosomal proteins, inhibiting protein synthesis and promoting the production of "nonsense" proteins. Precisely how this results in death of the bacterium, however, is not clear.

4. In vitro spectrum and bacterial resistance
Neomycin is active against most aerobic Gram-negative organisms and staphylococci, but resistant strains of *Escherichia coli*, *Klebsiella*, *Proteus*, *Shigella*, and *Salmonella* spp. are frequently encountered (1). Streptococci and Gram-positive bacilli are largely resistant.

The resistance of Gram-negative organisms to neomycin is largely mediated by plasmids that also confer resistance to other antibiotics. These resistance factors, which can be transferred between bacteria, sometimes
convey the ability to produce enterotoxin (3). This suggests that widespread use of neomycin not only increases the frequency of antibiotic resistance but may also select for organisms with enhanced virulence.

5. Clinical efficacy

Acute diarrhoea

Several studies have examined the efficacy of neomycin in undifferentiated acute diarrhoea and have reported “cure” rates ranging from 50% to 100% (4–7). However, none of these studies incorporated placebo controls and, since most acute diarrhoeas are self-limiting, these reports of “cures” are not significant.

In one study in which patients were randomly allocated to treatment with neomycin plus kaolin or kaolin alone, neomycin appeared to have no effect on the outcome of diarrhoea (8). Moreover, results of a double-blind, placebo-controlled trial in patients with acute diarrhoea suggested that neomycin may actually increase the severity and duration of the disease (9).

*Escherichia coli*

There is no report of trials to assess the use of neomycin in the treatment of diarrhoea caused by enterotoxigenic, enteroadherent, enterohaemorrhagic, or enteroinvasive *E. coli*. There have, however, been extensive reports on the use of neomycin in the treatment of diarrhoea due to enteropathogenic *E. coli* (EPEC). Unfortunately, controlled studies are consistently lacking.

A number of uncontrolled clinical observations have reported excellent responses of EPEC infections to neomycin therapy (10–12), including cases that were refractory to other therapies (13, 14), but other investigators have noted little difference between neomycin and supportive therapy alone (15). In the light of the toxicity associated with oral neomycin (discussed below), it is unlikely that any controlled studies will be undertaken.

*Shigella* spp.

The role of antibiotics in altering the course of shigellosis has been firmly established (16), but not all antibiotics are equally efficacious. Although some early uncontrolled studies reported good results from the treatment of shigellosis with oral aminoglycosides (17–19), others showed bacterial and clinical cure rates of less than 50%. Two studies suggested that streptomycin (20) and neomycin (21) had no advantage over simple supportive care in shigellosis. A double-blind trial comparing neomycin with ampicillin
provided further evidence of the ineffectiveness of nonabsorbable antibiotics such as neomycin in the treatment of this disease (22).

*Salmonella* spp.

The role of antibiotics in the treatment of salmonella gastroenteritis was called into question when an epidemiological investigation suggested that antibiotic therapy actually prolonged the carrier state in such infections (23). Subsequent placebo-controlled trials of neomycin (24), ampicillin (25), and amoxicillin (25) have confirmed the lack of efficacy of antibiotic therapy in salmonella gastroenteritis. These studies have also confirmed that asymptomatic carriage may be prolonged (24) and clinical relapse more frequent (25) in patients treated with antibiotics.

6. Adverse effects

Neomycin can induce steatorrhoea, decrease disaccharidase activity, and cause malabsorption of lactose, sucrose, xylose, and calcium (26–28). After seven days of therapy, eosinophilic invasion of the lamina propria and destruction of the microvilli of the small intestine may be seen; significant changes can appear after as little as three days of therapy. The clinical relevance of these effects has been demonstrated in controlled trials in which extended courses of neomycin prolonged the duration of diarrhoea (9, 29).

Aminoglycosides are well known to cause ototoxicity and nephrotoxicity when administered parenterally. Because neomycin is used orally in the treatment of diarrhoea and is poorly absorbed, these should not be common complications of therapy, but there have been occasional case reports of ototoxicity in association with prolonged therapy, high doses, or renal failure (30, 31).

7. Formulations and drug interactions

Neomycin is seldom marketed as a single agent for the treatment of diarrhoea: it is usually combined with a variety of adsorbents or other antibiotics. None of these combination products has been reported to be effective. The hydroxyquinolines contained in several of these preparations have been banned or restricted in many countries because of their neurotoxicity (32), while kaolin and pectin components have been implicated in decreasing the bioavailability of certain essential antibiotics and antimalarials (33–37).
8. Conclusions

There is no good evidence to support the use of neomycin in the routine treatment of diarrhoea or in the treatment of diarrhoea caused by specific pathogens, including enteropathogenic *E. coli*. Widespread use of neomycin promotes resistance to antimicrobials, and the gastrointestinal toxicity of this antibiotic may actually increase the severity or duration of diarrhoea.

The use of neomycin in diarrhoea diverts attention and resources from more important aspects of management, such as rehydration, proper nutrition, and appropriate antibiotics for the treatment of dysentery. Oral preparations containing neomycin should not be used in the treatment of diarrhoea, and the production and sale of these antidiarrhoeals cannot be justified.

References


32. Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments. New York, United Nations, 1987.


Hydroxyquinolines

Abstract

Halogenated hydroxyquinolines are widely used for the routine treatment of diarrhoea, a disorder for which they have not been shown to be effective. Used alone, they are ineffective in the treatment of symptomatic amoebiasis. Severe neurological disorders such as optic neuritis and subacute myelo-optic neuropathy have been associated with their use. Considering their lack of efficacy and the availability of less toxic, more effective amoebicides, the use of halogenated hydroxyquinolines in acute diarrhoea cannot be justified and there is thus no rationale for their production and sale.

1. Formulations

Halogenated hydroxyquinolines have been advocated for the treatment of intestinal amoebiasis in many pharmacopoeias; however, they are currently widely promoted and used for all types of diarrhoea. A number of different products are available on the market, the most popular of which are clioquinol (iodochlorhydroxyquinoline) and iodoquinol (diodohydroxyquinoline); also available are broxyquinoline (dibromohydroxyquinoline) and chlorquinaldol (dichloromethylhydroxyquinoline) (1). These are marketed under various trade names, either as individual agents or, more commonly, combined with a wide variety of vitamins, antibiotics, or other agents (2, 3). Clioquinol is also commonly marketed as an antibacterial/antifungal agent in dermatological preparations (4).

2. Pharmacology

Systemic absorption of the hydroxyquinolines was originally thought to be minimal, but it is now evident that they are absorbed in substantial quantities (5). Though most of the drug is excreted in the faeces, up to 25% of an oral dose is conjugated in the liver and can be recovered in the urine (6, 7). A green chelate of clioquinol and ferric iron found on the tongue and in the urine of patients taking clioquinol is further evidence of systemic absorption (4).

3. Mechanism of action

The mechanism of action of the hydroxyquinolines is unknown (8). They are active against both motile and cyst forms of amoeba and have
some in vitro activity against a number of enteric bacteria (9). The in vivo effect of these agents on the microbiological flora of the gut, however, has remained largely unexplored.

4. Efficacy

Amoebiasis

In spite of the early reports of success with hydroxyquinolines in the treatment of amoebiasis (10), it is clear that these agents function only as luminal amoebicides; high failure rates have been noted when they are used alone in the treatment of amoebic dysentery (11, 12). The efficacy of hydroxyquinolines in the treatment of amoebic dysentery appears to be improved when they are combined with antibiotics such as tetracycline or erythromycin (13, 14). Since few of these antibiotics are amoebicidal, however, the rationale behind this therapy is unclear. No well-controlled trials have compared these combinations with the current treatment standard, metronidazole.

Studies in institutionalized patients have suggested that luminal amoebicides such as the hydroxyquinolines may be of some value in the prophylaxis of amoebiasis (15), but the usefulness of this approach is limited by the cost and side-effects of therapy (16).

Hydroxyquinolines have also been advocated for the treatment of asymptomatic cyst-passers (17), but failure rates of up to 25% have been noted (12) and up to three weeks’ therapy is usually required. Metronidazole, on the other hand, has produced comparable cure rates after only 10 days of therapy (18). A number of reasons can be cited for not treating asymptomatic cyst-passers. For instance, the majority are colonized with non-pathogenic zymodemes of Entamoeba histolytica (19); the natural history of E. histolytica is such that up to 90% of cases will clear spontaneously within 12 months (20, 21); in highly endemic areas, the probability of reinfection is high, further limiting any benefits of treatment (16).

In view of the wide availability of nitroimidazoles such as metronidazole, tinidazole, ornidazole, and nimorazole, there is no need to use hydroxyquinolines in the treatment of amoebic diseases. Concern about the higher cost of the nitroimidazoles has been greatly alleviated by the availability of low-cost generic metronidazole, which can be obtained at a wholesale cost of US$ 0.34–0.68 per course of treatment (22).

Acute diarrhoea

There are no controlled studies documenting the usefulness of halogenated hydroxyquinolines in the treatment of undifferentiated acute diarrhoea,
yet as indications for these drugs physicians’ drug references include bacillary dysentery, colitis, gastroenterocolitis, summer diarrhoea, dyspepsia, and, in one case, diarrhoeas “of the most diversified etiology... with or without infective and protozoan involvement” (2, 3). The very nature of many of the formulations in which the hydroxyquinolines appear suggests that they have been designed and are marketed for non-selective use in diarrhoea.

Clioquinol was widely promoted in the past for the prevention of traveller’s diarrhoea. One manufacturer’s reports of two non-blind, non-randomized trials suggested that it might be effective for this complaint (23, 24), but a double-blind trial in American and Canadian students in Mexico was unable to demonstrate any beneficial effect of the drug (25). A study of tourists returning to Sweden from the Mediterranean actually suggested that travellers taking hydroxyquinolines might be at increased risk of diarrhoea and prolonged carriage of salmonellae (26). Another report suggested that clioquinol was effective in the prevention of diarrhoea in children in Honduras (27), but this study suffered from an unusually high frequency of diarrhoea in the control group and non-blinding of the observers. Studies in which prophylactic tetracycline and clioquinol were compared in a rabbit model did not support the use of clioquinol to prevent intestinal infections caused by *Vibrio cholerae* and *Escherichia coli* (28).

### 5. Adverse effects

A number of adverse effects of hydroxyquinolines have been observed, including abdominal discomfort, diarrhoea, skin rash, acne, headaches, and enlargement of the thyroid gland (4), but the most notable have been the severe neurological complications described in numerous reports.

The most extensively studied neurological disorder associated with hydroxyquinolines is subacute myelo-optic neuropathy (SMON), a disorder characterized by abdominal pain or diarrhoea followed by painful dysesthesias and visual disturbances (29). Between 1955 and 1970, about 10 000 cases were diagnosed in Japan, of whom 5% died and up to 15% were left completely disabled; 75% of the cases were associated with the ingestion of clioquinol. There was also evidence of an association between the amount of drug consumed and the extent of visual impairment (30). A dramatic fall in the number of cases following the withdrawal of clioquinol from the Japanese market provided further evidence of a causal link between clioquinol ingestion and SMON (1).

Although the disorder initially appeared to be limited to users of clioquinol in Japan, neurological disorders associated with this and other hydroxyquinolines were soon reported from Australia, Denmark, India, Netherlands, Sweden, Switzerland, the United Kingdom and the USA (1, 31). One review
of neurotoxic reactions associated with halogenated hydroxyquinolines occurring outside Japan classified 111 of 220 cases as either possibly or probably related to the drug (31); the most common reactions noted were optic atrophy and acute reversible encephalopathy.

Many of the neurological side-effects of the hydroxyquinolines do not accord with the classical definition of SMON; optic atrophy has been reported in association with broxyquinoline (33) and iodoquinol (34) as well as clioquinol; unusual disturbances of gait were noted in 20 of 4000 patients in the USA treated with clioquinol (15); transient global amnesia has also been linked to clioquinol use (35).

6. Conclusions

Halogenated hydroxyquinolines are often marketed for the treatment of undifferentiated acute diarrhoea, a disorder in which they clearly play no role.

There is little if any practical role for hydroxyquinolines in the treatment of amoebiasis. A wide variety of less toxic and more effective compounds is currently available, which can be substituted for the hydroxyquinolines in the rare circumstances in which a luminal amoebicide is required.

The side-effects associated with hydroxyquinolines, while not common, can be severe. The use of these products in the treatment of acute diarrhoea and amoebiasis cannot be justified, and there is thus no rationale for their continued production and sale.

References


Nonabsorbable sulfonamides: sulfaguanidine, succinylsulfathiazole, phthalylsulfathiazole

Abstract

Nonabsorbable sulfonamides were once considered the drugs of choice in the treatment of shigella dysentery and other intestinal infections, and are still widely used for this purpose. However, their lack of efficacy and concern about their toxicity have led to a critical reassessment of their role as antidiarrhoeal agents, and their distribution and sale have been banned in several countries. There is no justification for their continued use.

1. Formulations

Nonabsorbable sulfonamides are marketed for the treatment of intestinal infections, particularly bacillary dysentery, and as agents to “sterilize” the bowel before surgery (1). They are sold alone or in combination with other drugs (2, 3).

2. Pharmacology

Sulfonamides are derived from sulfanilamide, which is a metabolite of Prontosil, an azo dye (4). All sulfonamides have the same antimicrobial spectrum, and differ only in their pharmacokinetic properties (5).

The action of sulfaguanidine, succinylsulfathiazole, and phthalylsulfathiazole is confined primarily to the large intestine, and most of the ingested drug is excreted in the stool. However, a portion is absorbed in the small intestine, diffuses widely in the tissues and body fluids, and is bound to plasma proteins. Some of the absorbed drug undergoes acetylation to an inactive conjugate in the liver (4, 6). Sulfonamides and their acetylated derivatives are rapidly excreted by the kidney.

Systemic absorption of sulfaguanidine is slow and erratic (7, 8); between 15% and 50% of the drug is systemically absorbed and excreted by the kidneys (9). Like many of the older sulfonamides, sulfaguanidine is less soluble in its acetylated form, and tends to form crystals in the urine (4, 9).

Succinylsulfathiazole and phthalylsulfathiazole are derivatives of sulfathiazole, another sulfonamide. Both drugs are hydrolysed to their parent compound by bacteria in the colon, and sulfathiazole is presumed to be
the major bacteriostatic product. About 5% of ingested succinylsulfathiazole and phthalylsulfathiazole is systemically absorbed (1, 10, 11).

When succinylsulfathiazole is used for several days in a patient on a low-bulk diet, the faeces become gelatinous, semiliquid, less bulky, and relatively odourless (10, 12). Treatment with phthalylsulfathiazole after a low-residue diet tends to make stools adherent and stringy, and may require the use of cathartics for bowel evacuation (12).

Although the bacterial count of sensitive organisms in the bowel is markedly reduced in patients taking a nonabsorbable sulfonamide, the stool never becomes sterile, and bacterial counts return to previous levels as soon as the drug is discontinued (10–12).

3. Mechanism of action

The sulfonamides are bacteriostatic agents. They are structural analogues of p-aminobenzoic acid, which is essential for folic acid synthesis, and thus interfere with bacterial utilization of p-aminobenzoic acid to synthesize folic acid (4, 5). Sulfonamides have no effect on folic acid synthesis in humans.

The antibacterial action of sulfonamides is inhibited by tissue breakdown products, blood and pus (4).

4. In vitro spectrum and bacterial resistance

Sulfonamides are effective against many Gram-positive and Gram-negative organisms, but acquired bacterial resistance has considerably narrowed their therapeutic range (4, 6). Since all sulfonamides have the same mechanism of action, bacteria resistant to one are resistant to all drugs of this class (5).1

Some bacteria are inherently resistant to sulfonamides; others have acquired resistance by spontaneous mutation or by acquisition of plasmids from resistant organisms (4, 6). Bacteria that were originally sensitive to sulfonamides can become resistant during the course of treatment (6, 13). Most shigella strains are now resistant (1, 6, 14); by 1965 almost 60% of Shigella flexneri and 90% of Shigella sonnei were insensitive to sulfonamides (4). Resistant strains of Escherichia coli and all other Enterobacteriaceae have become common, particularly in hospitals (6, 14). Although active against typhoid organisms in vitro, sulfonamides have never proved useful for the treatment of typhoid fever or salmonella enteritis (7, 14, 15).

1 Co-trimoxazole consists of trimethoprim, an antibacterial agent, and sulfamethoxazole, a sulfonamide. Because trimethoprim exercises a synergistic effect by blocking bacterial utilization of folic acid for purine synthesis (5, 6), organisms that are resistant to the sulfonamides may still be sensitive to co-trimoxazole.
Part 2. Antimicrobial agents

5. Efficacy

In the 1940s, nonabsorbable sulfonamides were considered ideal antimicrobial agents for treating bacillary dysentery (16) and other diarrhoeal illnesses. In the years that followed, however, recognition of their lack of efficacy and their potential toxicity led to a critical reassessment of their role. Importation and/or production of sulfaguanidine has been prohibited in several countries. In the United States, sulfathiazole, the active ingredient in succinylsulfathiazole and phthalylsulfathiazole, has been banned as an ingredient in systemic preparations and prohibited for export (17).

Nonabsorbable sulfonamides were developed with the idea of delivering a large concentration of the drug to the bowel while avoiding the systemic toxicity associated with earlier sulfonamides. Sulfaguanidine became available in 1940, and was widely employed in the armed forces during the Second World War (7). When used to treat troops with bacillary dysentery, sulfaguanidine reportedly brought about a prompt clinical response, even in chronic cases (18). The incidence of adverse effects was described as very low.

A report summarizing a 6-year field study of diarrhoeal diseases in the general population, undertaken by the National Institutes of Health in the United States, described experience with nonabsorbable and systemically absorbed sulfonamides in the treatment of bacillary dysentery. All sulfuro drugs tested were effective when compared with untreated controls, but the authors found that the response to systemically absorbed sulfonamides was more rapid (19).

The use of sulfonamides to treat shigella dysentery in both adults and children was described in a series of studies (20–23). Sulfaguanidine, the first sulfonamide employed in the series, was hailed as a promising drug that brought about a prompt clinical response (20), but in subsequent studies it was found to be less effective than the systemically absorbed sulfonamides (21–23). Succinylsulfathiazole was first described in 1941 (10). It was initially used for “sterilization” of the large intestine before surgery, but was also used for the treatment of dysentery (9) since early studies suggested that it was less toxic than sulfaguanidine. However, its antibacterial action was reported to be strongly inhibited by watery diarrhoea caused by irritation of the mucosa, and its effectiveness was diminished in the presence of hard stool or ulcerated intestinal mucosa (8–10). Phthalylsulfathiazole was first used in human subjects in 1942 (11). Its properties resembled those of succinylsulfathiazole, but it was observed to offer some advantages: it required a smaller dose, produced formed stools, and was effective even in the presence of watery diarrhoea (11, 12).

Although nonabsorbable sulfonamides continued to be widely used in the post-war years, a growing number of studies questioned their efficacy
in shigella dysentery (13, 15, 16, 24–26). Some reviewers felt that this lack of efficacy stemmed from the nature of the drugs themselves: shigella dysentery was no longer regarded as a disease confined to the intestinal lumen but as a systemic ailment requiring systemically absorbed drugs for its treatment. It is difficult to reconcile this view with earlier studies reporting a high success rate when sulfaguanidine and other nonabsorbable sulfonamides were used to treat bacillary dysentery. Although there is little doubt that nonabsorbable sulfonamides eventually proved to be less effective than systemically active sulfonamides in this disease, it seems likely that their loss in efficacy over the years stemmed primarily from the emergence of resistant strains of bacteria.

Although *Vibrio cholerae* is sensitive to sulfonamides *in vitro* (4), nonabsorbable and systemically absorbed sulfonamides have often proved ineffective in the treatment of cholera (7, 15). In one controlled study (27), children and adults hospitalized with cholera were treated with one of three sulfonamides described as particularly effective against *Vibrio cholerae*: sulfaguanidine, formosulfathiazole and formosulfacetamide. All patients were given fluids intravenously. There was no difference in the duration of *Vibrio cholerae* excretion between the treated and control groups, and the mortality rate was somewhat lower in the control group than in the groups treated with sulfonamides; uraemia contributed to the deaths of several patients treated with formosulfathiazole.

In another controlled study, the efficacy of tetracycline, chloramphenicol and sulfaguanidine was compared in hospitalized men with stools positive for *Vibrio cholerae*. All patients were given fluids intravenously. Although the duration of diarrhoea was shorter in the groups treated with antibiotics, sulfaguanidine had no significant effect on the volume of diarrhoeal stool or the duration of vibrio excretion (28).

The efficacy of nonabsorbable sulfonamides as agents to “sterilize” the bowel preoperatively has also been questioned in a number of reviews (1, 5, 12, 13).

### 6. Adverse effects

Untoward effects of sulfonamides can involve nearly every organ system, and can be due to sensitization or to a direct toxic effect of the drug (4). Although less of the drug is absorbed, nonabsorbable sulfonamides share the toxicities of systemically absorbed sulfonamides. Patients allergic to one sulfa drug are likely to be allergic to all sulfonamides, and should not be given these drugs. Allergic skin rashes are not uncommon as a side-effect of sulfonamide use, and the Stevens-Johnson syndrome, a sometimes fatal hypersensitivity reaction, has been described in association with all sulfonamides (6).
Sulfonamides occasionally cause haemolysis; this reaction is not dose-dependent, and is probably due to prior sensitization. Sulfonamides can also cause haemolysis in patients deficient in the enzyme glucose-6-phosphate dehydrogenase; children and black people are particularly susceptible (29). Agranulocytosis has been reported following the administration of sulfonamides, including sulfaguanidine and succinylsulfathiazole (9, 30, 31).

Because sulfonamides compete with bilirubin for binding sites on albumin, they may cause jaundice if given to premature or newborn infants or to pregnant women before term; sulfonamides are contraindicated for these groups (6, 12).

Early sulfa drugs and their acetylated metabolites were relatively insoluble in urine, and frequently caused renal damage from crystalluria (6). The reported incidence of crystalluria and renal calculi in patients taking sulfaguanidine ranges from 13% to 31% (32). The acetyl derivatives of succinylsulfathiazole and phthalysulfathiazole are more soluble in urine than that of sulfaguanidine, but crystalluria has also been reported in patients receiving succinylsulfathiazole (15); development of urinary tract complications may be asymptomatic and detectable only by examination of the urinary sediment (29).

By altering the normal intestinal flora, nonabsorbable sulfonamides may interfere with the bacterial synthesis of nicotinic acid and vitamin K (9, 12); a case of nicotinamide deficiency apparently triggered by sulfaguanidine has also been reported (33).

7. Drug interactions

Sulfonamides may potentiate the effects of warfarin anticoagulants, antidiabetic sulfonylureas, and hydantoin anticonvulsants (4, 5), and adjustment of the doses of these drugs may be necessary if they are given concurrently with sulfonamides.

8. Conclusions

Sulfaguanidine, succinylsulfathiazole and phthalysulfathiazole were developed as agents primarily active against organisms in the intestine. They are marketed for intestinal infections and as drugs that “sterilize” the intestine before surgery. Nonabsorbable sulfonamides were once considered the drugs of choice for bacillary dysentery, but because of their demonstrated lack of efficacy and the risk of serious side-effects associated with their use they are no longer advocated for this purpose.

Co-trimoxazole, which contains a systemically absorbed sulfonamide is, in most areas, the drug of choice for shigella dysentery. However, periodic
assessment of sensitivity patterns of locally isolated shigella strains should be carried out to confirm the suitability of the drug.

Drug resistance has narrowed the therapeutic range of all sulfonamides, and overuse of antibiotics has led to the emergence of bacteria with multiple resistance.

Adverse reactions to sulfonamides can involve almost every organ system and may be life-threatening.

There is no justification for the use of nonabsorbable sulfonamides, or of systemically absorbed sulfonamides other than co-trimoxazole, to treat diarrhoea or dysentery.

References


17 Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments. New York, United Nations, 1987.


PART 3

Adsorbents
Part 3. Adsorbents

Kaolin and pectin

Abstract

Although they are widely used in the treatment of diarrhoea, kaolin and pectin have been shown to induce only a slight change in stool consistency. There is no evidence that they can reduce the duration or the severity of diarrhoeal illness; they do not reduce fluid and electrolyte losses and may interfere with efficacy of antibiotics when these are indicated. Their use cannot be recommended in the treatment of diarrhoea, and there is thus no rationale for the production and sale of products that contain kaolin or pectin.

1. Formulations

Kaolin and pectin are frequently combined in suspensions and marketed under a variety of different brand names, but are more often sold in combination with antibiotics, vitamins, or other drugs (1, 2).

2. Pharmacology

Kaolin is a hydrated aluminium silicate powder (3). It is a naturally occurring clay, which is not absorbed when taken orally; it is excreted essentially unchanged in the stool.

Pectin is a carbohydrate isolated from the rinds of citrus fruits or green apples (3). Its major constituent is polygalacturonic acid, and it is almost completely digested and absorbed in the intestine (4).

3. Mechanism of action

Claims have been made that kaolin adsorbs toxins (5–7), alters bacterial flora (5), and can “coat” the intestinal lining to produce a “general protective effect” (3). While it appears to be able to bind cholera toxin, it exhibits little in vitro binding of the heat-stable toxin of enterotoxigenic Escherichia coli (8). It does not appear to have any bactericidal action (5), nor is it able to “adsorb” bacteria (9). It has been postulated that the ability of kaolin-pectin to bind bile acids is another mechanism for its antidiarrhoeal action (4).
4. Efficacy

Kaolin has been used as an antidiarrhoeal agent for centuries (3). Pectin became popular after the use of apple-powder diets as a simple remedy for diarrhoea in the early 1900s (10). Combinations of these two products are currently in wide use despite the absence of documented clinical efficacy (11).

Kaolin-pectin has been shown to decrease toxin-induced intestinal secretion when the combination is injected into pig intestine simultaneously with enterotoxigenic E. coli (12). Studies in dogs also demonstrated a significant reduction in the volume of diarrhoea when kaolin was administered before or simultaneously with cholera toxin (7); however, when the toxin was administered before the kaolin, kaolin treatment did not affect the severity of diarrhoea. In monkeys with diarrhoea induced by a diarrhoeogenic diet or administration of cholera toxin, kaolin, pectin, and kaolin-pectin were shown to induce significant changes in stool consistency, but to have little effect on stool frequency (3).

In the early 1900s it was reported that kaolin could reduce mortality among patients with cholera (5, 6); similar results were noted in other diarrhoeal diseases (3, 13). None of these reports, however, was based on controlled clinical trials. It was not until 1970 that a controlled clinical trial showed kaolin to be ineffective in the treatment of cholera (7). In this study, in which cholera patients received either fluids alone, fluids plus kaolin, fluids plus tetracycline, or all three, tetracycline had a significant effect on the course of diarrhoea whereas kaolin had no effect on either stool volume or duration of diarrhoea.

In another study, 97 children with acute diarrhoea were treated with either kaolin or supportive therapy alone (14): no difference was observed in the duration of diarrhoea, mean number of stools per day, or the clinical course of the disease.

A placebo-controlled trial of kaolin, pectin and kaolin-pectin in children with acute diarrhoea showed that the kaolin-pectin combination resulted in more “formed” stools, but that neither of the agents alone or in combination led to any difference in stool frequency or stool weight (15). Similar results were seen in a trial in which 76 patients with acute diarrhoea were treated with kaolin-pectin or dietary changes only (16).

5. Adverse effects

The exaggerated loss of sodium and potassium in the stool seen in rats given a kaolin-pectin combination (11) has led to fears that kaolin-pectin may aggravate electrolyte disorders in children with severe diarrhoea. Kaolin-
pectin has also been shown to lead to significantly increased losses of fat and nitrogen in the stool (4, 17).

6. Drug interactions

Multiple interactions have been demonstrated between kaolin-pectin and other drugs. Among the best documented of these are the decreased bioavailability of chloroquine (18, 19), pyrimethamine (18), digoxin (20), trimethoprim (21, 22), and lincomycin (23) when administered simultaneously with kaolin-pectin. The interaction with trimethoprim is of special concern for the management of diarrhoeal diseases as trimethoprim/sulfamethoxazole (co-trimoxazole) is a drug of choice for the treatment of shigella dysentery. Substantial binding of neomycin by clays has also been observed \textit{in vitro} (24) and, although this interaction has not been clearly established \textit{in vivo} (25), it is surprising that a large number of currently available anti-diarrhoeal compounds use this precise combination (1, 2).

7. Conclusions

Although kaolin-pectin can improve stool consistency in some children with acute diarrhoea, there is no evidence to suggest that kaolin, pectin or a combination of the two can reduce the duration of diarrhoea, stool frequency, or stool fluid losses. The improvement in stool consistency does not justify the expense of treatment (26) and may lead to an underestimation of the extent of fluid and electrolyte losses. Kaolin and pectin may also interfere with the efficacy of antibiotics when these are indicated.

Rather than contributing to the effective treatment of acute diarrhoea, the use of products containing kaolin-pectin diverts attention and resources from more important aspects of treatment, such as rehydration, proper nutrition, and, for cholera and dysentery, appropriate antibiotics. Kaolin and pectin cannot be recommended for the treatment of diarrhoea, and there is thus no rationale for the production and sale of products that contain these agents.

References


Activated charcoal

Abstract

Although activated charcoal has been used empirically as an anti-diarrhoeal for many years, there is no clinical evidence that it shortens the duration of diarrhoea, or that it reduces the number or volume of stools. Its action as an adsorbent causes it to bind other drugs, including tetracycline, and digestive enzymes and intestinal micronutrients, which may be undesirable. There is thus no rationale for the use of activated charcoal for the treatment of diarrhoea in children.

1. Formulations

Activated charcoal is marketed alone, in tablet form, and in combination with antacids and/or antimitility drugs. It is promoted for the treatment of flatulence, indigestion, and diarrhoea (1, 2).

Activated charcoal is also sold as a powder to be mixed with water for the treatment of poisoning and drug overdose (1, 2). The doses recommended for treatment of acute poisoning (50–100 g for adults and 20–50 g for children) are up to 100 times larger than the recommended daily doses (750–1500 mg for adults) for antidiarrhoeal use (1–3).

2. Pharmacology

Charcoal is a fine, odourless, tasteless, black powder which can be derived from the destructive distillation of animal, mineral or vegetable substances (1, 4, 5). Activated charcoal is charcoal that has been treated to increase its adsorptive surface; the most effective form has small particle size, large surface area, a high drug-binding capacity, and low mineral content (3, 6). Activated charcoal preparations differ in their base material, the excipients used in their manufacture, and the affinity with which they bind drugs. Different preparations may vary as much as 50-fold in their adsorptive capacities (4), and this variability might explain the conflicting claims found in early reports about the effectiveness of activated charcoal as an antidote in poisoning and drug overdose (3).

Powdered charcoal is insoluble in most solvents; when used as an antidote it is given with water as a slurry.

Activated charcoal is not systemically absorbed. Its action as an adsorbent in the intestine depends on a number of factors, including the preparation and dose used, contents and pH of the stomach, type of medications
or toxins in the gastrointestinal tract, and intestinal transit time (3). Activated charcoal may colour the stool black.

3. Mechanism of action

Activated charcoal adsorbs and inactivates a number of organic and inorganic compounds even when it is administered several hours after their ingestion. By tightly binding medications and toxins in the intestinal lumen, charcoal creates a concentration gradient which favours diffusion of the compounds from the systemic circulation back into the intestinal lumen (1, 7). It interrupts the enterohepatic circulation of drugs such as tetracycline (3, 8), and may also reduce tissue levels of parenterally administered drugs that diffuse or are secreted into the intestine (7). Activated charcoal may adsorb amino acids, digestive enzymes, vitamins and nutrients in the digestive tract (4, 9).

Although some manufacturers claim that it adsorbs intestinal gases (2), the ability of activated charcoal to adsorb gases in vitro has not yet been demonstrated (10).

4. Efficacy

Powdered charcoal has long been advocated as an adsorbent in patients with dyspepsia and diarrhoea, but its lack of demonstrated effectiveness led to a decline in its use for many years (4). Recently, it has been studied in the treatment of flatulence (10, 11) and diarrhoea associated with irritable or spastic colon (12), although its proponents admit that data on its effectiveness have been meagre.

Recent studies have investigated the use of charcoal as a possible adjunct to oral rehydration salts in the treatment of acute diarrhoea. The ability of activated charcoal to bind toxins in the gut has been studied in animal and human models. In two separate animal studies (13, 14), activated charcoal reduced enterotoxin-induced intestinal secretion, but only when it was administered with the enterotoxin; when given before perfusion with enterotoxins, it had little or no effect on intestinal secretion. The authors of both studies concluded that activated charcoal was unlikely to prove useful in the treatment of diarrhoea.

Activated charcoal has not been found effective in cholera patients in controlled clinical trials: in one trial it did not bind free, luminal cholera enterotoxin, and it had no effect on the purging rate or the duration of illness in comparison with a control group (15). In a controlled study of patients with cholera and severe non-cholera diarrhoea (8), the administration of activated charcoal to both groups of patients during the first four
hours of oral therapy led to a significant increase in the volume of diarrhoeal stools and to prolonged excretion of *Vibrio cholerae* compared with controls. (The authors also found that activated charcoal, when mixed with oral rehydration salts before administration, decreased the osmolality of the solution and significantly altered the potassium and glucose composition. The clinical significance of this finding is not clear.)

The authors postulated that the prolonged vibrio excretion in patients treated with activated charcoal was caused by adsorption by the charcoal of tetracycline, which was administered to all patients in the study. There was no difference in the duration of diarrhoea between the two groups.

A study comparing the effectiveness of diphenoxylate, kaolin-pectin and activated charcoal in adults with acute diarrhoea found no difference in the consistency of the stools or the number of stools per day after two and four days compared with controls in whom treatment consisted of advice about following a conventional diet (16).

In a controlled study, a group of children hospitalized with diarrhoea were given oral rehydration salts and intravenous fluids (compound solution of sodium lactate), with or without activated charcoal. There was no significant difference between the two groups, in terms of either duration of diarrhoea or total consumption of oral rehydration salts and intravenous fluids (17).

5. Adverse effects

Activated charcoal is relatively free from serious side-effects when administered by mouth although vomiting has been reported in some patients (1, 8). When it is used in high doses as an antidote, charcoal has been reported by some authors to have a constipating effect (1, 7); one brand, however, containing 18 mmol of sodium per 5-g sachet (18), caused diarrhoea when given in repeated doses (19).

6. Drug interactions

Because of its affinity for a wide range of drugs and for vitamins and other macromolecular substances in the intestine, activated charcoal cannot be considered a harmless drug. Even in the low doses recommended for diarrhoea, activated charcoal can bind to and inactivate other drugs commonly used in paediatrics, such as aspirin, paracetamol, penicillin, tetracycline and sulphonamides (4, 7). Some drug manufacturers caution that activated charcoal may adsorb other medications in the gastrointestinal tract (2), and chronic use of activated charcoal has been discouraged (4).
The rational use of drugs in the management of acute diarrhoea in children

7. Conclusions

As an adsorbent, activated charcoal has been shown to be an effective antidote in the emergency treatment of poisonings and drug overdoses. However, clinical studies have failed to demonstrate its efficacy as an antidiarrhoeal drug; it has not been shown to alter the number or volume of stools, or to shorten the duration of acute diarrhoea. Activated charcoal adsorbs commonly prescribed medications such as tetracycline, and binds to vitamins and intestinal enzymes in the bowel lumen.

There is thus no role for activated charcoal in the treatment of acute diarrhoea in children, and it should not be used.

References


Part 3. Adsorbents


Attapulgite and smectite

Abstract
Attapulgite and smectite, mineral clays similar to kaolin in composition, are marketed as antidiarrhoeal drugs that protect the intestinal mucosa and bind bacterial toxins. Although they may change the consistency and appearance of the stool, there is no conclusive evidence that they affect the loss of fluids and electrolytes in acute diarrhoea. Like other adsorbents, they may bind and inactivate other drugs. Attapulgite and smectite do not have significant antidiarrhoeal activity, and should not be used to treat diarrhoea in children.

1. Formulations
Activated attapulgite and smectite are marketed alone and in combination with other drugs. Although they differ slightly in their crystalline structure (1), they are similar in their physical properties.
Activated attapulgite is advocated for the treatment of diarrhoea in children and adults because of its adsorbent properties (2). In 1986 the United States Food and Drug Administration (FDA) classified it as “safe and effective” for use as an over-the-counter antidiarrhoeal drug (3, 4).¹
In France, attapulgite and smectite are also advertised as agents that strengthen and protect the digestive mucosa (1, 5). Activated attapulgite is marketed as a combination with guar gum, a bulk-forming agent, for the treatment of “colopathy with constipation” in children and adults (5, 6). The manufacturer also produces smectite as an antidiarrhoeal drug.
Smectite is advertised as a remedy for acute and subacute diarrhoea in children. Although its manufacturer claims that the “mucostabilizing” action of smectite protects the bowel from “germs and their toxins”, it cautions against using the drug to treat “toxi-infectious diarrhoea” accompanied by dehydration; in such cases smectite is promoted only as an adjuvant to rehydration therapy (1, 5). Attapulgite and smectite have been advocated for a wide variety of other acute and chronic digestive disorders, including gastritis, oesophagitis, peptic ulcer and colitis (1, 5, 6).

¹ FDA definition of an antidiarrhoeal: “A drug that can be shown by objective measurements to treat or control the symptoms of diarrhoea”. The FDA based its classification of the drug on a report (4) indicating that attapulgite reduced the number of bowel movements, improved stool consistency and relieved cramps in diarrhoea.
2. Pharmacology

Attapulgite and smectite are fine, cream- or buff-coloured powders composed of silicates of aluminum and magnesium arranged in parallel layers. In their physical properties they are similar to kaolin. Attapulgite is referred to as “activated” when it has been heated to increase its adsorptive capacity (2). As an adsorbent, attapulgite is comparable to charcoal (6), and, according to its manufacturer, smectite can adsorb eight times its weight of water (1).

Attapulgite and smectite are not systemically absorbed.

3. Mechanism of action

Attapulgite and smectite are marketed as antidiarrhoeal drugs on the basis of their adherent and adsorbent qualities. Some studies have suggested that attapulgite and smectite form bonds with glycoproteins in the mucus lining of the digestive tract, thereby “strengthening” the mucus barrier and enhancing its protective effects (1, 5). However, the significance of this finding with respect to fluid and electrolyte loss during diarrhoea has not been explained.

As adsorbents, attapulgite and smectite have been promoted as agents that bind bacterial toxins in the intestine (1, 5). Attapulgite has been shown to adsorb bile salts (7), and smectite reportedly adsorbs fibrinogen and several other clotting factors (1). The clinical significance of these findings is uncertain.

Like other adsorbents used for diarrhoea, attapulgite and smectite may bind other drugs in the intestine, thereby delaying absorption or causing inactivation. Smectite has been shown to adsorb tetracycline and trimethoprim, antibiotics that are sometimes indicated for children with diarrhoea (8). One manufacturer of preparations containing attapulgite and smectite cautions against administering them together with other drugs (1, 5).

There is no evidence that either attapulgite or smectite has a significant effect on intestinal motility. In a series of animal studies smectite did not affect intestinal transit time, even when administered for several months (1).

4. Efficacy

Like kaolin, attapulgite and smectite can change the appearance and consistency of the stool by adsorbing water from the intestinal lumen. However, this effect is merely “cosmetic”; treatment with attapulgite and smectite may produce more formed bowel movements, but it does not affect the loss of water and electrolytes in the diarrhoeal stool.
Attempts to demonstrate the adsorption by attapulgite in vitro of whole bacteria or bacterial endotoxins have yielded mixed results. A comparative study of adsorptive qualities found that activated attapulgite adsorbed Staphylococcus aureus better than two other clays, but that none of the clays adsorbed Proteus vulgaris, Salmonella enteritidis or Shigella paradysenteriae (9). Another in vitro study, however, demonstrated binding by activated attapulgite of the endotoxins of enteropathogenic Escherichia coli and Shigella sonnei (10). The significance of this finding to the potential therapeutic effect of activated attapulgite is unclear.

In a study in animals, investigators reported that activated attapulgite could inhibit the intestinal fluid secretion induced by Vibrio cholerae and Escherichia coli enterotoxins, but only if it was preincubated with the toxin or if toxin and adsorbent were administered together; attapulgite was ineffective when given after administration of the toxin (11). It was therefore considered unlikely that activated attapulgite would prove to be clinically useful in the prevention or treatment of diarrhoea caused by enterotoxins.

Other investigators found that smectite showed some ability to increase fluid absorption in normal rabbit intestinal loops, and exercised a similar effect when the loops were injected with toxigenic Escherichia coli. These results suggest that smectite may enhance the absorption of water and electrolytes in the intestine (12), but they have not been confirmed in other studies.

Another animal study looked at the effect of smectite on changes in gastrointestinal motility caused by administration of cholera toxin and mannitol (13). Researchers found that treatment with smectite transiently altered gastric motility following administration of cholera toxin and delayed the onset of diarrhoea following mannitol. Since the effect of smectite on stool volume was not mentioned in the study, the relevance of these findings to the possible efficacy of smectite as an antidiarrhoeal is not clear.

In a similar study, the effect of smectite on gastrointestinal transit was investigated in mice treated with T-2 toxin, a mycotoxin that may cause severe gastrointestinal illness (14). Smectite delayed a toxin-induced acceleration of gastric emptying and intestinal transit, but only when it was incubated with T-2 toxin for 24 hours before administration. When administered simultaneously with the T-2 toxin, smectite had no significant effect on toxin-induced disturbances in intestinal transit.

A number of clinical trials have been conducted using smectite to treat diarrhoea in children (1, 15 – 18). The investigators emphasize that the first step in diarrhoea therapy should be the correction and prevention of dehydration with oral rehydration salts; smectite is proposed as an adjunct to this therapy. The duration of smectite treatment necessary to achieve the desired effect — reduction in the number of stools and/or "normalization" of stools
— ranged from 2 to 10 days.

The course of diarrhoeal illness is variable and can be quite short; with proper diet and fluid replacement, most cases will subside within 72 hours (19). It is therefore essential that the efficacy of an antidiarrhoeal drug be demonstrated in placebo-controlled studies. The ultimate test of antidiarrhoeal efficacy is the extent to which the drug checks the loss of fluids and electrolytes; thus it is also essential to measure stool weight or stool volume in clinical trials, and not merely to report on a change in stool appearance or consistency.

To date, it seems that only one placebo-controlled study has been conducted according to these guidelines. The study was conducted in Egypt, and smectite or placebo was administered to 90 hospitalized male children less than 3 years of age (20). Criteria for inclusion in the study were acute diarrhoea of less than three days’ duration, and clinical evidence of moderate dehydration. None of the subjects had been given antidiarrhoeal drugs before admission to hospital. In all cases dehydration was treated with oral rehydration salts according to WHO guidelines. There was no statistically significant difference between the groups in the major outcome variable, total diarrhoeal stool output in g/kg of body weight, but the duration of diarrhoea, measured from time of hospital admission, was significantly reduced in children given smectite (54 hours, compared with 73 hours in the placebo group; P <0.001). It would appear that smectite has little effect on stool output during the early, high purging phase of acute diarrhoea, but can alter the stool consistency and frequency as the acute attack wanes and intestinal transit time increases.

A number of clinical trials with children and adults have been conducted in Africa using a preparation containing attapulgite and homatropine (21–23). This is promoted by the authors as a new antidiarrhoeal agent without antibiotics which, in conjunction with increased fluid intake, is effective in cases of mild to moderate diarrhoea. The authors reported that the drug reduced both the duration of diarrhoea and the number of stools. Since stool volume was not measured, it is unclear whether the results reflect a decrease in stool output or merely a change in stool consistency. It is not possible to comment on the role played by attapulgite in these studies, since it was one ingredient in a combination drug.

---

1 Homatropine is an antimuscarinic similar to atropine. Antimuscarinic drugs may reduce the motility and secretory activity of the gastrointestinal system, but usually only at doses high enough to cause systemic effects, such as tachycardia, dry mouth, and blurred vision (24). In view of their toxic effects, they are not recommended for use as antidiarrhoeal drugs.
Studies comparing activated attapulgite (3) and smectite (25) with loperamide as antidiarrhoeal agents in adults reported that the adsorbents were equal in efficacy to loperamide; the majority of patients were considered cured in two days. Neither study employed a control group, and stool weight was not measured.

5. Adverse effects

No serious adverse effects have been associated with attapulgite or smectite in published studies.

6. Drug interactions

Like other adsorbents, activated attapulgite and smectite may bind other drugs in the intestine. Depending on their affinity for a particular drug, the adsorbents may inactivate it or delay its onset of action. Smectite binds tightly to cortisone, diazepam, propranolol, tetracycline and trimethoprim in vitro, and may interfere with the clinical efficacy of these drugs in vivo (8). The French manufacturer of preparations containing attapulgite and smectite warns that they should be administered separately from other drugs (1, 5).

7. Conclusions

Activated attapulgite and smectite are marketed as antidiarrhoeal agents that strengthen and protect intestinal mucus and adsorb bacterial toxins.

While these agents may change the consistency and appearance of the stool by adsorbing fluid in the intestinal lumen, there is no conclusive evidence that they affect the water content of the stool or prevent the fluid and electrolyte losses sustained in acute diarrhoea. Furthermore, attapulgite and smectite may bind and inactivate other drugs such as antibiotics administered to patients with diarrhoea. Smectite and attapulgite have no place in the management of acute diarrhoea in children and should not be used.

References


Selected WHO publications of related interest

The treatment and prevention of acute diarrhoea. Practical guidelines, 2nd ed.
1989 (49 pages) 11.— (7.70)

1991 (in press)

1985 (25 pages) 3.— (2.60)

Further information on these and other World Health Organization publications can be obtained from Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland.

* Price in parentheses applies in developing countries.
An estimated 4 million children under 5 years of age die annually as a direct result of diarrhoea, and many others from causes that are aggravated by diarrhoea. Adequate feeding during and after diarrhoeal episodes and timely action to prevent or treat dehydration could substantially reduce these numbers, yet the inappropriate or injudicious use of drugs frequently diverts attention and resources away from these simple measures.

A number of pharmaceutical agents have been – and continue to be – promoted for the treatment of acute diarrhoea. At best, many of these are of questionable therapeutic value, and at worst they may be positively harmful. This book reviews experimental and clinical experience of the use of a range of these agents. Extensive evidence is cited in support of its conclusions – that use of adsorbents or of drugs purporting to reduce intestinal motility cannot be justified, and that paediatric use of antibiotics and antiparasitics should be strictly confined to cases of diarrhoea of specific etiology. For cholera, shigella dysentery, amoebiasis and giardiasis, when drug treatment becomes essential, the antimicrobial agents of choice, and correct dosages for children are detailed.

In providing a basis for a rational approach to the treatment of acute diarrhoea in childhood, and dispelling many of the misconceptions that can lead to appreciable wastage of resources, this book will find application at all levels, from the individual health worker to the national programme for control of diarrhoeal diseases.