

Management of Acute Gastroenteritis: A Comprehensive Approach



Reviewed by:

Dr Neeraj Tulara

MBBS, MD-General Medicine,
Post Graduate Diploma in Infectious Disease
Consultant Physicians and Infectious Disease specialist,
Internal Medicine Dr L.H Hiranandani Hospital,
Powai, Mumbai

Acute Gastroenteritis: A Common Cause of Morbidity and Mortality

Acute gastroenteritis, characterized by diarrhea or vomiting (or both) which does not last more than 14 days duration, remains one of the most common infectious diseases seen around the world, and its associated morbidity and mortality are greatest among those at the extremes of age, children and the elderly.¹⁻⁴ According to the World Health Organization (WHO), it is a leading cause of mortality worldwide, accounting for millions of deaths each year in young children, mostly in developing countries.^{5,6} In the developed countries, gastroenteritis is a major cause for morbidity across all age groups, and is a common reason for presentation to general practice or emergency departments and for hospitalization.^{1,3,6}

Prevalence Estimates

Acute gastroenteritis is widely prevalent and is a major killer of the very young worldwide; current estimates suggest that acute gastroenteritis affects 3 to 5 billion children below 5 years of age each year, and accounts for 1.5 to 2.5 million deaths per year. In developed countries, acute gastroenteritis accounts for around 300 deaths per year.^{1,7,8} Of note, developing countries have a higher rate of hospital admissions as compared to developed countries. In particular, it is estimated that every child encounters at least one episode of rotavirus gastroenteritis by the age of 5 years. Alarming, these infections cause more than 500,000 deaths annually among children up to 5 years of age worldwide and most of these deaths occur

in the developing countries.^{7,9} Particularly in India, acute gastroenteritis remains a leading cause of post-neonatal mortality among under-five year children, accounting for about 13% of mortality in this age group, equivalent to almost 300,000 deaths each year.^{10,11}

Etiological Basis of Acute Gastroenteritis

Although the underlying pathology may be multifactorial, different classes of microorganisms and parasites, which include viruses, bacteria, protozoa, and helminths, constitute the most common cause for acute gastroenteritis. Viruses are the most important etiology and are accountable for approximately 70% of the cases of acute gastroenteritis in children (Table 1). Worldwide, rotavirus is the most common intestinal virus causing acute gastroenteritis and accounts for almost 30% to 72% of all the hospitalizations and 4% to 24% of acute gastroenteritis at the community level. Moreover, rotaviruses are the most common cause of severe watery diarrhea in young children, and are accountable for 40% of cases of dehydrating diarrhea. Other viruses, such as calicivirus, adenovirus and astrovirus also play a role in the etiology of gastroenteritis. Rates of virus infection are comparable in both developed and developing countries.^{1,3,7,12-14}

Bacterial pathogens account for 10% to 20% of all the acute gastroenteritis cases. In developing countries, as a group, bacterial enteropathogens are responsible for the majority of diarrheal diseases. Among them, diarrheogenic *Escherichia coli* is the most important group, followed by *Campylobacter*, *Aeromonas*, *Shigella*, and *Salmonella* spp. *Vibrio cholerae* remains a major cause of diarrhea, particularly in endemic areas and conditions. Improvement in sanitation, although may not decrease the disease prevalence of viral infection, but can be effective in prevention of parasites and bacterial infections.^{7,14-16}

Table 1: Microbial etiology of acute gastroenteritis

Viruses (~ 70% cases)	Bacteria (10-20% cases)	Protozoa (<10% cases)	Helminths
• Rotaviruses • Noroviruses (Norwalk-like viruses) • Enteric adenoviruses • Caliciviruses • Astroviruses • Enteroviruses	• Campylobacter jejuni • Non-typhoid Salmonella spp • Enteropathogenic Escherichia coli • Shigella spp • Yersinia enterocolitica • Shiga toxin producing <i>E. coli</i> • Salmonella typhi and <i>S. paratyphi</i> • Vibrio cholerae	• Cryptosporidium • Giardia lamblia • Entamoeba histolytica	• Strongyloides stercoralis

Clinical Presentation of Acute Gastroenteritis

As previously stated, acute gastroenteritis, which is also known as acute diarrhea, is consistently characterized by diarrhea that is often accompanied by abdominal pain, nausea, vomiting, and fever. The WHO defines acute diarrhea as the passage of three or more loose or liquid stools per day, for three or more days and for less than 14 days.^{1,9,17}

Onset is usually sudden, and is accompanied with anorexia, nausea, vomiting, abdominal cramps, and diarrhea (with or without blood and mucus). Malaise, myalgias, and prostration may also occur. An important feature of acute gastroenteritis is the presence of hyperactive bowel sounds (borborygmi) on auscultation even without diarrhea. The most common symptoms associated with rotavirus infection include watery diarrhea and vomiting, which sometimes aggravate resulting in severe dehydration requiring hospitalization. In children, vomiting is more prominent than diarrhea, while in adults, diarrhea usually predominates. Further, patients may also experience fever, headache, and myalgias.^{9,18}

Bacterial gastroenteritis (shigella, salmonella) is more likely to result in high fever and may be associated with blood and white blood cells in the stool. *E. coli* infection may cause hemorrhagic colitis (with severe bloody diarrhea), which may be complicated by hemolytic uremic syndrome.¹

Abdominal Spasm and Pain: An Important Manifestation in Gastroenteritis

Abdominal spasms, also referred as colic, are involuntary contractions of the muscles of the abdomen characterized

by pain that increases and decreases abruptly in its intensity with varying period of absence intermittently. The spasm usually occurs due to an obstruction in any hollow viscus, and is the result of attempt to relieve it by smooth muscle contractions. Most abdominal spasm/pain arise from an abdominal pathology; while a few causes may be of extra-abdominal origin.¹⁹⁻²¹

Gastroenteritis represents the most common non-surgical condition implicated in acute abdominal pain. Its pathophysiologic mechanism can be directly related to visceral pain receptors, which are located on the serosal surface, in the mesentery, within the intestinal muscle, and the mucosa of hollow organs. These pain receptors are triggered in the presence of mechanical and chemical stimuli, such as stretching, tension, and ischemia. As a result, diffuse abdominal tenderness before diarrhea and severe cramping abdominal pain develops. Besides, the intensity of accompanying dehydration indicated by certain clinical signs, such as weight loss, prolonged capillary refill, poor turgor, reduced urinary output and abnormal respiration warrant immediate medical care in order to avoid any untoward complications.^{22,23}

Management of Gastroenteritis

Gastroenteritis is managed by combining various therapeutic agents, targeting either the etiology or the pathophysiologic mechanism.²³ Prevention of dehydration is the hallmark of gastroenteritis treatment. Most patients with gastroenteritis with minimal or no dehydration can be managed at home, and should be encouraged to continue usual diet and drink adequate fluids.²⁴ The American Academy of Pediatrics (AAP), Centers for Disease Control and Prevention (CDC), European Society for Pediatric Gastroenterology and Nutrition, and the WHO all strongly encourage the use of oral rehydration

Table 2: Management approaches for acute gastroenteritis

Therapeutic approaches	Comments
Rehydration therapy	- Oral rehydration: Administered in the form of oral liquids in small frequent increments (each 15-30 minutes) - Intravenous rehydration: Preferred for severe cases of dehydration. Intravenous solutions used for rehydration include Ringer's lactate and isotonic saline solution (0.9%). Glucose solutions are not preferred
Antiemetics	Vomiting is a common presentation of acute gastroenteritis. Severe vomiting can interfere with the oral rehydration process, which can negatively affect the success of the oral therapy. Ondansetron is one such agent, widely used in the pediatric emergency department for vomiting
Zinc supplementation	Zinc is an antioxidant and anti-inflammatory agent, which is significantly lost in diarrhea. Its use can alleviate the duration and severity of diarrhea in children. Zinc is considered crucial for epithelial barrier integrity, tissue repair, cell-mediated immunity, and immune function
Probiotics	Probiotics are known to ameliorate the intestinal microbial balance of the host, avoid outbreaks of community-acquired diarrhea, reduce colonization of pathogenic microorganisms in infants, reduce the duration and severity of diarrhea, and exert overall beneficial effects on health
Antimicrobial therapy	Includes antibiotics such as penicillins, cephalosporins, metronidazole and others
Symptomatic therapy	Abdominal pain is one of the most burdensome symptoms of gastroenteritis. In cases with recurrent abdominal pain, drotaverine hydrochloride can be administered, which is an effective and tolerable pharmaceutical agent. Along with antispasmodic drugs, mild antiinflammatory analgesic, such as paracetamol (acetaminophen) should also be included in the treatment regimen. Combination of antiinflammatory analgesics and antispasmodics helps in better relief of spasmodic pain experienced during acute gastroenteritis. Addition of paracetamol also controls the fever in patients with gastroenteritis.

therapy as the first-line therapy for the treatment of acute gastroenteritis, except in cases of severe dehydration. A large slew of studies have substantiated the effectiveness of oral rehydration therapy in treating acute gastroenteritis, with mild to moderated dehydration.⁷ The self-limited nature of vomiting and its tendency to ameliorate with the correction of dehydration precludes the use of pharmacotherapy; however, pharmacotherapy may be needed for symptomatic treatment. Indeed, the complaint of abdominal pain and spasm may warrant treatment even before rehydration therapy is considered (Table 2).^{1,23-25}

Management of Spasmodic Pain in Acute Gastroenteritis

Abdominal pain and spasms are frequently encountered in gastrointestinal disorders; however, there is unmet need with respect to recognition and treatment. Pain management merits multifaceted consideration with well-defined role of pharmacologic therapy including antispasmodic agents after accounting for risk-benefit ratio. Antispasmodics are considered important for treatment of mild-to moderate pain.²⁶ Antispasmodic agent, such as drotaverine has suitable relaxing effect on

intestinal smooth muscle that aids in relieving pain and is devoid of anticholinergic side-effects. Drotaverine thus renders effective analgesia in colicky pain.^{27,28}

Conversely, anticholinergics used in pain management have several limitations. They are required to be administered 30-45 minutes before meal in order to alleviate pain. In clinical experience, the individual response to this therapy is variable and unimpressive. In addition, side-effects like dry mouth, urinary retention, blurred vision, insomnia, restlessness and constipation further support its limited prescription for management of gastrointestinal symptoms.²⁹

Drotaverine: A Drug of Choice for Spasm in Acute Gastroenteritis

Drotaverine, a benzyloquinoline derivative, is an effective spasmolytic agent. It is a more potent spasmolytic agent than papaverine and it is used in the symptomatic treatment of various conditions, such as gastrointestinal diseases, biliary dyskinesia and vasomotor diseases associated with smooth muscle spasm.³⁰

Drotaverine is a preferred drug in treatment of abdominal spasms owing to its characteristic

properties. Drotaverine has significant inhibitory effect on phosphodiesterase (PDE) enzyme. Drotaverine is a selective inhibitor for phosphodiesterase IV (PDE IV), an enzyme responsible for breakdown and inactivation of cAMP and cGMP, which regulates the contractile activity of smooth muscles; thereby drotaverine controls the contractile activity of abdominal muscles to provide relief in abdominal spasms.^{31,32}

Additionally, few studies have also delineated that PDE IV inhibitors may also exert an anti-inflammatory activity that can be utilized in cases of spastic and inflammatory conditions. Good tolerability of drotaverine have been established in various toxicological studies due to its wide therapeutic index and LD50 values > 1000 mg/kg on oral administration, unlike other anticholinergic antispasmodics, which are associated with a range of adverse effects. It does not have morphine-like effect and therefore does not induce addictive potential (Box 1). The drug also demonstrates its suitability for both oral and parenteral administration with excellent absorption from the small intestine (90%).^{31,32}

The anti-spasmodic and pain-relieving effect of drotaverine does not mask the symptoms of acute abdomen, and it does not interfere with diagnostic precision while providing optimum pain control; this may have relevant application in practice. Due to its strong antispasmodic effect, drotaverine is extensively employed in biliary, intestinal and renal colic, dysmenorrheal and prior to various instrumental investigative procedures. Drotaverine has also found an important place in emergency medicine. Its versatile pharmacokinetic properties such as rapid absorption, early onset of action, rapid response to IV dosing and wide therapeutic window favorably contribute to its utility in emergency conditions.^{27,31,32}

Various studies have been conducted highlighting the role of drotaverine in management of different types of spasmodic pain. One such study was performed by Rai and colleagues³² on 180 patients with irritable bowel syndrome (IBS), randomized to drotaverine and placebo treatment groups. It was observed that abdominal pain frequency decreased considerably in 22 (25.9%), 51 (60%), and 66 (77.7%) patients in the drotaverine group, at the end of 2nd, 3rd, and 4th week, respectively, as compared with 8 (9.4%), 18 (21.2%), and 26 (30.6%) in the placebo group (Figure 1). Moreover, compared to placebo, drotaverine HCl was shown to provide considerable amelioration in

Box 1: Advantages of drotaverine

- Site specific - PDE IV inhibitor; acts directly on abdominal smooth muscles
- Wide therapeutic index (well-tolerated in frequent & repetitive dosing)
- Does not induce anticholinergic side effects (constipation, urinary retention, dry mouth and visual disturbances) as seen with other anticholinergic antispasmodics such as dicyclomine or hyoscyamine
- No addictive potential unlike opioids
- Synergistic combination with NSAIDs such as aceclofenac, mefenamic acid and paracetamol
- Limited drug-drug interactions
- Neither masks the symptoms of acute abdomen nor interferes with diagnosis
- Well tolerated by all age groups
- Effectively maintains a state of spasmolysis

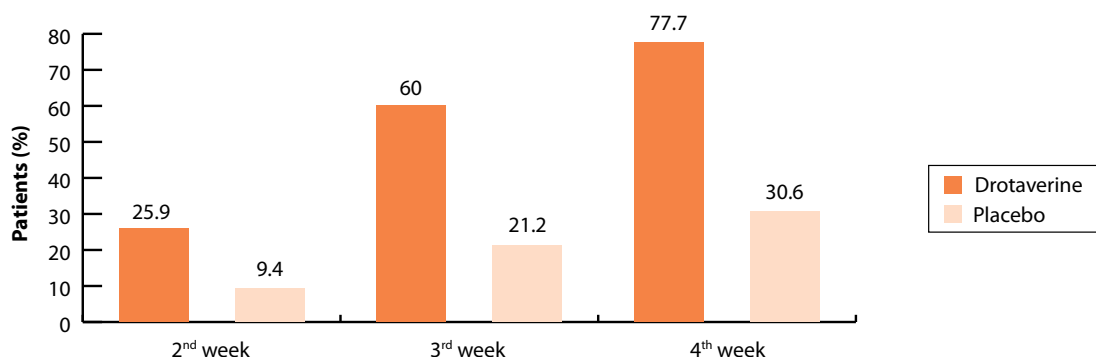
Abbreviations: PDE IV - Phosphodiesterase IV, NSAIDs - Non-steroidal anti-inflammatory drugs

global relief in abdominal pain as perceived by the patient (85.9% versus 39.5%) and the clinician (82.4% versus 36.5%).

In another study, Narang and colleagues³³ tried to evaluate efficacy of drotaverine in cases of recurrent abdominal pain. The participants were 132 children (age 4-12 years) with recurrent abdominal pain. They were randomized to receive drotaverine (n=66) or placebo (n=66) orally. The primary outcome measures were number of episodes of pain during 4 weeks of use of drug/placebo and number of pain-free days. The results revealed a considerable reduction in mean number of episodes of abdominal pain (10.3 versus 21.6) and lesser school absence (mean, 0.25 versus 0.71) in children receiving drotaverine in comparison to those who received placebo (Figure 2).

In yet another study, Xue and colleagues³⁴ aimed to assess the efficacy and safety of drotaverine hydrochloride in alleviating abdominal pain in patients with IBS. A total of 144 patients with IBS were included and randomly categorized into treatment group and placebo group in a 1:1 ratio. Patients received drotaverine or placebo 80-mg tablet, 3 times daily for a total of 4 weeks. The primary outcome included abdominal pain, measured by the visual analog scale (VAS), and weekly stool frequency. It was observed that the total and different types of IBS in VAS, stool frequency, and Bristol score were significantly

Figure 1: Proportion of patients with decrease in pain frequency after treatment with drotaverine or placebo



better in the treatment group than those in the placebo group at the end of 4-week treatment (Table 3). There were no serious and significant differences in adverse events in and between both groups. The findings were suggestive of the promising efficacy of drotaverine in ameliorating symptoms of IBS including abdominal pain.

Based on the aforementioned clinical evidences, drotaverine may be regarded as a potent anti-spasmodic agent, in treatment of spastic and motility disorders of the smooth muscle, and different pathological conditions accompanied by spastic pain; it may be effective either alone or in combination with other analgesics such as aceclofenac, in managing spasmodic pain originating from various organs. Importantly, drotaverine is effectively used in combination with antibiotics for the treatment of gastroenteritis accompanied with gastrointestinal spasm.³¹⁻³⁵

Combination Therapy With Drotaverine and Acetaminophen (Paracetamol)

Smooth muscle spasm is often associated with colicky abdominal pain. In such cases, combining a spasmolytic agent with an analgesic may result in prompt and adequate relief, improving both spasm and pain. Such combinations have been well accepted for a long time. In light of this, therapy comprising acetaminophen (paracetamol) and drotaverine may be beneficial.³³

Paracetamol is usually regarded as a safe analgesic/ antipyretic agent, and is believed to be virtually without any gastrointestinal side-effects. It is frequently used in pain management; it has been shown that it may help in alleviating visceral pain. It thus seems appropriate to include antispasmodics and analgesics in the treatment regimen; while antispasmodics are established in relieving spasmodic pain in gastrointestinal disorders, paracetamol may have a certain degree of role as it is useful in visceral pain relief. In addition, antipyretic action of paracetamol may also help in treatment of fever in gastroenteritis.^{36,37}

Figure 2: Episodes of abdominal pain in children receiving drotaverine versus placebo

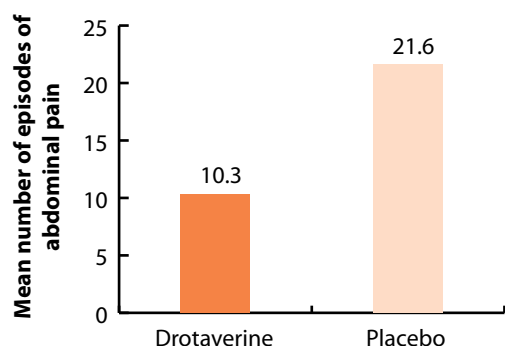


Table 3: Study outcomes with drotaverine versus placebo in patients with irritable bowel syndrome at the end of 4 weeks treatment

Outcomes	Treatment group (drotaverine) (n=72)	Placebo group (n=72)	p-value
Abdominal pain (visual analog scale)	1.8 ± 0.7	4.4 ± 1.5	<0.01
Stool frequency	1.4 ± 0.6	2.9 ± 0.9	<0.01
Bristol score	5.1 ± 0.6	5.6 ± 1.0	<0.01

Fixed-Dose Combination of Drotaverine and Paracetamol: An Effective and Well-Tolerated Antispasmodic Agent in the Treatment of Abdominal Pain Associated With Acute Infectious Gastroenteritis

In a recent study, Narang and Koli³⁸ aimed to evaluate the efficacy and safety of fixed-dose combination of drotaverine hydrochloride (80 mg) and paracetamol (PCM) (500 mg) in amelioration of abdominal pain in acute infectious gastroenteritis.

This was a randomized double-blind controlled trial, wherein adults (n=252, male and female, age range 18-59 years) with acute infectious diarrhea (≥ 3 unformed, watery, or soft stools with symptoms at least within the last 24 h preceding randomization with duration of illness not more than 72 h) presenting with moderate-to-severe abdominal pain were treated with either a fixed-dose combination of oral drotaverine hydrochloride plus PCM (n=126) or oral PCM (n=126) t.i.d for 3 days. Study outcomes included mean pain intensity difference, total pain relief at 2 h, onset of pain relief, decrease in number of pain episodes, global improvement, and adverse effects. Of the 252 study participants, 242 completed the study. Using VAS, a statistically significant improvement was observed in the mean pain intensity difference at 60 minutes after administration of the study medication in the fixed-dose combination group. Moreover, a statistically significant improvement was also observed in total pain relief at 2 hours (using both VAS and Verbal Rating Scale) in the fixed-dose combination group. The fixed-dose combination group (Drotaverine plus PCM) also demonstrated a significantly better onset of pain relief when using VAS.

Thus, findings of this study substantiate that fixed-dose combination of drotaverine hydrochloride (80 mg) and paracetamol (500 mg) is an effective and well-tolerated antispasmodic agent in the treatment of abdominal pain associated with acute infectious gastroenteritis.

Variable	Drotaverine + PCM group (n=126)	PCM group (n=126)	p-value
mPID60 (VAS)	36.11 $\pm$ 7.12	32.58 $\pm$ 7.32	<0.001
TOTPAR 2 (VAS)	103.57 $\pm$ 12.31	97.54 $\pm$ 12.37	<0.001
Onset of pain relief (VAS) (min)	34.76 $\pm$ 7.74	37.02 $\pm$ 8.84	0.032

Abbreviations: mPID60, mean pain intensity difference at 60 minutes; PCM, paracetamol; TOTPAR 2, summed, time-weighted pain relief at 2 hours; VAS, visual analog scale.
Values in Mean $\pm$ SD

Paracetamol, besides being an effective antipyretic, also inhibits prostaglandin synthesis, thereby exerting rapid analgesic action, which complements the fast antispasmodic action of drotaverine. Moreover, no adverse interactions have been reported between drotaverine and paracetamol. By virtue of their different mechanisms of action, the combination of drotaverine and paracetamol proves to be a potential therapeutic alternative that provides rapid pain relief.³³

Conclusion

Acute gastroenteritis clinically presents as sudden onset of diarrhea with or without vomiting. Morbidity and mortality associated with acute gastroenteritis are greatest among

those at the extremes of age, children and the elderly specially due to dehydration. Acute gastroenteritis is accompanied with anorexia, nausea, vomiting, abdominal cramps, and diarrhea. Diffuse abdominal tenderness before diarrhea and severe cramping abdominal pain may also be noted. Prevention of dehydration is the hallmark of gastroenteritis treatment; however, the complaint of abdominal pain and spasm may warrant treatment even before rehydration therapy is considered. Drotaverine is a preferred drug in treatment of abdominal spasms owing to its characteristic properties. Drotaverine is a highly potent and tolerable spasmolytic agent, suited for oral administration, and capable of relieving or preventing smooth muscle spasms, including those of

gastroenterological origin. It is well tolerated and effective even when used in combination with acetaminophen. Combining a spasmolytic agent with an analgesic may result in prompt and adequate relief, improving both spasm and pain.

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