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EFFICACY AND SAFETY OF DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE FOR THE TREATMENT OF TRAVELER'S DIARRHEA

General Medicine

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ABSTRACT

Background: Traveler's diarrhea (TD) is a major health concern in people traveling to developing countries. The current study aimed to determine the effectiveness and safety of Lomotil, a combination of diphenoxylate hydrochloride and atropine sulfate, and its applicability in TD. **Methods:** This was a cross-sectional, non-randomized, multicentric observational study. Patients of either sex, aged > 18 years, with 4-6 stools per day and symptoms of fever, nausea, vomiting, and abdominal cramps were included. Patients were given diphenoxylate hydrochloride & atropine sulfate. Outcomes were i) assessment of stool frequency, stool consistency, and abdominal cramps/gas from baseline to subsequent follow-ups (Days 1, 2, 3, 4, and one week) and ii) assessment of the occurrence of infection and adverse drug reactions. **Results:** A total of 327 patients were involved in the study, of which the majority were men (74.62%). The mean age of patients was 34.08 years and the most common (74%) symptom was vomiting. Post-treatment, patients showed a significant reduction in, i) stool frequency (5.09 vs. 0.20, $p<0.0001$), ii) stool consistency (5.00 vs. 0.20, $p<0.0001$), and iii) daily abdominal gas/discomfort (4.93 vs. 0.27, $p<0.0001$) from baseline to week 1, respectively. A majority (59.63%) of patients had not reported adverse drug reactions with only 39.60% stating feeling dizzy or drowsy. The majority (47.48%) of the patients stated that they liked the treatment very much and 60% of physicians reported overall improvement in the patients. **Conclusion:** Diphenoxylate hydrochloride and atropine sulfate were demonstrated as effective in reducing symptoms of diarrhea, with minor adverse drug reactions signifying its use in the immediate relief of TD.

KEYWORDS

Lomotil, Traveler's Diarrhea, Immediate Symptomatic Relief, Real-world Setting

INTRODUCTION

Traveler's diarrhea (TD) is an important health issue across the world and is reported as a major health concern by travelers visiting developing countries, with an incidence rate of 20-60% per month.[1,2] It is defined as the passage of ≥ 3 unformed stools within 24 hours in the case of adults or a ≥ 2-fold increase in the frequency of unformed stool in a pediatric population.[3] It is primarily caused by bacterial, viral, and parasitic infections or as a side effect of drugs.[4] The TD is associated with symptoms such as fever, nausea, abdominal cramps, vomiting, fecal urgency, and blood/mucous in the stool.[3] It is usually an acute, self-limiting condition that resolves within one to five days; however, its occurrence and severity can be reduced by personal hygiene, pre-travel vaccination (if needed), and cautious use of antimicrobial and antimotility agents.[3-5]

Lomotil, the fixed-dose combination (FDC) of diphenoxylate (2.5 mg) and atropine (0.025 mg) approved by the Food and Drug Administration (FDA) in 1960, was found effective in the management of both acute and chronic diarrhea.[6-8] Diphenoxylate is an active ingredient of commonly available antimotility medications, which act as an opioid receptor that primarily acts on presynaptic opioid receptors (often known as mu receptors). It also reduces the release of fluid and electrolytes by the epithelium, enabling active absorption of these substances.[7] Atropine, another drug from the FDC, acts as a competitive inhibitor of the acetylcholine receptor with an anti-diarrheal effect and is added to subtherapeutic concentrations to prevent abuse of the drug diphenoxylate.[7,8] The rationale for using diphenoxylate hydrochloride and atropine sulfate in TD is its ability to reduce stool frequency and improve stool consistency, providing symptomatic relief for the affected travelers.[3] Clinical recommendations support the use of antimotility agents in TD, suggesting that they can be used as a supplement to rehydration therapy, and in certain situations, antibiotic therapy.[9]

For the symptomatic treatment of TD, diphenoxylate hydrochloride and atropine sulfate remain a valuable tool, particularly when immediate relief is required and the likelihood of invasive microorganisms is low. The present study provides a comprehensive assessment of these drugs' efficacy and safety in treating TD. Moreover, the study aimed to provide significant insights to guide clinical practice and improve patient outcomes in the post-marketing phase by leveraging a multicenter approach and diverse patient population in real-world clinical practice.

METHODOLOGY:

Study Design

This was a cross-sectional, non-randomized, multicentric, post-marketing observational study conducted across multiple centers. The study protocol was approved by the Independent Ethics Committee (IEC). The study was conducted in compliance with Good Clinical Practice (GCP) guidelines and the principles of the Declaration of Helsinki. Informed Consent was obtained from each participant before the study.

Study Population

Patients of either sex, aged >18 years, with clinical presentation of 4-6 stools per day with symptoms of fever, nausea, vomiting, and abdominal cramps were included in the study. However, patients who were on any other antimotility agents, and other concomitant therapy or antibiotics which could interfere with the antidiarrheal effects of diphenoxylate were excluded from the study. Additionally, patients with a history of gastrointestinal disorders (Ulcerative colitis, Crohn's disease) and pregnant or breast-feeding women were excluded.

Data Collection

Patients were administered diphenoxylate hydrochloride 2.5 mg & atropine sulfate 0.025 mg. Data related to demographics, clinical and laboratory investigation, concomitant medication, and safety outcomes were collected from eligible patients.

Endpoints

The primary endpoint of the study was the assessment of i) stool frequency, ii) stool consistency, and iii) abdominal cramps/gas, from baseline to subsequent follow-ups (Days 1, 2, 3, 4, and one week). Secondary outcomes were assessment of i) occurrence of enteric infection or mild diarrhea, ii) occurrence of adverse drug reactions, and iii) physician's assessment for overall improvement

Sample Size

Given the post-marketing non-randomized, observational study, no formal sample size was calculated. Instead, to ensure a thorough investigation of the included population, the study aimed to include all eligible cases within the available data or within a predetermined timeframe.

Statistical Analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS). Categorical variables were presented as numbers and percentages while continuous variables were presented as mean and standard deviation (SD). Comparative analysis of baseline and follow-up data was performed using a paired sample t-test. A $p < 0.05$ was considered as statistically significant.

RESULTS

Demographic and baseline characteristics are mentioned in Table 1. A total of 327 patients were involved in the study, of which the majority were men (74.62%). The mean (SD) age of the patient was 34.08 (11.20) years. The most common symptom was vomiting, reported by ~74% of patients, followed by fever and nausea, presented by 53.21% of patients each. The majority of patients (73.09%) reported mild diarrhea, followed by enteric infection (26.91%). All the included patients (100%) experiencing diarrheal symptoms showed consumption of ORS as a rehydration therapy. However, the majority (40.06%) of patients showed domperidone, followed by Enterogermina (26.91%) and pantoprazole (25.38%) as concomitant medications.

Post-treatment of diphenoxylate hydrochloride and atropine sulfate significant improvements were reported (Table 2). The frequency of occurrence of stool was significantly decreased from baseline to week 1 (5.09 vs. 0.20, $p<0.0001$). The change from daily stool consistency was found significant from baseline to week 1 (5.00 vs. 0.20, $p<0.0001$). Daily abdominal gas or discomfort was decreased from pre- (baseline) to post-treatment till day 4 (4.93 vs. 0.27, $p<0.0001$), after which it remained unchanged till week 1 (0.27, $p<0.0001$).

Safety outcomes are documented in Table 3. The majority (59.63%) of the patients had not reported adverse drug reactions. However, feeling dizzy or drowsy was reported as a primary adverse reaction by 39.60% of patients, followed by nausea presented by 20.81%. More than 98% of patients had not shown discontinuation of the treatment.

Post-treatment evaluation was carried out by gathering insights from the physicians and patients (Figure 1). The majority (47.48%) of patients were satisfied with the treatment and stated that they liked the treatment very much. Moreover, around 60% of physicians reported improved outcomes in the patients.

DISCUSSION

The study was aimed to assess the efficacy, and safety of diphenoxylate hydrochloride and atropine sulfate in patients with diarrhea. The outcomes of the study will help to effectively treat the traveler's diarrhea. The key outcomes were a decrease in the frequency of stool, daily stool consistency, and daily abdominal gas/discomfort from baseline to subsequent follow-up of day 1, 2, 3, 4, and week 1. Adverse drug reactions were not reported by most of the patients, however, feeling dizzy or drowsy and nausea were the most common adverse drug reactions. Most of the patients were satisfied with the treatment and most physicians observed improved overall outcomes.

The TD is considered as a crucial health concern among people who travel to developing countries like India. The overall pooled rate of incidence of TD was estimated as 39% among international travelers visiting India.[5] However, the recent meta-analysis by Carroll et al. reported pooled incidence of 2.9%, 8.1%, and 23.6% accounted for severe, moderate, and mild cases of TD. According to estimates, 20–56% of foreign visitors ought to anticipate developing TD during their travel, under 100 days. However, most cases are mild, about 3% of all travelers experience a condition that interferes with daily activities or requires medical attention. The study further accounted for a younger age, longer travel destinations, tourism, backpack travel style, and pre-trip health state were the risk factors for TD in travelers coming from high-income countries (HIC).[10] Recent management techniques have resulted in a notable decline in the incidence rate of developing TD. Centers for Disease Control and Prevention (CDC) Yellow Book 2024, recommended treatment recommendations for TD; i) treatment with bismuth subsalicylate or loperamide was suggested for mild diarrhea, ii) in case of moderate diarrhea, treatment can be comprised of antibiotics and antimotility drugs were recommended whereas the use of loperamide was suggested as a mono- or adjunct- therapy, iii) antibiotic treatment (fluoroquinolones, rifaximin, azithromycin) is recommended with loperamide as an adjunctive therapy, in severe diarrheal cases.[11] Additionally, other techniques for the management of TD include fluid replacement, continuous rehydration, and medicines for symptomatic relief.[12] Several observational studies also support the use of antimotility medications to treat mild diarrhea.[13] Hill et al reported that 48% of travelers used antimotility agents to treat TD in a large cohort study. Furthermore, self-treatment was found effective (in 91% of travelers) in treating TD among the American population who traveled to developing countries.[14]

In the present study, the safety and efficacy of the antimotility agent lomotil (diphenoxylate hydrochloride and atropine sulfate) was studied. The mean age of patients included in the study was 34 years. The result was consistent with a previous retrospective study, where a mean age of 33 years was reported in the patients of TD.[15] Caroll et al reported a mean and/or median age of around 33 to 50 years in patients with TD.[10] Lalani et al. reported age as one of the risk factors where the maximum (116) number of participants shown to meet the criteria for TD in the age group of 26-55 years. Additionally, women patients were prevalent in presenting TD among included study participants (men: women – 120:150) demonstrating females as an independent risk factor for TD.[16] The present study reported the prevalence of men.

Apart from diarrhea, other symptoms reported by travelers include nausea or vomiting, constipation, and abdominal pain.[17] In the present study, vomiting (73.70%) along with fever and abdominal cramps (53.21% each) were the most prevalent symptoms followed by nausea presented by ~40% of patients.

The present study demonstrated improved symptoms of diarrhea with respect to a decrease in stool frequency (5.09 vs. 0.20, $p<0.0001$), stool consistency (5.00 vs. 0.20, $p<0.0001$), and daily abdominal gas/discomfort (4.93 vs. 0.27, $p<0.0001$) from baseline to week 1. The results were consistent with the study by Khare et al. The efficacy of Lomotil was demonstrated in patients with chemotherapy-induced diarrhea. The mean frequency of stool (3.58 vs. 0.42, $p < 0.001$), stool consistency (3.67 vs. 0.10, $p < 0.001$), and abdominal pain (2.69 vs. 0.18, $p < 0.001$) were significantly decreased from baseline to week1 demonstrating the effectiveness of Lomotil in symptomatic relief of diarrhea.[18] Lomotil showed similar efficacy to that of another antimotility agent loperamide. However, a study by Dom et al. reported maximum (42%) proportion of patients required 2 or 3 tablets of loperamide to manage diarrhea, whereas, only 23% of the patients from the diphenoxylate and atropine group needed a similar dose.[19]

Palmer et al. also demonstrated comparable efficacy of diphenoxylate to that of loperamide in the symptomatic relief from chronic diarrhea.[20] The present study reported minimum adverse drug reactions using Lomotil in the treatment of TD. The results were consistent with previous reports with fewer adverse events.[18]

Managing symptoms (stool frequency) of TD, is challenging because travelers are in different locations and it might be challenging to get immediate medical care. Antimicrobials for self-treatment of TD are still permissible because TD causes disruptions to activities, however, use of antibiotics is advised in severe TD. Hence it would be appropriate to counsel travelers about the prudent use of these antimicrobials and reserve them in severe cases.[17] Although rehydration therapy can be employed as an adjuvant treatment, it does not provide instant symptom relief. Additionally, addressing other symptoms (such as stool consistency and discomfort due to gas and abdominal pain) is equally important. In such cases, treatment options that provide rapid symptom relief are crucial. Diphenoxylate with atropine has been demonstrated effective in managing instant relief from these symptoms. While the drug may cause minor adverse effects, its cautious use in emergencies is considered feasible.

The present study has demonstrated the efficacy and safety of diphenoxylate and atropine combination in alleviating diarrhea symptoms. This real-world clinical data from multiple centers strongly supports its use in patients with TD. However, the study is limited by the scarcity of existing literature on the efficacy of this drug in managing TD, which limits its comparative analyses across diverse populations. Despite this, the study provides a significant contribution to the existing data on the effective management of TD symptoms with this drug.

CONCLUSION

Diphenoxylate hydrochloride and atropine sulfate were found to be beneficial in reducing stool frequency, stool consistency, and

abdominal discomfort. It can be used in TD where immediate relief is crucial.

Table 1: Demographic and Baseline Characteristics

Parameters	No. of patients (N=327)
Age (years), Mean (SD)	34.08 (11.20)
Gender	
Men	244 (74.62)
Women	83 (25.38)
Symptoms	
Fever	174 (53.21)
Nausea	132 (40.37)
Vomiting	241 (73.70)
Abdominal cramps	174 (53.21)
Infection	
Enteric infection	88 (26.91)
Mild diarrhea	239 (73.09)
Treatment/Concomitant medication	
Domperidone	131 (40.06)
Enterogermina	88 (26.91)
Omeprazole	25 (7.65)
Pantoprazole	83 (25.38)
Ciprofloxacin plus tinidazole	27 (8.26)
Metronidazole	65 (19.88)
Norfloxacin plus Tinidazole	52 (15.90)
ORS	327 (100)
Data presented as n (%), unless otherwise specified. ORS, oral rehydration solution.	

Table 2: Treatment Outcomes

Parameters	Frequency of stool	Daily stool consistency	Daily abdominal gas/discomfort
Baseline	5.09 (0.82)	5.00 (0.82)	4.93 (0.77)
Day 1	4.33 (0.47)	4.33 (0.47)	4.33 (0.47)
Mean difference (95% CI; p value)	0.76 (0.68-0.83; p<0.0001)	0.67 (0.59-0.75; p<0.0001)	0.60 (0.51-0.68; p<0.0001)
Baseline	5.09 (0.82)	5.00 (0.82)	4.93 (0.77)
Day 2	2.93 (0.77)	2.93 (0.77)	2.94 (0.68)
Mean difference (95% CI; p value)	2.16 (2.08-2.24; p<0.0001)	2.07 (2.00-2.14; p<0.0001)	2.00 (1.89-2.10; p<0.0001)
Baseline	5.09 (0.82)	5.00 (0.82)	4.93 (0.77)
Day 3	1.53 (0.50)	1.53 (0.50)	0.87 (0.50)
Mean difference (95% CI; p value)	3.56 (3.46-3.66; p<0.0001)	3.47 (3.36-3.58; p<0.0001)	4.06 (3.98-4.15; p<0.0001)
Baseline	5.09 (0.82)	5.00 (0.82)	4.93 (0.77)
Day 4	0.87 (0.34)	0.80 (0.40)	0.27 (0.44)
Mean difference (95% CI; p value)	4.23 (4.12-4.33; p<0.0001)	4.20 (4.10-4.31; p<0.0001)	4.66 (4.59-4.74; p<0.0001)
Baseline	5.09 (0.82)	5.00 (0.82)	4.93 (0.77)
Week 1	0.20 (0.40)	0.20 (0.40)	0.27 (0.44)
Mean difference (95% CI; p value)	4.89 (4.81-4.97; p<0.0001)	4.80 (4.70-4.90; p<0.0001)	4.66 (4.58-4.75; p<0.0001)
Data presented as mean (SD). CI, confidence interval.			

Table 3: Safety Outcomes

Parameters	Number of patients (N=327)
Adverse drug reaction	
Yes	132 (40.37)
No	195 (59.63)
Adverse reactions reported (n=149)	
Feeling dizzy or drowsy	59 (39.60)
Headache	20 (13.42)
Loss of appetite	19 (12.75)
Nausea	31 (20.81)
Stomach pain	20 (13.42)
Complications (n=10)	
Increased heart rate	5 (50%)
Trouble urinating	5 (50%)
Patient discontinued treatment	
Yes	6 (1.83)
No	321 (98.17)
Data presented as n (%).	

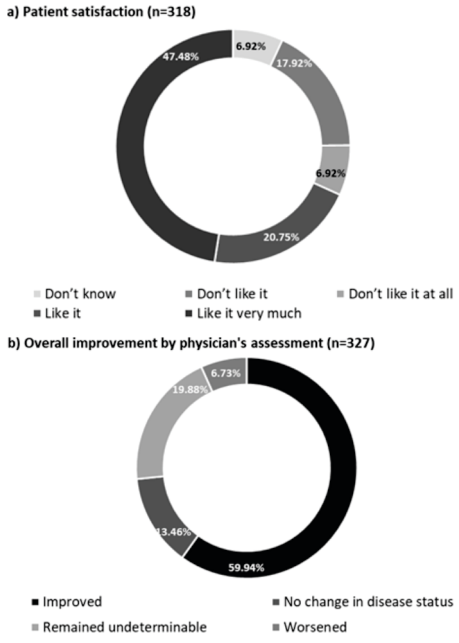

Figure 1: Post Treatment Assessment: a) Patient Satisfaction b) Overall Improvement by Physician's Assessment

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