PERSPECTIVE

Loperamide Therapy for Voluminous Diarrhea in Ebola Virus Disease

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The number of cases of Ebola virus disease (EVD) in West Africa has surpassed 19 000 [1]. Efforts to identify, isolate, and provide medical care to patients with EVD are ongoing, and efforts to improve clinical care must focus on improved management of massive gastrointestinal fluid loss. Gastrointestinal fluid losses, largely through diarrhea, are a hallmark manifestation of EVD that contribute to hypovolemic shock, severe electrolyte abnormalities, and high mortality [2, 3]. In contrast to cholera toxin–mediated diarrheal losses, in which oral rehydration solution alone dramatically reduces mortality [4], oral rehydration for patients with EVD is often insufficient to accomplish resuscitation or repletion of ongoing fluid losses. However, EVD is a systemic viral illness with profound and debilitating manifestations, including high fever, asthenia, myalgia, and delirium, that limit self-directed oral rehydration. New strategies are needed to limit mortality related to cholera-like gastrointestinal fluid losses in EVD.

Massive gastrointestinal fluid and electrolyte losses may be successfully man- aged in resource-rich settings through careful estimation of volume losses, close laboratory monitoring of electrolytes and organ function, and replacement of fluid losses through balanced intravenous infusions over the course of illness [3]. This same level of intensive monitoring and care cannot be achieved in most EVD treatment units in West Africa, where high case loads, staffing shortages, and limited time in personal protective equipment because of the risk of heat exposure prohibit extended patient care interactions. In this setting, administration of antidiarrheal agents to limit gastrointestinal fluid and electrolyte losses may provide "a solution that prevents the problem at its source". However, use of antidiarrheal agents for the management of EVD-mediated diarrhea is infrequently reported, and no safety and efficacy data to guide use in EVD exist.

Although the mechanism of EVD-mediated diarrhea has not yet been characterized, the large volume of watery stool suggests a secretory process. Tolerance of enteral feeding when gastrointestinal symptoms are adequately controlled suggests that the small intestine structure and function remain intact. Autopsy studies of patients with EVD who died show mild inflammation of small intestinal lamina propria, suggesting the possibility of an inflammatory component to a secretory form of diarrhea, as well [5]. Clinically significant gastrointestinal bleeding observed in a small subset of patients with EVD, estimated to be <5% [2], raises the possibility that gastrointestinal inflammation may contribute to disease pathogenesis.

Loperamide is a potent antidiarrheal agent with antiperistaltic and antisecretory effects [6]. Reducing EVD diarrheal losses with loperamide might allow for correction of negative fluid balance, reduce hypovolemic shock, limit electrolyte losses, and consequently improve survival. Recently, one author (D. S. C.) and colleagues reported that oral antiemetics and antidiarrheal therapy improved symptoms and reduced gastrointestinal fluid loss and environmental contamination in patients with EVD [2]. The reduction in environmental contamination may also lower the risk of nosocomial transmission to healthcare personnel and other patients under evaluation.

There are limited data on the use of loperamide for EVD-mediated diarrhea [2]. Reluctance to use loperamide for EVD-mediated diarrhea may be based on the perception that it is of no benefit for the secretory diarrhea observed in cholera or concern about the risk of toxic megacolon when used to treat some bacterial inflammatory causes of diarrhea, such as *Clostridium difficile* infection [7]. Animal and human studies of shigellosis in the 1960s and subsequent case reports

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of adverse events raised concern that antimotility drug use in patients with infectious diarrhea might contribute to a worse outcome [8]. However, multiple randomized, placebo-controlled, double-blinded trials of loperamide in combination with antibiotic therapy for management of infectious diarrhea in adults have demonstrated its safety and efficacy [9]. A meta-analysis of 13 clinical trials of loperamide use in children aged ≤12 years with infectious diarrhea and predominantly mild dehydration demonstrated a decrease in the duration and frequency of diarrhea [10]. Serious adverse events associated with loperamide use, including death, ileus, or lethargy, were reported only in children <3 years of age.

The Food and Drug Administration does not recommend loperamide use in children <24 months of age, and use is contraindicated in patients with dysentery (ie, stool with mucus or blood), but it may be used in combination with antibiotic treatment [11]. Loperamide should not be given to patients with suspected or documented ileus or intestinal paresis. Use of loperamide in patients with EVD to control gastrointestinal fluid losses and reduce environmental contamination appears rational, based on existing clinical observations and the available published data. However, controlled clinical trials of loperamide treatment of diarrhea in patients with EVD, in combination with oral rehydration solution, to assess safety and efficacy in adults and children, including its possible impact upon improving survival, are urgently needed. Until strategies to improve management of gastrointestinal fluid and electrolyte losses are refined and widely implemented in the management of EVD in West Africa, the presently observed high case-fatality will persist.

Notes

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