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Ralph Nader, Founder

CITIZEN'S PETITION

January 7, 1993

David A. Kessler, MD, JD
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Citizen's Petition for a Ban and/or Relabeling of Antidiarrheal Drugs

Dear Dr. Kessler:

The World Health Organization (WHO) has recently published a report entitled "*The Rational Use of Drugs in the Management of Acute Diarrhea in Children*,"[1] which is a thorough review of studies of the efficacy and safety of the most commonly used antidiarrheal preparations. The report concludes, with respect to the drugs evaluated, that "Antidiarrheal drugs should never be used. None has any proven value and some are dangerous."[1] These findings were recently echoed by the U.S. Centers for Disease Control and Prevention (CDC) which concluded that "Little evidence exists to support the use of nonspecific drug therapy in children, and much information exists to the contrary."[2] At least ten developing countries namely Indonesia, Korea, Lebanon, Libya, Mexico, Pakistan, Peru, Philippines, Sri Lanka, and Turkey have acted more expeditiously than the U.S. in reacting to the WHO report by banning or relabeling some or all of the drugs addressed in this petition.

Public Citizen, a nationwide consumer organization with over 140,000 members, hereby petitions the Food and Drug Administration, pursuant to the Federal Food, Drug and Cosmetic (FDC) Act 21 U.S.C. Section 355 (e) (3), 21 C.F.R. 10.30 to:

A. Ban the pediatric prescription dosage forms of diphenoxylate hydrochloride with atropine sulfate (Lomotil and others, available by prescription only). The WHO report concludes that "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 diarrheas and thus no rationale for the production and sale of liquid and syrup preparations for pediatric use."[1] There were 30,000 prescriptions of liquid diphenoxylate filled in U.S. retail pharmacies in 1991, mainly for pediatric use.

B. Ban the pediatric prescription and over-the-counter dosage forms of loperamide hydrochloride (Imodium, Imodium-AD, Pepto Diarrhea Control, and, others available by prescription and over-the-counter). The WHO report concludes that "loperamide has no place in the routine management of diarrhea in children and there is thus no rationale for the production and sale of liquid or syrup formulations for pediatric use."[1] Imodium A-D, the number one over-the-counter antidiarrheal drug sold in the U.S., is the liquid formulation which we seek to have banned. (Imodium-AD also comes in a caplet form.)

Adult formulations of diphenoxylate hydrochloride-atropine sulfate, and loperamide hydrochloride remaining on the market should have a boxed warning contraindicating their use in children.

C. Ban both adult and pediatric formulations of the following over-the-counter and prescription drugs:

(1) kaolin and pectin (Donnagel-PG and others). The WHO report concludes that "Kaolin and pectin cannot be recommended for the treatment of diarrhea, and there is thus no rationale for the production and sale of products that contain these agents."[1]

(2) activated charcoal (Charcoal Plus, Charcocaps, and others). The WHO report concludes that "[C]linical studies have failed to demonstrate its efficacy as an antidiarrheal drug .... There is thus no role for activated charcoal in the treatment of acute diarrhea in children, and it should not be used."[1] Activated charcoal is frequently used for the treatment of ingestions of poisons. We are not seeking a ban for this indication; and

(3) attapulgite (Diasorb, Donnagel, Kaopectate, Rheaban, and others). The WHO report concludes that "[A]ttapulgite [has] no place in the management of acute diarrhea in children and should not be used."[1]

Charcocaps, Diasorb, Donnagel, Imodium A-D, Kaopectate, Pepto Diarrhea Control and others are available over-the-counter. Many parents may be unaware of the ineffectiveness and/or potential hazards of these drugs or of the appropriate therapy for the management of diarrhea. Parents can thus take immediate action to protect their children by no longer using these ineffective and potentially hazardous medications and using Oral Rehydration Solution (ORS) instead.

These drugs are marketed in the U.S. for the treatment of diarrhea, although there has never been any convincing evidence of their effectiveness in reducing the fluid and electrolyte losses associated with this disease. By contrast, management of diarrhea with ORS is considered one of the most important medical advances of this century.[3] ORS is a simple, low-cost, and easily obtainable method to prevent or correct the dehydration (the loss of body

fluids and salts) that often accompanies diarrhea.[4,5]

There are multiple problems associated with the widespread use of these drugs in diarrhea. The CDC report has summarized these succinctly "[S]ide effects of these drugs are well known, including opiate-induced ileus (cessation of the function of intestines), drowsiness and nausea due to atropine effects, and binding of nutrients and other drugs .... In addition, reliance on antidiarrheal agents shifts the therapeutic focus away from appropriate fluid, electrolyte, and nutritional therapy; can interfere with oral therapy; and can unnecessarily add to the economic cost of the illness."[2] Recently at least six infant and child deaths with loperamide were reported from Pakistan,[6] and hundreds of poisonings in children in the U.S. have been attributed to diphenoxylate.[7]

The WHO review mentioned above is the product of the work of a worldwide panel of experts and summarizes the current knowledge regarding the use of antidiarrheals (it has over 300 references). The WHO prepared this report at the request of health professionals worldwide who asked for scientific documentation of the efficacy and safety of these antidiarrheal drugs.[8] The review concluded that antidiarrheal drugs including these five ingredients are "without established benefit in any field of pediatric practice."[1] This petition thus echoes the WHO report and seeks to codify its findings. At least ten developing countries (Indonesia, Korea, Lebanon, Libya, Mexico, Pakistan, Peru, Philippines, Sri Lanka, and Turkey. See Table below) have acted more expeditiously than the U.S. in reacting to the WHO report by banning or relabeling some or all of the drugs addressed in this petition [Tulloch J, WHO, Geneva, Switzerland, personal communication, June 24, 1992]. If the Food and Drug Administration is to protect American consumers as rigorously as the drug regulatory authorities in these developing countries protect their citizens, it must immediately implement the requests outlined in this petition.

Regulatory actions concerning antidiarrheal drugs use in children*

	Country	Drugs affected	Action	Date
1.	Indonesia	Pediatric formulations of loperamide. 94 antidiarrheal products containing antibiotic mixtures, hydroxyquinolines, non-absorbable sulfonamides, and other substances	Banned Deregistration of solid and liquid formulations	Nov 1990 Oct 1991

2.	Lebanon	Products containing loperamide, diphenoxylate, difenoxine and furazolidone.	Restriction on use in children, deregistration and banning of products	Aug 1991
3.	Libya	10 antidiarrheal products, which include antimotility drugs, antimicrobials, and adsorbents	Use in children banned	May 1990
4.	Mexico	5 pediatric products, containing loperamide and diphenoxylate	Deregistered	Dec 1990
5.	Pakistan	Drop and syrup formulations of loperamide and diphenoxylate	Banned and deregistered	June 1990
6.	Peru	Pediatric formulations of loperamide	Deregistered	Oct 1990
7.	Philippines	Loperamide and diphenoxylate	Deregistered	Sept 1991
8.	Republic of Korea	Loperamide	Restriction on use in children	May 1991
9.	Sri Lanka	Syrup formulations of loperamide	Deregistered	Nov 1990
10.	Turkey	Drop and syrup formulations of loperamide	Banned	Sept 1991

*There are other countries that have regulated antidiarrheals which are not included in this list because action was taken before 1990 or was not officially reported to us (Tulloch J, WHO, Geneva, Switzerland, personal communication. June 24, 1992).

A. ACTION REQUESTED

We request

(1) a ban on pediatric prescription formulations of diphenoxylate hydrochloride with atropine sulfate including Lomotil (liquid; Searle) and generic versions,

(2) a ban on all pediatric formulations of loperamide hydrochloride including Imodium (liquid; Janssen), Imodium A-D (liquid; McNeil-CPC), Pepto Diarrhea Control (solution; Procter & Gamble), and generic versions,

(3) a ban on all pediatric and adult formulations of kaolin, and/or pectin including Donnagel-PG (liquid; AH Robins), Parepectolin (suspension; Rhone-Poulenc Rorer), and generic versions,

(4) a ban on all pediatric and adult formulations of activated charcoal including Charcoal Plus (tablets; Kramer) and Charcocaps (capsules; Requa). [Activated charcoal is frequently used for the treatment of ingestions of poisons. We are not seeking a ban for this indication],

(5) a ban on all pediatric and adult formulations of attapulgite including Diasorb (liquid and tablets; Columbia), Donnagel (liquid and chewable tablets; Robins Consumer), Kaopectate (concentrated liquid, children's liquid, chewable tablets, and caplets; Upjohn), Parepectolin (suspension; Rhone-Poulenc Rorer), and generic versions,

(6) relabeling of all adult antidiarrheal preparations of diphenoxylate-atropine sulfate and loperamide to include a boxed warning alerting doctors and parents to (i) the great number of severe gastrointestinal and central nervous system side effects reported with diphenoxylate-atropine sulfate and loperamide and (ii) the lack of evidence of efficacy for diphenoxylate-atropine and loperamide in reducing the rate of fluid and electrolyte loss in children, and

(7) that in the interim period (until a ban and relabeling is imposed) a Dear Doctor/Pharmacist letter be sent to all physicians/pharmacists notifying them of the ineffectiveness and/or detrimental effects of these drugs in children and adults.

B. STATEMENT OF GROUNDS

Acute Diarrhea in Children

Diarrheal diseases are a leading cause of childhood morbidity and mortality in developing countries. An estimated 4 million children under 5 years of age die each year from diarrhea.[1] In addition, diarrhea aggravates undernutrition and predisposes to death from other diseases. Of all infectious diseases, the diarrheal diseases (along with measles) have the greatest adverse effect on the growth of children.[9] Dehydration is a frequent result of diarrhea and can be rapidly fatal in children. According to the WHO, correct prevention and treatment of dehydration with ORS, appropriate feeding during and after diarrhea, the judicious use of antibiotics for cholera and dysentery, and antiparasitic drugs for amebiasis and giardiasis could substantially reduce this heavy toll.[1]

In the U.S., diarrheal illnesses remain among the most common problems seen by pediatricians. An estimated 16.5 million children in the United States younger than 5 years old experience between 21 and 37 million episodes of diarrhea each year. Of these, 2.1 to 3.7 million episodes lead to a physician visit, resulting in 220,000 hospitalizations, representing 10.6% of all hospitalizations in this age group.[10] The annual incidence of hospital admissions for diarrhea in babies under 1 year old is 7.9 cases per 1000, with an average stay of 4.4 days.[11] In day care centers in the U.S., diarrhea rates range up to 3.64 cases per child per year.[12] Approximately 500 children (400 infants) die each year with diarrhea listed as a principal cause of death. These deaths represent approximately 10% of the preventable deaths in infants between 1 month and 1 year of age.[13] Diarrheal deaths occur in about 1/15,000 live births or 1/500 children hospitalized.[10]

Thus diarrheal diseases represent a considerable disease burden and cause economic loss in both developed and developing countries.[14] By contrast, drug companies, including U.S. multinationals, continue to reap profits peddling the ineffective and often dangerous drugs named in this petition. In the U.S., the non-prescription antidiarrheal drug market was $120 million in 1990, $155 million in 1991, and is expected to surge to $170 million in 1992. Of this the best seller is Imodium A-D with approximately 50% ($60-85 million) of the market share, followed by Kaopectate with approximately 33% ($40-55 million) [Kline & Co, Fairfield, NJ, personal communication, November 13, 1992]. The sale of ORS in the U.S. was $40 million in 1990 and $55 million in 1991 [Pritech, Arlington, VA, personal communication].

ORS is effective in 90-95% of cases of acute watery diarrhea.[15] Unfortunately, however, such proper treatment of diarrhea "remains the exception rather than the rule."[16] In particular, studies of current patterns of diarrhea treatment have shown that a large number of pharmaceutical agents of dubious efficacy and potential toxicity are widely used.[1] For example, 59 of 75 pharmacies in three Asian developing countries recommended drugs for the treatment of acute diarrhea.[17]

Studies have clearly demonstrated that ORS is also little used by U.S. parents[18] and pediatricians despite its endorsement by the American Academy of Pediatrics,[19] the Centers for Disease Control and Prevention,[2] and the National Research Council.[20] A recent marketing survey found that less than 20% of infants with diarrhea received ORS from their U.S. parents.[18] By contrast, at least one third of all families in the developing world now use ORS.[5] Outmoded feeding practices like the slow reintroduction of food are still common even though available evidence indicates that continued human milk feeding during diarrheal illness results in reduced severity of diarrhea and may also decrease the duration of illness.[21,22] Thus, U.S. children are far behind their developing world counterparts in the proper treatment for acute diarrheal

illnesses, with ineffective and/or dangerous antidiarrheal drugs too often supplanting the use of ORS. Similar findings have been reported in Newcastle, England.[23] There is no longer any excuse for ignoring the long-established and proven guidelines for oral rehydration and feeding of infants and children with diarrhea.[24]

Acute Diarrhea In Older Adults

The elderly also have a substantial risk of hospitalization and death from diarrheal diseases. In the U.S., in adults aged 55 years and above, 22,430 deaths due to diarrhea were reported from 1979 to 1987.[25,26] There are few studies which address diarrheal treatment issues in the elderly, but ORS appears to perform as well in older age groups as it does in children.[27]

Regulatory History

The 1962 amendments to the FDC Act required that all products be proven effective as well as safe. In 1972, the FDA commenced a review of all over-the-counter drug products (OTC Review). An FDA Advisory Panel of experts studied twenty-four active ingredients in over-the-counter antidiarrheal products for safety and effectiveness in the treatment of diarrhea. Of the products reviewed in this petition, the panel in 1975 classified attapulgite, activated charcoal, kaolin, and pectin to be in Category III (available data are insufficient to classify as safe and effective, and further testing is required).[28] The FDA has now reclassified attapulgite to Category I (generally recognized as safe and effective and not misbranded). In so doing, the FDA overruled the advice of its own Advisory Panel which had recommended Category III status for attapulgite.[29] (Please refer to the attapulgite section for details as to why attapulgite still lacks evidence of effectiveness.) The remaining drugs, diphenoxylate (Lomotil) and loperamide (Imodium), that are the subject of this petition were not part of the OTC Review as none were available over-the-counter at that time.

In 1977, Public Citizen sued the FDA for permitting the continued marketing of Category III drugs. The Court accepted our argument that it was illegal for a manufacturer to sell Category III drugs since the FDA had determined that the evidence to support the sale of those drugs was insufficient to establish their safety and efficacy. A court order was issued invalidating the FDA regulation that permitted the agency to classify ingredients in Category III in a final OTC Monograph. However, the FDA took more than two years to amend its regulations to conform to the Court's decision, and even then adopted a regulation which we believe is also illegal. Under the new regulation, the FDA allows manufacturers to continue to market drugs that have not been proven safe and effective while testing is undertaken so long as it had not made a decision in a final monograph.

In 1981, Public Citizen filed a second lawsuit against the FDA to challenge the new Category III regulation and seeking a court order requiring the FDA to expedite the OTC Review. The court rejected our arguments with respect to Category III, but the case is still pending as to the issue of expediting the OTC Review; the decision has been appealed. It has been more than 20 years since the OTC Review began but the FDA has still not published the *Final Monograph on Antidiarrheal Drug Products for OTC Use* and so consumers are continually being exposed to unsafe and ineffective medications.

Under sections 505 and 201(p) of the Federal FDC Act, 21 U.S.C. 355, 321(p), the FDA plainly has the authority to ban these products by announcing that they do not meet applicable legal standards. Section 505(a) prohibits the introduction or delivery for introduction into interstate commerce of any "new drug" unless an application to market the drug has been approved by the FDA. Section 301(d), 21 U.S.C. 331(d), subjects any person who violates section 505 to civil and criminal penalties. Since none of the drugs other than diphenoxylate and loperamide that are the subjects of this petition have an approved new drug application (NDA), their sale is prohibited if they are "new drugs."

The term "new drug" is defined under section 201(p) as "any drug" that is not "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective." An FDA advisory panel determined that available data are insufficient to classify attapulgite, activated charcoal, kaolin, and pectin, as safe and effective, and further testing is required.[29] That is a sufficient basis for the FDA to make an administrative determination that the product is a new drug.

Petitioners are aware that since 1972 the FDA has as a matter of its enforcement discretion not enforced the FDC Act against any over-the-counter drugs alleging that a drug is not effective if the agency has not issued a final decision for that drug under the OTC Review. Petitioners would point out that this enforcement policy is not binding and is also no real bar to requiring new labeling [Community Nutrition Institute v. Young, 818 F.2d 943 (D.C. Cir. 1987)].

In light of the serious public health concerns raised in this petition, we therefore urge the FDA to implement a ban and relabeling of these products by announcing that the agency considers them to be illegal and that manufacturers will immediately be subject to enforcement actions for any products that are marketed after a certain date. Any grace period should be very short.

Review of Efficacy and Safety Data

In the following sections, we review in detail the data on the

efficacy of each of these drugs, and briefly summarize the WHO's assessment of their safety. Only controlled studies have been considered, as other research designs contribute little to evaluations of drug efficacy in this setting. We believe further that all efficacy studies must be placebo-controlled. The WHO report says,

> **The ultimate test of antidiarrheal 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.**[1]

Drugs that have not been shown to diminish fluid and electrolyte losses under the experimental conditions outlined above cannot be considered effective. Studies that report decreases in stool frequency alone or suggest changes in stool consistency ("cosmetic" effects, according to the WHO) are also not considered acceptable evidence of antidiarrheal efficacy. This is because frequency of stool correlates poorly with fluid loss and is more reflective of whether the diarrhea is an upper or lower bowel disorder [Greenough WB, personal communication, November 23, 1992].

In addition to the studies reviewed in the WHO report, we have conducted MedLine (National Library of Medicine, Bethesda, MD) searches for the drugs in this petition to identify studies published since that report, and for attapulgite we have reviewed the FDA docket for unpublished studies.

1. Diphenoxylate hydrochloride (Lomotil)

Diphenoxylate (known best in the U.S. as Lomotil), is chemically related to narcotics, and hence may be habit-forming if taken in doses larger than usual. To discourage abuse of diphenoxylate, a small amount of atropine is combined. If higher than normal doses are taken, the unpleasant effects of atropine (dry mouth, blurred vision, dizziness, etc.) make it difficult to take the combination repeatedly. Antimotility drugs like diphenoxylate-atropine slow down the contractile functions of the gut.

Efficacy

We are aware of eight double-blind trials which looked at the efficacy of diphenoxylate in the management of acute diarrhea. The first trial included 81 patients between the ages of 5 and 61 years (91% of the patients were over 16) and diphenoxylate was compared with clioquinol.[30] In the second trial, 244 subjects between the ages of 5 and 61 years and over (93% were over 16) were assigned to either diphenoxylate or clioquinol therapy.[31] With respect to both time for frequency of bowel movements to become normal and time taken for consistency of bowel movements to become normal, neither of these trials were able to attribute any significant benefit to

diphenoxylate. Neither of the trials were placebo-controlled. The third trial included 213 patients between the ages of 9 and 82 years (median age 31 years).[32] In this study a single 5 mg dose of diphenoxylate was observed to have no effect on the subsequent passage of unformed stools. In a fourth double-blind trial, 152 patients with acute diarrhea aged between 18 and 70 years were randomly allocated to receive either diphenoxylate or matching placebo.[33] There were no differences between the two treatment groups. Of the patients receiving diphenoxylate, 80% stated that the medication "helped a lot", but 75% of those receiving a placebo reported the same effect. In a fifth trial involving 50 children up to the age of 8 years (74% of children were over 1 year old), there was no clear pattern to suggest that diphenoxylate altered the course of the disease with regard to frequency of bowel movements or duration of illness.[34] The sixth trial, involving only 15 infants with acute diarrhea, who were assigned either to diphenoxylate or placebo, showed a significantly shorter duration of hospitalization for the infants treated with diphenoxylate.[35] In view of the small numbers, an analysis of the comparability of the two groups at the outset of treatment would have been useful.[1] In the seventh trial, 80 children (aged between 3 and 11 years) with acute diarrhea were randomized to either kaolin-pectin, kaolin alone, pectin alone, diphenoxylate-atropine, or placebo. With respect to frequency, weight, or water content of stools, the authors were unable to demonstrate any benefit of the drugs over placebo.[36] Finally, in the eighth trial, Swedish investigators randomized 228 adult outpatients to kaolin-pectin, activated charcoal, diphenoxylate, and placebo and were unable to demonstrate superiority of any of the treatment arms with respect to either stool frequency or consistency.[37] In none of these eight trials did diphenoxylate decrease fluid and electrolyte loss in diarrhea.

Safety

The diphenoxylate-atropine combination has been associated with severe central nervous system (CNS) toxicity including drowsiness, sedation, respiratory depression, coma, and even death. Abdominal distension is a frequent side effect. The difference between therapeutic and toxic doses is unpredictable and severe CNS toxicity even after normal therapeutic doses has been reported. Diphenoxylate-atropine is also a common cause of accidental poisoning in toddlers. The 1990 Annual Report of The American Association of Poison Control Centers National Data Collection System lists 1654 cases of diphenoxylate-atropine poisonings, including 1,004 cases (61%) involving children less than 6 years old, and two deaths.[7]

According to the consultants of *The Medical Letter* "Lomotil can relieve the symptoms of acute gastroenteritis in children, but it can also mask the signs of dehydration and cause fatal toxic reactions .... use of this combination for treatment of diarrhea in children is hazardous."[38]

As far back as 1980 the WHO concluded that these products "are of no use in the prevention and treatment of dehydration and are not indicated in the routine treatment of acute diarrheal disease .... They may greatly slow intestinal peristalsis (gut contractions) and delay the elimination of the causative organisms. They can be very dangerous (even fatal) if used in infants."[39]

The WHO report concludes:

> **Diphenoxylate appears to have some effect in relieving symptoms of mild chronic diarrheas in adults, but there is no clear evidence of a beneficial effect in acute diarrhea in either children or adults. Diphenoxylate does not diminish the fluid losses associated with diarrhea 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 diarrheas and thus no rationale for the production and sale of liquid and syrup preparations for pediatric use.**[1] [emphasis added]

2. Loperamide hydrochloride (Imodium)

Loperamide (best known in the U.S. as Imodium) is a synthetic opiate analog antimotility drug developed specifically for use in diarrhea. The liquid formulation (Imodium-AD Liquid), which has been associated with at least six infant and child deaths,[6] is the number one antidiarrheal brand sold over-the-counter in U.S. pharmacies.[40]

Efficacy

We are aware of three double-blind, placebo-controlled clinical trials which looked at the efficacy of loperamide using conventional doses (0.2 mg/kg/day) in the treatment of acute diarrhea in infants and children. All these trials failed to demonstrate any significant advantage of loperamide over placebo. The first clinical trial was carried out in two centers, in Liverpool, England and Benghazi, Libya.[41] Fifty patients aged three months to four years were entered into the study in Liverpool. The Benghazi site also recruited fifty children aged one month to two years. Children were randomly assigned to receive either loperamide or a placebo at each site. There was no statistically significant difference in the duration of diarrhea, length of hospital stay, or weight gain after 48 hours of admission between the loperamide and the placebo group in either center. In the second trial, 100 Egyptian children aged less than 2 years with acute diarrhea were assigned to the recommended dose of loperamide (0.24 mg/kg/day) or a matching placebo.[42] ORS was allowed ad libitum (as desired) and

a record of intake was kept. With regard to stool output as well as the weight gain after rehydration, there was no difference between the loperamide group and the placebo group. In the third trial, 41 Finnish infants aged 4 months to 3 years with acute diarrhea were randomized into 3 groups, to receive either cholestyramine (4 gm/day), a placebo, or loperamide (0.1 mg/kg/day).[43] There was no significant difference in the duration of diarrhea between loperamide and placebo.

We are aware of three studies in which loperamide was given in higher than the normal recommended dose (0.4 mg and 0.8 mg/kg/day). The most significant effect was seen in children given four times the usual dosage (0.8 mg/kg/day). In one study, 315 children with acute diarrhea in England, were administered ORS and assigned to either loperamide at two dose levels (0.4 and 0.8 mg/kg/day) or placebo.[44] The results of this study indicated that children receiving 0.8 mg of loperamide had the shortest duration of diarrhea, and the fastest weight gain compared to placebo. Similar results were noted by researchers in Saudi Arabia.[45] In another trial, reported from South Africa, 30 infants (aged 6 weeks to 1 year) with acute diarrhea were given loperamide (0.8 mg/kg/day) plus ORS, compared to 30 matched control infants who received ORS alone.[46] This study also demonstrated that using loperamide at four times the recommended dose lowers stool output and shortens the duration of diarrhea. However, two infants in the loperamide group were withdrawn from the study because of serious side effects notably ileus (cessation of the function of intestines) and persistent vomiting. Drowsiness was observed in another four. These trials suggest that loperamide's ability to shorten the duration of diarrhea may only occur at higher doses. However, the occurrence of potentially serious side effects in 20% of children in the closely monitored hospital-based study casts doubts on the safety of loperamide.[47]

Safety

Paralytic ileus (cessation of the function of intestines), transient ileus or abdominal distension, drowsiness, central nervous system depression, coma, and even death are major toxic effects reported with the use of loperamide.[6] It has been reported that loperamide may be responsible for the lethargy and toxic delirium in a child.[48] As a result of loperamide's potential to cause abdominal distension and fatal paralytic ileus, the drug's leading manufacturer has halted the sale of loperamide drops worldwide and withdrawn the distribution of loperamide syrup in countries where the WHO has a program for control of diarrheal diseases.[49] However, the company has not withdrawn the liquid formulation in the U.S.

The WHO report concludes:

> **Loperamide has not been shown to reduce losses of fluid**

and electrolytes in acute diarrhea. While the drug may have a modest effect on the duration of diarrhea .... this effect is dose-dependent and of questionable clinical importance .... Loperamide has no place in the routine management of diarrhea in children, and there is thus no rationale for the production and sale of liquid or syrup formulations for pediatric use.[1] [emphasis added]

3. Kaolin and Pectin (Donnagel-PG)

Kaolin is a naturally-occurring clay which is not absorbed orally and is excreted essentially unaltered in the stool. Pectin is a carbohydrate occurring naturally in the rinds of green apples and citrus fruit. Both are claimed to manifest antidiarrheal activity by adsorbing bacteria and toxins.[1,37] Goodman & Gilman's standard textbook of pharmacology disputes these claims: "However, adequately controlled clinical studies that demonstrate the efficacy of these popular but minimally effective antidiarrheal mixtures are lacking."[50]

Efficacy

We are aware of only four randomized trials of the efficacy of these ingredients in the treatment of acute diarrhea. In the first study, conducted in 49 adult East Pakistani (now Bangladeshi) patients with cholera, kaolin was found to be ineffective in either decreasing stool volume or the duration of diarrhea.[51] In a second trial, 80 Guatemalan inpatients between 3 and 11 years of age were randomized to kaolin-pectin, kaolin, pectin, diphenoxylate-atropine, and placebo. With respect to frequency, weight, or water content of stools, the authors were unable to demonstrate any benefit of the drugs over placebo. The stools of subjects in the kaolin-pectin group had a modest tendency to be more formed than those in the other treatment groups but neither kaolin or pectin alone nor in combination led to a difference in stool frequency or stool weight.[36] Swedish investigators randomized 228 adult outpatients to kaolin-pectin, activated charcoal, diphenoxylate, and placebo and were unable to demonstrate superiority of any of the treatment arms with respect to either stool frequency or consistency.[37] Finally, in a study of acute outpatient diarrhea in The Gambia, 97 subjects between 3 and 18 months of age were randomized to either ORS or kaolin plus ORS. The two groups were similar with respect to duration of diarrhea before and after treatment, stool water content, number of stools per day, and change in body weight.[52]

Safety

The WHO report documents interactions between kaolin-pectin and chloroquine, pyrimethamine, digoxin, trimethoprim, lincomycin, and perhaps neomycin.[1] Thus the drug may diminish the effectiveness of antibiotics in those cases where they are in fact indicated.

An FDA Advisory Panel of experts evaluated the safety and effectiveness of over-the-counter products containing kaolin and pectin for the treatment of diarrhea. **The panel classified kaolin and pectin to be in Category III (available data are insufficient to classify as safe and effective and further testing is required).**[29]

The WHO report concludes:

> **[T]here is no evidence to suggest that kaolin, pectin or a combination of the two can reduce the duration of diarrhea, stool frequency, or stool fluid losses. The improvement in stool consistency does not justify the expense of treatment and may lead to an underestimation of the extent of fluid and electrolyte losses. Rather than contributing to the effective treatment of acute diarrhea, the use of products containing kaolin-pectin diverts attention and resources from more important aspects of treatment ..... Kaolin and pectin cannot be recommended for the treatment of diarrhea, and there is thus no rationale for the production and sale of products that contain these agents.**[1] [emphasis added]

4. Activated Charcoal (Charcoal Plus)

Activated charcoal is the product of the destructive distillation of animal, mineral, or vegetable substances. The charcoal is treated to increase the surface area for adsorption of toxic substances; activated charcoal is frequently used for the treatment of ingestions of poisons. We are not seeking a ban for this indication.

Efficacy

Four randomized studies have examined the efficacy of activated charcoal in the treatment of acute diarrhea. In one study, 51 Indian adults with severe cholera and non-cholera diarrhea were rehydrated intravenously for three hours, started on a course of oral tetracycline, and then randomized to continued intravenous fluids, ORS, or ORS with charcoal. For cholera and non-cholera subjects, the duration of diarrhea was unaffected by treatment regimen but charcoal-treated subjects exhibited a tendency toward more vomiting and slower clearance of the pathogenic organisms. Among cholera patients, charcoal-treated subjects had almost twice as much stool output as the other treatment arms groups, a finding attributed by the authors to binding of tetracycline by charcoal.[53] A second study failing to document the efficacy of charcoal has been referred to in the section on kaolin and pectin.[37] In a third study, investigators in Bangladesh randomized 46 adolescent and adult patients with severe cholera to intravenous ganglioside-charcoal, charcoal, or water in addition to ongoing intravenous fluids. There were no differences between the water and charcoal groups with respect to stool output rates, duration of diarrhea, or

clearance rates of the cholera organism.[54] Finally, in a controlled study of pediatric inpatients, 39 subjects aged between 45 days and 10 years were administered oral and intravenous electrolyte solutions; in addition, the treatment group was given activated charcoal. There was no difference between the groups in the duration of diarrhea and consumption of oral or intravenous fluids.[55]

Safety

The WHO report documents that charcoal inactivates aspirin, acetaminophen, penicillin, tetracycline and the sulphonamides, even in the low doses advocated for the treatment of diarrhea.

An FDA Advisory Panel of experts evaluated the safety and effectiveness of over-the-counter products containing activated charcoal for the treatment of diarrhea. **The panel classified activated charcoal, to be in Category III (available data are insufficient to classify as safe and effective, and further testing is required).**[29]

The WHO report concludes:

> **[C]linical studies have failed to demonstrate its efficacy as an antidiarrheal drug .... There is thus no role for activated charcoal in the treatment of acute diarrhea in children, and it should not be used.**[1] [emphasis added]

5. Attapulgite (Kaopectate; Donnagel)

Attapulgite is a mineral clay similar to kaolin, and is advocated as an antidiarrheal drug due to its adsorbent properties. In France, attapulgite and its related clay, smectite, are also advertised as "agents that strengthen and protect the digestive mucosa."[1]

Efficacy

The WHO report lists only a single placebo-controlled trial of the efficacy of smectite in the treatment of acute diarrhea. There is no comparable trial for attapulgite. Ninety hospitalized Egyptian males under the age of three with acute diarrhea were randomized to either smectite or placebo in addition to ORS. Although duration of diarrhea was somewhat decreased, the major relevant outcome variable, weight-adjusted total diarrheal output, was unaffected by the treatment. [Madkour A. Smectite in acute diarrhea of children. Presented at Second National Symposium on Diarrheal Disease and its Management. Alexandria, 27-28 September, 1990 (in preparation). Cited in cite 1] A second study cited by the WHO found similar lack of efficacy in reducing the number of bowel movements and improving stool consistency for loperamide and attapulgite in adult outpatients with nonspecific diarrhea, but had no placebo group.[56]

Due to the ongoing assertions of attapulgite efficacy by its manufacturers and the FDA reclassification mentioned above, we have reviewed the docket at the FDA for additional studies. Two additional studies, both unpublished, were mentioned by the FDA in its letter to Pfizer Pharmaceuticals on October 14, 1982, notifying them of the FDA's intent to reclassify attapulgite from Category III to Category I.

The first, the so-called "1974 study" (Docket No. 78N-036D OTC Volume 090133) compared the efficacy of a combination of attapulgite and pectin to placebo in the treatment of acute adult diarrhea. As the FDA stated in the aforementioned letter, because the study compared only the combination and not the single ingredients to placebo, "the study cannot be used to demonstrate the effectiveness of attapulgite alone."

The second study, the so-called "1980 study" (Docket No. 78N-036D) was a double-blind, placebo-controlled trial of attapulgite versus placebo in 50 patients aged 12 to 75. Although this study claimed effectiveness for attapulgite in such outcomes as physician and patient subjective assessment of efficacy, use of substitute therapy, and total number of bowel movements, fluid and electrolyte loss was not adequately assessed. In particular, the failure to measure stool volume or weight (in addition to number of stools) precludes any assessment of the drug's efficacy in preventing dehydration.

MedLine searches identified two additional recent studies. The first compared loperamide and attapulgite in 194 Mexican patients over the age of 17. Loperamide was judged more efficacious in reducing the number of unformed stools and in reducing the time to the last unformed stool. However, the absence of a placebo group precludes the assessment of efficacy of either drug.[57]

A second study, a placebo-controlled, multicenter study of the efficacy of attapulgite in infants and children (mean age 28 months) with acute diarrhea has been reported in a French publication.[58] Both the time to first formed stool and the time to resumption of normal diet were reduced by approximately one day in the attapulgite group. However, the investigators failed to measure the weight or volume of the stool output and thus the efficacy of these drugs in preventing loss of fluids and salts cannot be assessed.

Safety

Like other adsorbents, attapulgite binds to other drugs; the WHO report states that depending on its affinity for a particular drug, it may inactivate it or delay its onset of action. The WHO report states that cortisone, diazepam, propranolol, tetracycline, and trimethoprim have all been shown to bind to smectite and notes that the French manufacturer of attapulgite and smectite warns not to

administer these compounds with other drugs.[1]

As mentioned above, an FDA Advisory Panel of experts evaluated over-the-counter products containing attapulgite for its safety and effectiveness in the treatment of diarrhea. **The Panel classified attapulgite to be in Category III (available data are insufficient to classify as safe and effective, and further testing is required).[28] The FDA has now reclassified attapulgite to Category I (generally recognized as safe and effective and not misbranded) based on new data. However, we feel that studies on the basis of which FDA made this reclassification has flaws (See the Attapulgite Efficacy section above).[29]**

The WHO report concludes:

> **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 diarrhea .... Smectite and attapulgite have no place in the management of acute diarrhea in children and should not be used.[1]** [emphasis added]

C. ENVIRONMENTAL IMPACT STATEMENT

The requested action will have no significant impact on the environment.

D. ECONOMIC IMPACT STATEMENT

The requested action will reduce or eliminate manufacturers' revenues from the sale of antidiarrheal drugs but will increase the sale of ORS. This will mean a more rational use of drugs in the management of acute diarrhea and thus large potential savings.[59]

E. CERTIFICATION

The undersigned certify that, to our best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

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NEWS RELEASE

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PUBLIC CITIZEN URGES BAN, RELABELING ON ANTI-DIARRHEA DRUGS FOR CHILDREN

Prescription and over-the-counter medications seen as ineffective, potentially dangerous

WASHINGTON, D.C. -- Public Citizen has asked the Food and Drug Administration to ban or relabel five of the most common prescription and over-the-counter drugs used in the treatment of pediatric diarrhea, basing its request on findings by the World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC) that the drugs are ineffective and may be dangerous and even fatal to children.

Included in the petition is a request for a ban on pediatric dosage forms both of Imodium A-D (loperamide hydrochloride) -- the number one over-the-counter antidiarrheal drug sold in the U.S. -- and the popular antidiarrheal prescription drug, Lomotil (diphenoxylate hydrochloride with atropine sulfate).

The petition also calls for a ban on adult and pediatric formulations of drugs containing kaolin and pectin (Donnagel-PG and others), activated charcoal (Charcoal Plus, Charcocaps and others) and attapulgite (Diasorb, Donnagel, Kaopectate, Rheaban and others).

Their recommendations are based on a WHO review undertaken by a worldwide panel of experts that concluded that "[a]ntidiarrheal drugs should never be used. None has any proven value and some are dangerous." A recent CDC report reached a similar conclusion.

All five drugs included in the petition are largely ineffective, and, varying from drug to drug, cause any of a number of adverse side effects in young patients, Public Citizen

MORE

reports. These include drowsiness and nausea, harmful binding of nutrients and other drugs, respiratory and nervous system depression and even death.

The use of these drugs also shifts focus away from the use of Oral Hydration Solution (ORS), a simple, low-cost therapy to reduce the fluid and electrolyte losses that frequently accompany acute diarrhea. In combination with appropriate nutrition and the judicious use of antibiotics and antiparasitic drugs, ORS has been found to be effective in 90-95 percent of cases of acute watery diarrhea, Public Citizen reports.

Public Citizen's petition that antidiarrheal drugs be banned or relabeled contraindicating their use for children was sent to FDA Commissioner Dr. David Kessler on Jan. 7, 1993. The petition was signed by Dr. Sidney M. Wolfe, Director of the Public Citizen Health Research Group; Dr. Syed Rizwanuddin Ahmad of the Clinical Pharmacology Division of the Georgetown University Medical Center, and Dr. Peter Lurie of the Institute for Health Policy Studies at the University of California, San Francisco.

Diarrheal diseases are a leading cause of childhood mortality in developing countries, where an estimated 4 million children under five years of age die each year from diarrhea. In the U.S., diarrheal illnesses remain among the most common problems seen by pediatricians and are listed as a principal cause of death for 500 children annually.

"The tragic toll of acute diarrhea could be avoided with proper treatment, built around the use of Oral Rehydration Solution, rather than the largely useless and often dangerous drugs described in the petition," said Dr. Wolfe.

The Public Citizen petition also noted that at least ten developing countries -- including Korea, Mexico, Pakistan and Turkey -- have acted more expeditiously than the U.S. in banning or relabeling antidiarrheal medications.

"Drug regulatory authorities in developing countries like Pakistan frequently look to the U.S. FDA when reaching a decision whether to approve or reject a drug," said Dr. Ahmad. "In the case of antidiarrheal drugs, the FDA can learn from the Third World experience.

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Public Citizen, founded in 1971, is a nationwide consumer advocacy organization with over 140,00 members.