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Mini Review

Oral Intestinal Adsorbents - are they the Next Therapy for Acute Diarrhea in Children: A Mini-Review

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Abstract

Current guidelines for the treatment of acute intestinal infection in children recommend oral rehydration therapy and use of anti-diarrheals is not widely endorsed, as there are reported safety concerns with some and they do not treat the underlying cause of the diarrhea. This article reviews the potential of oral intestinal adsorbents as an adjunct therapy to oral rehydration solution in the treatment of diarrhea in children with acute diarrhea. Oral intestinal adsorbents range from activate charcoal, clays and silicon-based materials, but they all have a common mode of action which is adsorption of the causal agent of diarrhea from the gastrointestinal tract and removal from the body in the stools. Clinical studies have shown the safety and efficacy of several intestinal adsorbents and their benefits over anti-diarrheals in the treatment of acute diarrhea in children. However, more robust studies and education of both health professionals and the general public is required, before inclusion of oral intestinal adsorbent into the guidelines and potential widespread uptake.

ABBREVIATIONS

AC: Activated Charcoal; CIS: Commonwealth Of Independent States; ESPGHAN: European Society For Pediatric Gastroenterology, Hepatology And Nutrition; GIT: Gastrointestinal Tract; MDD: Medical Device Directives; MDR: Medical Device Regulations; ORS: Oral Rehydration Salts; RCT: Randomized Clinical Trial; PMSPH: Polymethylsiloxane Polyhydrate; WHO: World Health Organization

INTRODUCTION

According to the World Health Organization diarrheal disease is the second leading cause of death in children under five years old. Globally there are approximately 1.7 million cases every year of childhood diarrheal disease which kills around 525 000 children under five, most often in developing countries [1]. Diarrhea most often is a result an infection in the gastrointestinal tract (GIT), which can be caused by a range of pathogens such as; bacteria, viruses and parasitic organisms [2]. The infection can be spread via contaminated drinking-water and food, or from direct contact with an infected person through poor hygiene.

Diarrheal disease is classified into acute or chronic based on symptom duration. Acute diarrhea has an acute onset and lasts up to 2 weeks, whereas chronic diarrhea lasts longer than 2 weeks. Childhood acute diarrhea is typically triggered by infection in the small or large intestine, although other conditions such as malabsorption syndrome and various enteropathies can cause diarrhea. Acute diarrhea is defined as the abrupt onset of 3 or more loose stools per day and may be considered mild to severe. The stools contain an increased water content due to disruption in the normal physiology of the small and large intestine which are responsible for absorption of ions, organic substrates, and water from the lumen.

Most cases of acute diarrhea are caused by enteric virus, the most common ones in children are rotavirus, whereas bacteria are a common cause of traveler's diarrhea. In low-income countries E. coli and rotavirus are the most common causes of moderate-to-severe diarrhea, although cryptosporidium and shigella species are also significant [1].

Dehydration is the most significant risk posed by diarrhea. Water and electrolytes such as; sodium, chloride, potassium and bicarbonate are lost through liquid stools and when these are not replaced, dehydration occurs. Rehydration with a glucose-based oral rehydration salts (ORS), solution is the most effective way to maintain hydration, as recommended by the WHO, by the ad hoc committee of European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and by the American Academy of Pediatrics [3]. The use of zinc supplements has proven effective in children in developing countries and is also recommended by the WHO [4].

In children the recommended use of other therapies such as drugs, medical devices, supplements and probiotics varies widely between countries. In the UK, the National Institute for Health and Care Excellence (NICE) guidance for children under 5 years is fluid and nutritional management, with antibiotics given in specific cases and no recommendations for use of anti-diarrheals for children under 12 years [5]. Likewise, in the US, antimotility

agents are not indicated for infectious diarrhea and antimicrobial therapy is only indicated for some non-viral diarrhea [6].

The duration of diarrhea symptoms is not reduced by standard rehydration management [7], and the challenge of treating either the underlying cause or the actual symptoms of childhood diarrhea in a safe and efficient manner remains. There is a real need for therapies that can decrease the duration of illness and reduce mortality, morbidity and attendances to primary care or emergency departments.

One such therapy is oral intestinal adsorbents, also called enterosorbents, which are not commonly known in western countries but are currently used worldwide for treatment of diarrhea [8].

MATERIALS AND METHODS

Oral intestinal adsorbents are a group of substances which include activated carbons (charcoals), polymeric and silicon-containing resins, inorganic minerals and natural materials of organic origin. The main mechanism of therapeutic action of any oral intestinal adsorbent is through the process of adsorption. Adsorption is the ability of materials to physically retain (adsorb), molecules of different size, shape and molecular mass on their surface, owing to their large surface area and well-developed porous structure. Enterosorption is defined as the process in which an adsorbent moves along the GIT where it can adsorb molecules, but itself is neither absorbed into the systemic circulation, nor metabolized and is thereby excreted in the stools unchanged [9].

Nikolaev et al., 2005, identified several mechanisms that may contribute to the therapeutic action of oral intestinal adsorbents [10]. These include; sorption of exogenous and endogenous toxic substances and metabolites in the GIT; sorptive modification of the diet; fixation of physiologically active substances on their surface; increase of the volume of the lumen; and catalytic decomposition of toxic substances on the surface. Other mechanisms suggested include indirect effects such as improving intestinal motility, humoral environment and immune status [11]. Generic key criteria that adsorbents should satisfy include: non-toxic; easy evacuation from stomach; no damaging effect on GIT; high sorption capacity; easy consumption and good organoleptic properties [12]. Unlike other pharmaceutical drugs, an intestinal adsorbent should not demonstrate pharmacokinetics, i.e., it should not dissolve or be adsorbed by the body but rather bind the target substances and be evacuated from the organism naturally. This is the reason why many intestinal adsorbents are classified as medical devices in Europe, where they are listed in the category of gastrointestinal detoxifier.

RESULTS AND DISCUSSION

Types of oral intestinal adsorbents

Activated charcoals: Charcoal has been used for hundreds of years for medical purposes, but its gastrointestinal adsorbent capacity was only established in the 1940s [13]. In the emergency setting activated charcoal (AC), can be used to prevent acute poisoning by adsorbing the poison from the GIT and preventing uptake by the body [14]. AC has been used as a remedy to treat traveler's diarrhea. Although a review of recent studies of AC concluded that it might be able to adsorb the precursors of diarrhea; bacterial infection, and unlike many anti-diarrheal treatments it has relatively few side-effects, but further research is needed to determine effectiveness in diarrhea management [15]. AST-120 has been shown to eliminate neuroactive agents, bile acids, bacterial toxins, Toll-like receptor ligands and uremic toxins from the body. Much of the clinical studies surrounding AST-120 have been in chronic kidney disease where it has been suggested to slow disease progression in these patients [16]. AST-120 has also been shown to be useful in the short-term management of abdominal pain, stool consistency and bloating in patients with non-constipating irritable bowel syndrome [17].

Mineral clay adsorbents: Throughout history various types of clay have been used for medicinal purposes including as a remedy for diarrhea. Kaolin has been used as a traditional medicine in China, Africa and South America to treat stomach disorders and diarrhea. It is proposed that Kaolin acts by adsorbing water from the lumen, toxins and bacteria, which helps promote firmer stools. The most common clay mineral in use is diosmectite, a natural multilamellar clay composed of layers of aluminomagnesium silicate, which belongs to the dioctahedral smectite class. Diosmectite is classified both as a pharmaceutical drug and a medical device in Europe and is indicated for the treatment of acute diarrhea in children and infants. The literature has established that diosmectite has several pharmacological properties beneficial for diarrhea treatment [18]. Diosmectite has been shown to adsorb bacterial toxins [19], reduce production of hydrogen gas in the GIT20, and preserve the mucus layer which protects the underlying epithelium from attack [21]. In addition, it has been suggested that it may have a protective effect against inflammation in the GIT [22], and affect intestinal permeability and electrolyte balance [18,23].

Although diosmectite is not currently recommended for management of acute gastroenteritis in children in the updated ESPGHAN guidelines [24], American Centers for Disease Control and Prevention (CDC) [25], or the WHO, in many countries in central and eastern Europe, diosmectite (Smecta®) is frequently used for the treatment of acute infectious diarrhea. There have been several RCT studies published to support its use. The largest study by Dupont et al., investigated diosmectite's efficacy on stool reduction in 602 children with acute watery diarrhea in Peru (n=300), and Malaysia (n=302) [18]. Stool output decreased significantly with diosmectite use compared to placebo, in both countries, especially in rotavirus-positive children. Children had a mean stool output of 94.5 +/- 74.4 g/kg of body weight in the diosmectite group versus 104.1 +/- 94.2 g/kg in the placebo group (p= 0,002). The median duration of diarrhea was also reduced in the diosmectite group (p=0.001) and the treatment was well tolerated.

A recent 2015 Cochrane systemic review compared diosmectite to a control group in children (one month – 18 years) with acute infectious diarrhea [26]. They evaluated 18 trials with 2616 children, in hospital and community settings with the most studies including rotavirus infections. Results showed that diosmectite may reduce the duration of diarrhea by one day (14 studies; 2209 children, low-certainty evidence); may increase clinical resolution at day 3 (5 trials; 312 children, low-certainty

evidence); and may reduce stool output (3 studies; 634 children, low-certainty evidence). The authors concluded that based on low certainty evidence, the use of diosmectite as an adjuvant to ORS may reduce the duration of diarrhea in children with acute infectious diarrhea by a day and may reduce stool output, but has no effect on hospitalization rates or need for intravenous therapy. In a 2018 review and meta-analysis comparing interventions for acute diarrhea and gastroenteritis in children, with a moderate-to high-quality of evidence; diosmectite in combination with zinc demonstrated the best combination of evidence quality and magnitude of effect [27].

Silicon based adsorbents: Several oral intestinal adsorbents are based on silicon, such as; methylsilicic acid hydrogel (Enterosgel®), highly dispersed silicon dioxide or silica (Atoxil®, Polisorb®) and silicic acid gel (Silicolgel®, Silicea®). All are classified as medical devices recommended for use in the treatment of diarrhea. Silicon dioxide is recommended for children 1 year upwards, whereas, silicic acid is for children above 12 years of age. However, only Enterosgel® composed of methylsilicic acid or polymethylsiloxane polyhdrate (PMSPH), has undergone several RCTs in children with acute gastroenteritis.

PMSPH (Enterosgel®) is a hydrophilic/hydrophobic hydrogel, which is unique compared with activated charcoal (mostly hydrophobic) and mineral adsorbents such as silica and diosmectite (mostly hydrophilic). It has a porous structure composed of fused polymer nanoglobules and voids between filled with water [28]. Intestinal adsorbents are generally non-selective adsorbents, however, PMSPH has a unique adsorption profile, showing an increasing sorption capacity with the increase in the solute molecular weight, thus limiting unwanted adsorption of small molecules such as drugs and nutrients [29]. PMSPH is used worldwide and is listed in the governmental guidelines in CIS countries to treat wide range of pathologies from acute intestinal infections to side effects of chemo- and radiotherapy. In Europe it is recommended as an ancillary treatment for acute diarrhea in children from 1 year and for diarrhea predominant irritable bowel syndrome. The main mechanism of its therapeutic action is thought to be the removal of molecules such as; bacterial toxins (C. difficile, E coli, Shigella and Staphylococcus); inflammatory mediators and bile acids from the gastrointestinal tract [29-31].

Several clinical studies have confirmed that PMSPH improves outcome in children with acute diarrhea. In a randomized prospective open study, 148 children with acute intestinal infections received PMSPH, diosmectite or Kaolin [32]. There were no statistically significant differences between the treatment groups in the duration of diarrhea or other symptoms such as fever and nausea. A similar RCT comparing PMSPH with diosmectite and a control group, in 99 children with acute gastroenteritis, found that the treatment groups both significantly reduced the duration of diarrhea by more than one day (3.4 ± 0.4; 3.2 ± 0.5 vs 4.8 ± 0.3 respectively) and fever compared to the control (2.9 ± 0.4; 2.8 ± 0.4 vs 3.7 ± 0.2 days) [33]. A small open RCT of 50 children with acute intestinal infection that received PMSPH and standard care or antibiotic and standard care, showed by day 3 and 5 in the PMSPH group the frequency and stool consistency normalized faster [34]. A retrospective analysis of 95 children with non-infectious diarrhea syndrome compared treatment with PMSPH with standard care [35]. Normalization of stool consistency was significantly faster in the PMSPH group and hospital stay significantly reduced. These findings in children are supported by a recent randomized controlled UK study which demonstrated that PMSPH significantly reduced the duration of diarrhea in adults with acute diarrhea [36].

Natural adsorbents of organic origin: Natural based intestinal adsorbents include a wide range of material such as; alginates, lignin, pectins, chitin based and food or dietary fibers. Pectins are available from a variety of sources, and their adsorbent and bulk-forming properties suggest they could be helpful in treating constipation and diarrhea [37]. Pectin is an adsorbent that can bind to bacteria and other toxins and is also able to decrease the pH in the intestinal lumen which benefits irritated mucosa. Pectins can retain metal cations due to their high content of negatively charged groups and can be used as versatile adsorbents for heavy metals [38]. There also show potential as a prebiotic and for their cholesterol, serum glucose and insulin level lowering effect, and delay in gastric emptying [39].

Traditionally, AC and clays have been used to treat many conditions related to the GIT including diarrhea. However, in the West these adsorbents are less well recognized than anti-diarrheal drugs even though anti-diarrheals are not recommended for use in children with acute diarrhea and do not treat the underlying cause, unlike intestinal adsorbents which can remove the causal agents. In addition, certain anti-diarrheals such as loperamide have serious reported safety issues, unlike intestinal adsorbents which are not adsorbed by the body and have few side effects.

In future, to increase the acceptance of oral intestinal adsorbents, several factors need to be addressed. Health professionals and the general public will need to be educated on their availability, indications, safety and mode of action so that they can understand their potential and stop relying only on anti-diarrheal drugs. In practice, oral intestinal adsorbents will need to be recognized and included in the WHO and Western guidelines for child acute gastroenteritis, before their uptake improves dramatically. It is probable that this will not occur until more robust RCTs are conducted comparing different intestinal adsorbents against standard care, in different patient populations. At present, as many intestinal adsorbents are regulated under the current European Medical Device Directives (MDD), the level of clinical evidence scrutiny is not as stringent as for pharmaceutical drugs. This will change with the new Medical Device Regulations (MDR) which come into force in 2021 and place more emphasis on good quality clinical evidence on safety and efficacy and continued post-market clinical follow-up.

CONCLUSION

Oral intestinal adsorbents offer an alternative to anti-diarrheal drugs for the safe effective treatment of acute diarrhea caused by infectious or non-infectious etiology, in children from 1year.

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