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Systematic Review

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Activity of Nitazoxanide Against Viral Gastroenteritis: A Systematic Review

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Abstract

Introduction: Nitazoxanide is an oral anti-parasitic agent that has been found to have broad antiviral activity. Its role in the treatment of viral gastroenteritis is not well-studied. Given the worldwide prevalence of viral gastroenteritis, particularly in developing nations, a systematic review of this topic would be valuable.

Methods: A formal literature search with the assistance of a reference librarian included randomized controlled trials, cohort studies, case-control studies, and case reports. Studies were included if they pertained to nitazoxanide use for viral gastroenteritis and excluded if nitazoxanide was used for parasitic or other viral illnesses.

Results: Based on inclusion and exclusion criteria, 5 randomized controlled trials (2 in Egypt and 1 each in Peru, India, and Bolivia) were included in the systematic review. Four of the studies enrolled children only; one study included adults. All studies noted a statistically significant reduction in time from the first dose of nitazoxanide to resolution of illness (approximately one to 2 days) in patients compared to the receiving placebos (approximately 3 days). There were 9 case series or reports on nitazoxanide use for viral gastroenteritis in immunocompromised hosts; of these, only one case reported a noticeable effect of nitazoxanide in reducing symptom duration and severity.

Conclusion: Despite the limited number of studies and the potential risk of bias introduced by the funding source, a benefit of nitazoxanide in reducing duration of illness from viral gastroenteritis was demonstrated for immunocompetent children. Randomized controlled trials are needed to elucidate the role of nitazoxanide for treating viral gastroenteritis in immunocompromised hosts.

Keywords: Nitazoxanide, Gastroenteritis, Norovirus, Rotavirus

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Introduction

Nitazoxanide is a nitrothiazole benzamide compound that is widely used in Latin America and India for various intestinal parasitic infections.[1,2] In the United States, it received regulatory approval in 2002 for treating diarrhea caused by the parasites *Cryptosporidium parvum* and *Giardia lamblia* in children and adults.[3,4] In addition to its anti-parasitic activity, nitazoxanide has a broad range of activity against obligate and facultative anaerobic gram-positive and gram-negative bacteria. In recent years, nitazoxanide has been found to have broad antiviral activity and to be active against etiologies of viral gastroenteritis, such as rotavirus and norovirus.[1]

Gastroenteritis is a significant cause of morbidity and mortality in developing countries which are plagued by poverty, poor sanitation, and contaminated drinking water.[5] There are approximately 1.4 billion episodes of diarrhea per year in children less than 5 years of age.[6] Rotavirus is the most common cause of pediatric gastroenteritis in developing countries and may lead to half a million deaths per year in children less than 5 years of age.[5,6] In 2011, norovirus caused an estimated 71 000 childhood deaths worldwide.[7] Other common viral pathogens of gastroenteritis include adenovirus and astrovirus.[5]

Viral gastroenteritis has a profound impact on immunocompromised hosts such as solid organ transplant recipients or those undergoing chemotherapy. Norovirus is increasingly identified as a significant cause of viral gastroenteritis in immunocompromised hosts.[8] In such hosts, viral gastroenteritis can have a prolonged course. Approximately 17% of renal transplant recipients who may

be chronically infected with norovirus experience diarrhea, dehydration, and malnutrition; these symptoms can increase morbidity and even lead to death.[9]

A few studies have shown a potential benefit of nitazoxanide (compared to a placebo) against gastroenteritis caused by norovirus, rotavirus, and adenovirus.[10-12] The current study is a systematic review purposed to examine the effect of nitazoxanide on viral gastroenteritis.

Methods

A formal literature search with the assistance of a reference librarian included randomized controlled trials, cohort studies, case-control studies, and case reports. Included were all studies in any language that used nitazoxanide to treat viral (e.g., norovirus, rotavirus, and adenovirus) gastroenteritis. Studies on nitazoxanide for non-viral gastroenteritis, such as *Cryptosporidium* or *Giardia*, or for other non-gastrointestinal viral illnesses, such as influenza or hepatitis, were excluded. Databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from 1946 to 2017. Search terms included *nitazoxanide, viral gastroenteritis, rotavirus, norovirus, sapovirus,* and *astrovirus*.

Results

The search yielded 234 studies. Two independent investigators (E.M.T. and C.D.Z.) reviewed the studies for inclusion. Initially, 124 were excluded based on title and abstract screening which described the use of nitazoxanide for influenza, hepatitis, or non-viral gastroenteritis. Any disagreements on inclusion were defaulted to full-text retrieval and review, which led to the further exclusion of 96 studies due to incorrect study design. Ultimately, 14 studies were included in this review (Figure 1). Data extraction on the methods, population, interventions, and outcomes was performed for each of the studies. The Cochrane risk of bias was assessed based on sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

Five randomized controlled trials with sample sizes ranging from 50 to 100 participants were included (Table 1). Two studies took place in Egypt,[10,11] one in Peru,[13] one in India,[14] and one in Bolivia.[12] Participants varied slightly in age range but consisted largely of pediatric patients (1 month to 18 years in age). Patient populations consisted of immunocompetent children who lacked chronic or severe systemic disease. The studies had similar criteria for defining diarrhea, which required greater than or equal to 3 stools daily and stool testing positive for rotavirus, norovirus, or adenovirus.[10-14] Exclusion criteria were similar and included other non-viral enteric pathogens or severe systemic disease. All studies compared nitazoxanide to a placebo; the study by Teran et al. added a third group treated with probiotics.[12] No major baseline differences were noted among treatment groups for the 3 studies by Rossignol et al[10,11,13] and the study by Mahapatro et al,[14] but Teran et al[12] did note differences in age and nutrition status among the groups. All studies noted a statistically significant reduction in time from the first dose of

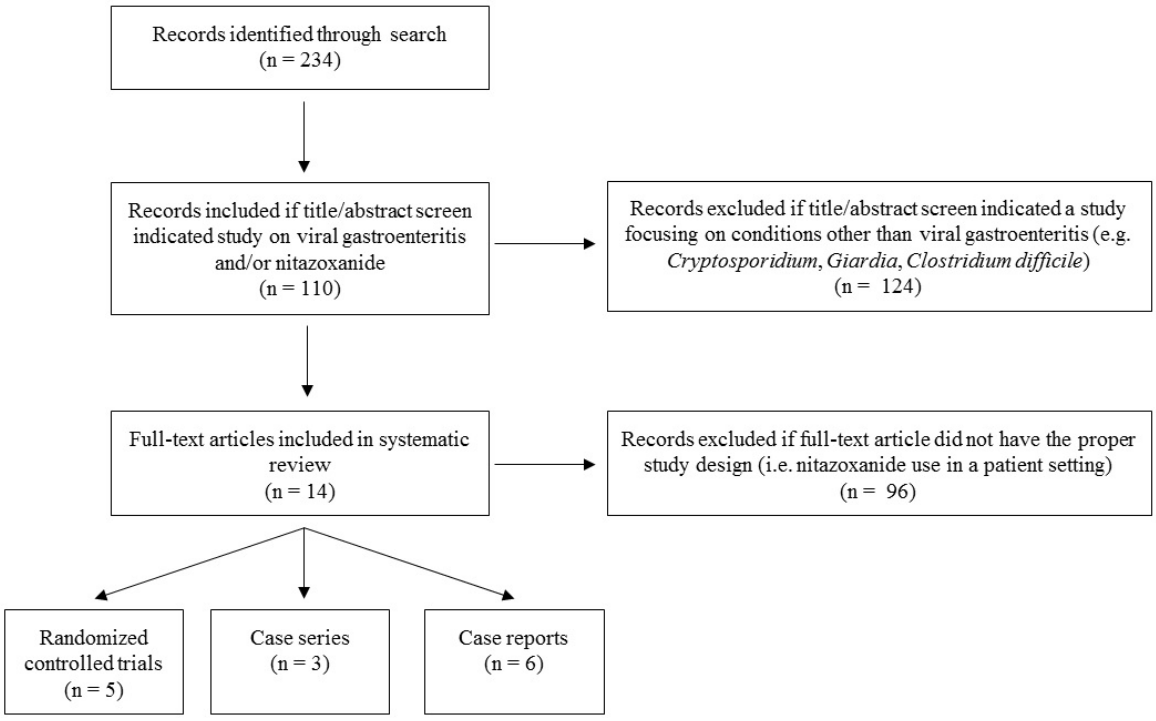

Figure 1. Flow Diagram Depicting Inclusion and Exclusion of Various Studies.
Records were identified using the following databases: Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from 1946 to 2017.

Table 1. Randomized Controlled Trials of Nitazoxanide for Viral Gastroenteritis

	Study 1		Study 2		Study 3		Study 4			Study 5	
Year of publication	2006		2006		2012		2009			2017	
Study design	Double-blind		Double-blind		Double-blind		Single-blind			Double-blind	
Study setting	Egypt		Egypt		Peru		Bolivia			India	
Inclusion criteria											
Age	<12 years		≥12 years		>12 months, <11 years		28 days to 24 months			12 months to 5 years	
Definition of diarrhea	≥3 stools per day		≥3 stools per day		≥3 stools per day for ≥3 days and <30 days		Watery diarrhea for < 3 h			≥3 unformed or loose stools in 24 h	
Stool tests	Positive for rotavirus		Positive for rotavirus, norovirus, or adenovirus		Positive for rotavirus, norovirus, adenovirus, or other enteric pathogens		Positive for rotavirus			Not defined	
Exclusion criteria	Other known or suspected causes of diarrhea or those with serious diseases incompatible with study		Other identified enteric pathogens or causes of diarrhea; pregnancy; lactation		Visible blood in stool; receipt of antimicrobials within 5 days of enrollment; immune deficiencies; serious systemic disorders		Severe malnutrition or chronic disease; systemic infection; presence of another enteric pathogen; antibiotics, probiotics, or nitazoxanide within 3 weeks before enrollment			Dysentery; severe malnutrition; coexisting systemic illnesses; chronic diseases	
Intervention	Nitazoxanide (NTZ) versus placebo (PBO)		Nitazoxanide (NTZ) versus placebo (PBO)		Nitazoxanide (NTZ) versus placebo (PBO)		Nitazoxanide (NTZ) versus placebo (PBO) versus probiotic (PRO)			Nitazoxanide (NTZ) versus placebo (PBO)	
Study population											
Number enrolled	50		50		100		75			50	
	NTZ	PBO	NTZ	PBO	NTZ	PBO	NTZ	PBO	PRO	NTZ	PBO
Age[a,b] (median, range, unless otherwise noted)	9.0 mo (5-92 mo)	12.0 mon (5-24 mon)	Mean 34.1 y (12-60 y)	Mean 32.9 y (12-54 y)	2.6 y (IQR 1.8-4.1 y)	2.5 y (IQR 1.6-3.5 y)	9.0 y (IQR 4.5-15.5 y)	12.0 y (IQR 7.5-13.0 y)	7.0 y (IQR 4.5-8.0 y)	26.0 mon	25.0 mon
Gender (% males)	50%	60%	38%	43%	58%	58%	64%	48%	48%	64%	68%
Median days of diarrhea at time of enrollment	7.0	6.0	6.5	7.0	5.8	5.4	Not reported			1.8	1.9
Outcomes											
Hours from first dose to resolution of illness (all P values < 0.02)	31.0	75.0	36.0	60.0	23.0	103.5	54.0	79.0	48.0	54.0	80.0
Duration of hospitalization (h)	Not measured		Not measured		Not measured		81.0	108.0	72.0	68.0	90.0
Adverse events in nitazoxanide group	None		Abdominal pain (n = 2), headache (n = 1)		Urine discoloration (n = 22)		Urine discoloration (unknown number)			None	
Cochrane risk of bias	Romark Institute was both study sponsor and distributor of nitazoxanide		Romark Institute was both study sponsor and distributor of nitazoxanide		Romark Institute was both study sponsor and distributor of nitazoxanide		Single-blind study			Randomization sequence generated by a person, not automatically	
Authors	Rossignol et al[10]		Rossignol and El-Gohary[11]		Rossignol et al[13]		Teran et al[12]			Mahapatro S et al[14]	

[a] The studies reported patients' ages in different units, some in months (mon) and some in years (y). Ages are reported with medians and ranges, unless otherwise noted.
[b] IQR = interquartile range.

nitazoxanide to resolution of illness, which was approximately one to 2 days for the nitazoxanide groups compared to approximately 3 days for the placebo groups.[10-14]

In the quality assessment for Cochrane risk of bias, the most notable point was that 3 of the studies were performed by one investigator who was also the founder of Romark Laboratories, which owns the intellectual property rights for nitazoxanide.[10,11,13] The study by Teran et al was designed as a single-blind trial in which nurses prepared the medication solutions and collected patient data.[12]

The literature search yielded 9 case series or reports[15-23] (Tables 2 and 3). In contrast to randomized controlled trials, the case series and reports focused on immunocompromised populations, which consisted of patients with solid organ transplants, hematologic malignancies or stem cell transplants, or congenital immunodeficiencies. It was difficult to assess the effect of nitazoxanide on diarrheal symptom duration, but one report definitively concluded that nitazoxanide led to a reduction in symptom duration. This patient was a 43-year-old male with relapsed refractory acute myelogenous leukemia and chronic graft-versus-host disease whose norovirus gastroenteritis improved within 24 hours of nitazoxanide initiation.[23]

Discussion

This systematic review yielded 5 small, randomized controlled studies on the use of nitazoxanide for viral gastroenteritis. The current review showed that among children with rotavirus, norovirus, or adenovirus gastroenteritis, there was a reduction in time from first dose of nitazoxanide to resolution of illness, defined as the resolution of all symptoms present at the time of enrollment. Though this reduction in time to resolution of illness was approximately one day, this expedited recovery may have a significant clinical benefit for the many children with viral gastroenteritis worldwide.

Nitazoxanide's mechanism of action against viruses, in general, involves the activation of protein kinases, which phosphorylate eukaryotic initiation factor 2 alpha and modulate the host's antiviral response.[24] Regarding rotavirus specifically, nitazoxanide inhibits structural glycoproteins involved in replication and prevents the maturation of rotavirus viral protein 7, which constitutes the outer portion of the virion.[1] The specific mechanisms of action against norovirus or adenovirus are not well-known.

The use of nitazoxanide for viral gastroenteritis is controversial, as most cases of viral gastroenteritis in children are self-limiting and may not require antimicrobial use.[25] Antimicrobial costs in a developing nation may also be prohibitive. On the other hand, antimicrobial use may be justified, given that diarrheal illness causes over one million childhood deaths annually in the developing countries of Africa and Asia.[26] Malnutrition is also an important cause of childhood mortality in developing countries and may be worsened by bouts of gastroenteritis.[27] Faster resolution of, even just a day may reduce childhood morbidity and mortality.

Viral gastroenteritis in the immunocompromised population, such as patients with human immunodeficiency virus (HIV) infection or in solid organ and hematopoietic

Table 2. Case Series on Nitazoxanide for Viral Gastroenteritis Due to Norovirus

Authors, Year	Median Age (y)	Gender (n, %)	Patient Population and Characteristics	Pertinent Findings and Outcome
Avery et al, 2016[15]	57	17 (54.8%) males	31 cases (25 kidney, 2 liver, 1 heart, 1 kidney/liver, 1 lung, 1 hematopoietic stem cell transplant recipients)	Nitazoxanide given to 23/31 (74%) patients. Outcome: Unknown effect of nitazoxanide.
Morris and Morris, 2015[16]	10	Not reported	14 cases (10 allogeneic and 2 autologous stem cell transplant recipients; 2 receiving chemotherapy)	Nitazoxanide given to 14/14 (100%) patients Outcome: Improvements in diarrhea, nausea and abdominal pain in 2 days.
Patte et al, 2017[17]	Not reported	Not reported	19 cases (19 intestinal transplant recipients)	Nitazoxanide given to 4/19 (21.0%) patients. Outcome: No change in duration of hospitalization or diarrhea.

Table 3. Case Reports on Nitazoxanide for Norovirus Gastroenteritis

Authors, year	Case #	Age, years	Gender	Medical history	Outcome with nitazoxanide
Jurgens et al, 2017[18]	1	61	Female	Cardiac transplant	No improvement.
Jurgens et al, 2017[18]	2	60	Male	Cardiac transplant	Unknown effect.
Jurgens et al, 2017[18]	3	34	Female	Cardiac transplant	Unknown effect.
Capizzi et al, 2011[19]	4	64	Male	Chronic lymphocytic leukemia and hypogammaglobulinemia	No improvement.
Crawford, 2014[20]	5	60	Male	Mantle cell lymphoma and autologous stem cell transplant	No improvement.
Echenique et al, 2016[30]	6	49	Female	Type 1 diabetes mellitus and pancreas transplant	No improvement.
Kempf et al, 2017[22]	7	10	Male	X-linked agammaglobulinemia	Initial improvement in severity and frequency of diarrhea, but treatment discontinued after 12 months because of no subsequent clinical response and persistent detection of norovirus.
Siddiq et al, 2011[31]	8	43	Male	Relapsed refractory acute myelogenous leukemia and chronic graft-versus-host disease	Decreased frequency of bowel movements from 10 to 2 per day within 24 h of nitazoxanide administration. Symptoms resolved to baseline in 4 days.

transplant recipients, can have a prolonged and debilitating course. For example, a pancreas allograft recipient had a chronic (2543-day) debilitating norovirus infection that required multiple hospitalizations and intensive nutritional support for dehydration, syncope, and acute kidney injury.[21] In addition, in patients with common variable immunodeficiency, there are reports of a severe norovirus-associated enteropathy characterized by intestinal villous atrophy and malabsorption, which can lead to debilitating symptoms of steatorrhea and malnutrition.[28]

With its antiviral properties and minimal side effects, nitazoxanide may be effective in the management of these patients. In one example, a patient with relapsed refractory acute myelogenous leukemia who underwent hematopoietic stem cell transplantation suffered from voluminous diarrhea due to norovirus gastroenteritis for 10 days (Case 8 in Table 3). One day after starting nitazoxanide, the frequency of bowel movements declined from 10 to 2 per day. The patient experienced clinical resolution of symptoms with a 7-day course of nitazoxanide.[23]

Although gastroenteritis due to norovirus may be self-limited, it may still pose a serious problem in healthcare settings. In a 2-year period in the United Kingdom, norovirus led to 4000 hospital outbreaks, 9000 days of ward closures, and a significant economic burden.[29] Crowded settings such as military camps would also be seriously debilitated by an outbreak of viral gastroenteritis. Such potential societal impacts may warrant the use of an effective treatment such as nitazoxanide, especially in developing nations where an outbreak might be devastating.[29]

Nitazoxanide use has been associated with some adverse effects such as headache (6%-8%), bronchitis (3%-5%), and oropharyngeal pain (2%-5%).[1] Interestingly, in phase 2b/3 clinical trials of patients with acute uncomplicated influenza-like illness, diarrhea (2%-8%) was noted to be a side effect of nitazoxanide.[1]

The current study was limited by the small number of randomized controlled trials on nitazoxanide use for viral gastroenteritis. In addition, 3 out of the 5 randomized controlled trials were performed by the same author (Rossignol), who is the founder of the company that owns the intellectual property rights for nitazoxanide. Despite the potential risk of bias introduced by the funding source, the 3 studies by Rossignol et al were double-blind and randomized.[10,11,13] Lastly, this study was unable to provide an aggregate estimate of the treatment effect in the form of confidence intervals, as the necessary data was not provided.

Larger studies to elucidate the effect of nitazoxanide on shortening illness duration, and reducing morbidity and mortality from diarrhea, particularly among children and immunocompromised hosts with viral gastroenteritis, are needed. This may require a large, multi-center randomized controlled trial to allow more generalizable conclusions to be made on the benefits of nitazoxanide on viral gastroenteritis.

Conclusion

Randomized controlled trials on nitazoxanide for viral gastroenteritis showed a clinical benefit in time-to-resolution of symptoms (diarrhea). Although viral gastroenteritis may be a self-limited condition, the use of nitazoxanide may be particularly beneficial in children in outbreak situations or in immunocompromised hosts.

Review Highlights

What Is Already Known?

Nitazoxanide may reduce the duration of diarrheal symptoms due to viral gastroenteritis in immunocompetent children.

What This Study Adds?

Though viral gastroenteritis may be self-limited in immunocompetent children, nitazoxanide may be particularly useful in reducing the burden of disease in outbreaks, crowded settings, or immunocompromised hosts, such as transplant recipients.

Authors' Contributions

EMT, KAC, CDZ, and IGS were involved in the initial study design. EMT and CDZ reviewed the studies for inclusion. EMT, KAC, CDZ, RSG, and IGS participated in manuscript review.

Conflict of Interest Disclosures

None of the authors have any conflicts of interest to disclose.

Ethical Approval

Not applicable.

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