

Dexlansoprazole is Effective in Relieving Heartburn during the Fasting Month of Ramadan

Hussein H. Rimmani Luma Basma O. Rustom Mahmoud A. Rahal
Rani H. Shayto Hani Chaar Ala I. Sharara

Division of Gastroenterology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

Keywords

Gastroesophageal reflux · Proton pump inhibitor · Acid reflux

Abstract

Background and Aims: Proton pump inhibitors are effective at reducing heartburn. No studies have evaluated their efficacy in Ramadan. Dexlansoprazole has a unique active formulation independent of time-of-day dosing or food. The aim is to investigate the efficacy of dexlansoprazole 60 mg during Ramadan in patients with symptomatic heartburn.

Methods: Subjects recruited using poster, radio, and SMS advertisements completed a diary using a mobile-friendly application and received daily SMS reminders. Dexlansoprazole was started on day 8 for 3 weeks. No placebo arm was used in this trial. Primary endpoint was relief of heartburn expressed as mean 24-h free heartburn percentage (24FH%) per weekly period. **Results:** A total of 32 patients were enrolled. During week 1, only 1 person (3.1%) was heartburn-free and mean 24FH% was $41.1 \pm 24.8\%$. On dexlansoprazole, mean 24FH% rose to 63.4 ± 23.8 and $81.6 \pm 24.5\%$ in weeks 2 and 4, respectively ($p < 0.001$ for both). Median 24FH% increased from 35.7% in week 1 to 71.4 and 85.7% in

weeks 2 and 4, respectively. Mean Gastroesophageal Reflux Disease Questionnaire (GERDQ) scores decreased from 10.0 ± 3.2 in week 1 to 6.53 ± 2.2 in week 2 ($p < 0.001$) and 5.87 ± 2.1 in week 4 ($p < 0.001$). Mean heartburn severity score decreased from 2.5 ± 1.0 to 1.7 ± 0.8 ($p = 0.001$). Early response was higher in patients with GERDQ scores ≥ 8 ($p = 0.012$). **Conclusion:** Dexlansoprazole is effective in the treatment of heartburn during Ramadan. Clinicaltrials.gov number: NCT03079050.

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Introduction

During the holy month of Ramadan, Muslims practice daily fasting from dawn to sunset. This commitment changes their daily food routine in terms of number of meals, quantity of caloric intake, and types of food consumed [1]. Most of the caloric intake in a Ramadan day is divided between iftar (after sunset meal: 70–100%) and

H.H.R. and L.B.O.R. contributed equally to the manuscript and should both be considered first authors.

suhoor (pre-dawn meal: 0–30%) [2]. This change in consumption pattern during Ramadan has an effect on metabolism and weight, sleeping pattern, and possibly gastric accommodation and emptying.

Gastroesophageal reflux disease (GERD) affects approximately 20–40 million people in the USA and is a common cause of GI-related morbidity [3]. Studies have reported that up to 20% of adults in the USA experience GERD symptoms at least twice weekly [3]. Moreover, several reports have demonstrated that nocturnal symptoms are common in GERD patients, occurring in 50–89% of patients [3, 4], and are more difficult to control compared to daytime symptoms [3]. A large population-based study showed that the prevalence and demographic determinants of GERD in Turkey are similar to Western populations [5]. Current medical therapy for GERD involves diet and lifestyle modification as well as pharmacotherapy with proton pump inhibitors (PPIs) [3]. Because of their mechanism of action, conventional PPIs must be taken 30–60 min prior to mealtime. In addition, a short plasma half-life of 1–2 h results in limited pharmacodynamics throughout the day [6]. In a study conducted by Fass et al. up to 40% of patients reported suboptimal response to once-daily PPI therapy [7].

The 2008 consensus guidelines for management of GERD from the American Gastroenterology Association recommend that patients who are still symptomatic on once daily PPI be stepped up to a twice-daily regimen [8]. During Ramadan, fasting consists in complete dietary restriction of solid food and liquids for as long as 16 h and food intake is restricted to the evening hours. During this month, patients suffering from GERD may have suboptimal relief of their symptoms with once daily PPI dose. Along with dyspepsia, bloating, and indigestion, peptic ulcers and duodenitis have also been reported to increase during the month of Ramadan [9].

Dexlansoprazole modified release, the R-enantiomer of lansoprazole, is approved for the management of erosive esophagitis and non-erosive reflux disease [3]. Dexlansoprazole has a unique dual delayed-release delivery system, with 2 separate pH-dependent release phases. A study conducted by Fass et al. [4] has shown that the use of dexlansoprazole 30 mg in patients with symptomatic GERD is significantly more effective than placebo in improving nocturnal heartburn, reducing GERD-related sleep disturbances, and consequently improving work productivity, sleep quality, and overall quality of life.

A critical consideration in Ramadan is that patients who have breakthrough symptoms during the fasting period of the day do not have the option to consume antac-

ids or on demand medications and there lies the importance of prolonged acid suppression during this period. Because of its pharmacokinetic and pharmacodynamics properties, dexlansoprazole may prove beneficial in optimizing the management of GERD symptoms in Ramadan such as increased nocturnal and breakthrough symptoms. Our study aims to investigate the efficacy of dexlansoprazole 60 mg taken once daily at iftar in patients with known symptomatic heartburn who are not on daily treatment.

Patients and Methods

This study was an open label trial conducted at the American University of Beirut Medical Center. Patients reporting to suffer from frequent GERD symptoms and who were planning to fast during the month of Ramadan were enrolled. Because of the time-sensitive nature of the study restricted to the month of Ramadan, enrollment occurred in a narrow window period of 2–4 weeks before Ramadan. Participants were solicited via different advertisement methods including posters in streets, clinics, and hospitals as well as radio advertisements, SMS, and social media campaigns. The body of the advertisement read as follows: “Do you suffer from heartburn that worsens during the month of Ramadan especially after Iftar and Suhoor?” Respondents were screened for proper inclusion criteria and were given additional information regarding the study by the research assistant. Patients with clear history of recurrent and frequent heartburn and regurgitation, and/or GERD Questionnaire (GERDQ) score ≥ 8 were enrolled. Other inclusion criteria were ages 18–75 years, fasting in Ramadan, no daily PPI use, owning of smartphone and web connectivity. Exclusion criteria were known erosive GERD on PPI, pregnant females, prior gastric surgery, long standing diabetes mellitus (≥ 10 years of disease), frequent NSAID use ($\geq 3\times/\text{week}$), morbid obesity (BMI > 35), history of recent (< 6 months) upper GI bleeding, known allergy to PPIs, known history of poor compliance or adherence, and active psychological problems which might impact adherence. No baseline endoscopy was required for enrollment in the study.

Patients who fit the research inclusion criteria were asked, 1 week prior to the start of Ramadan, to complete the GERDQ, the Nocturnal GERD Symptom Severity and Impact Questionnaire (N-GSSIQ) as well as an assessment of heartburn symptom severity and associated burdens. This baseline assessment also included age, gender, smoking status, prior PPI intake and frequency, use of antacid medications, NSAID intake, BMI, and waist circumference. The GERDQ is a patient-centered tool that was originally developed and validated by Jones et al. [10] for healthcare professionals to identify and manage patients with GERD. It consists of 6 domains with subscores of 0–3 and a total score ranging from 0 to 18 with higher scores increasingly correlated with the presence of GERD. The N-GSSIQ tool, on the other hand, is a reliable and validated questionnaire used to measure the severity, morning impact, and concern about nocturnal symptoms in patients suffering from GERD [11].

Participants received 1 box of dexlansoprazole 60 mg containing 21 tablets. They were instructed to take a pill once daily at iftar

time directly prior to first food consumption (breaking fast) starting day 8 of Ramadan. Patients completed a daily diary of symptoms using a mobile friendly web link and received daily SMS reminders to complete the diary and take their medicine (after week 1). The web link consisted of a series of 6 questions that asked consecutively about fasting, pill intake, suhoor consumption, presence of heartburn, time of heartburn, and GERD severity on a scale from 1 to 5. A live dashboard was monitored to ensure complete daily feedback by all patients. Patients who did not complete their daily diary through the mobile friendly web link were contacted on the next day and urged to complete the missing assignment. Patients were also asked to keep a medication log for each day (paper log and smartphone application log) which included, but was not limited to, a reminder to take the medication prior to eating, time of suhoor (if any), as well as adverse events on a daily basis. Patients were also asked to document the presence and severity of heartburn they had experienced on the day before (if any). A pill count was conducted over the phone on days 14 (week 2) and 30 (week 4) in order to document adherence to the medication. The N-GS-SIQ and GERDQ questionnaires were also administered at those time points to assess for symptom severity change after treatment.

Medications were provided free of charge to all enrolled patients. The primary efficacy variable was resolution of heartburn as expressed by the mean 24-h free heartburn percentage (24FH%) per week [4, 12]. Other assessments included median 24-h heartburn free percentage, as well as early symptomatic response, that is, the change in heartburn symptoms at week 2 as compared to baseline (week 1). Sample size calculation was based on existing evidence that as many as 40% of GERD patients treated with once-daily PPI report suboptimal response [3] and an estimated 85% optimal response on dexlansoprazole 60 mg once daily. Based on a 95% significance level and 80% power, the estimated sample size was 35 patients. Considering a 20% drop out rate, 40 patients were to be recruited. Data entry and analysis were conducted using IBM SPSS Statistics version 24. Categorical variables were interpreted through chi-square or McNemar's. Continuous variables were analyzed via paired sample *t* test. The study was approved by the Institutional Review Board and all participants provided written informed consent. All co-authors had access to the study data and had reviewed and approved the final manuscript.

Results

Forty participants presented for evaluation. On initial screening, 3 had no significant GERD symptoms, and 1 patient could not be enrolled due to travel commitments. During the first week of Ramadan, 4 patients dropped out from the study due to inability to keep up with the fasting rituals and never received any study drug. Thirty-two patients were enrolled. Table 1 shows the characteristics of the patients at baseline. Mean age was 36.2 ± 12.3 years and mean BMI was 27.1 ± 5.7 kg/m². Of those, 23 patients (71.9%) had prior use of PPIs on demand and 9 (28.1%) had prior use of anti-acids. Thirteen patients (40.1%) were smokers. Only 2 of 32 patients (6.3%) were reported

Table 1. Baseline demographics of study subjects

Characteristics	Patients (<i>n</i> = 32)
Age, years, mean \pm SD	36.2 \pm 12.3
BMI, kg/m ² , mean \pm SD	27.1 \pm 5.7
Males, <i>n</i> (%)	22 (68.8)
Smokers, <i>n</i> (%)	13 (40.1)
History of on-demand PPI use, <i>n</i> (%)	23 (71.9)
Anti-acid use, <i>n</i> (%)	9 (28.1)
Heartburn-free over last 1-week period prior to enrollment, <i>n</i> (%)	2 (6.3)
GERDQ score \geq 8, <i>n</i> (%)	24 (75)
Nocturnal reflux, <i>n</i> (%)	19 (59.4)

PPI, proton pump inhibitor; GERDQ, gastroesophageal reflux disease questionnaire.

to be completely free of heartburn over the last 7-day period at baseline. Thirty-one patients (96.9%) reported episodes of evening reflux while 19 patients (59.4%) described nocturnal reflux (after bed time). Figure 1 shows the study flow chart.

During week 1 of Ramadan, only 1 of 32 patients (3.1%) was completely free of heartburn and the mean 24FH% was $41.1 \pm 24.8\%$. After initiation of dexlansoprazole on day 8, the mean 24FH% rose to $63.4 \pm 23.8\%$ ($p < 0.001$) and $81.6 \pm 24.5\%$ ($p < 0.001$) in weeks 2 and 4, respectively (ITT analysis, Fig. 2). Twelve patients (38.7%) became completely free of heartburn during week 4. The continued improvement in mean 24FH% between weeks 2 and 4 was indicative of continued and sustained improvement ($p = 0.002$; paired *t* test). Median 24FH% were 35.7% in week 1 increasing to 71.4 and 85.7% in weeks 2 and 4, respectively (Fig. 3). The mean number of days without heartburn was 2.9 ± 1.7 days in week 1 increasing to 4.4 ± 1.7 days in week 2 ($p < 0.001$), and 5.7 ± 1.7 days in week 4 ($p < 0.001$). Moreover, the mean GERDQ scores decreased significantly from 10.0 ± 3.2 in week 1 to 6.53 ± 2.2 in week 2 ($p < 0.001$) and to 5.87 ± 2.1 in week 4 ($p < 0.001$, Fig. 4). When stratified by baseline GERDQ scores, the improvement (delta) in heartburn-free days from week 1 (off treatment) to week 2 (on treatment) was significantly higher in patients with GERDQ scores \geq 8 (2.1 ± 1.9 days) versus those with scores $<$ 8 (0.0 ± 1.9 days, $p = 0.012$). After initiation of dexlansoprazole, 23 patients (71.9%) reported heartburn on 1 or more days during week 2. However, their mean heartburn severity score diminished significantly from 2.5 ± 1.0 to 1.7 ± 0.8 compared to their mean severity scores at their week 1 baseline ($p < 0.001$). The suhoor

Fig. 1. Study flow chart. GERDQ, gastroesophageal reflux disease questionnaire; NGSSIQ, nocturnal GERD symptom severity and impact questionnaire.

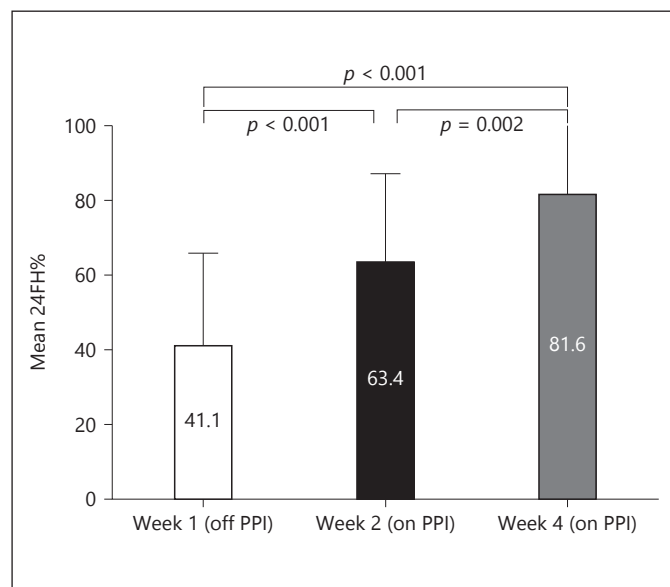
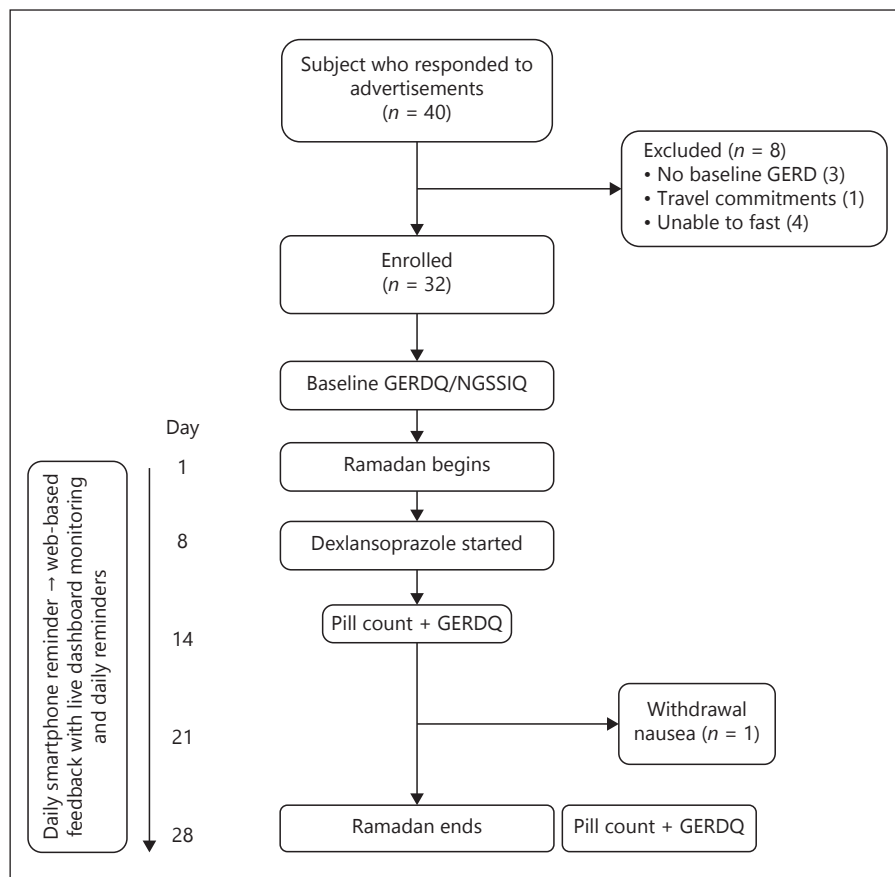


Fig. 2. Mean 24FH% between week 1, 2, and 4. 24FH%, 24-h free heartburn percentage; PPI, proton pump inhibitor.

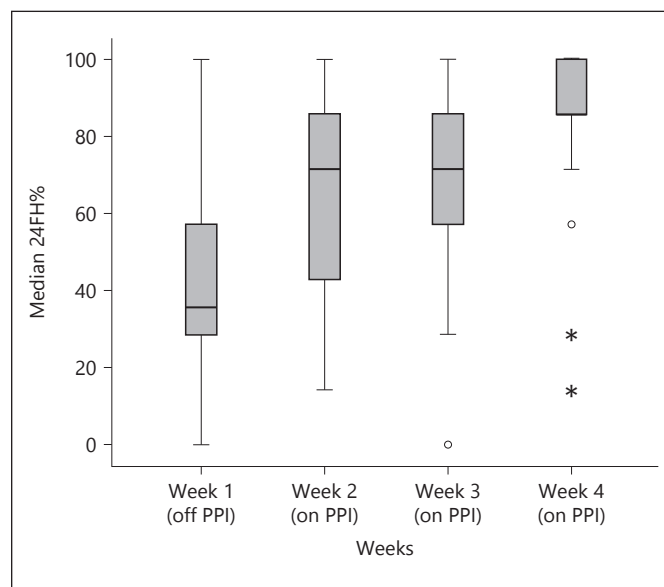


Fig. 3. Median 24FH% in weeks 1, 2, 3, and 4. 24FH%, 24-h free heartburn percentage; PPI, proton pump inhibitor.

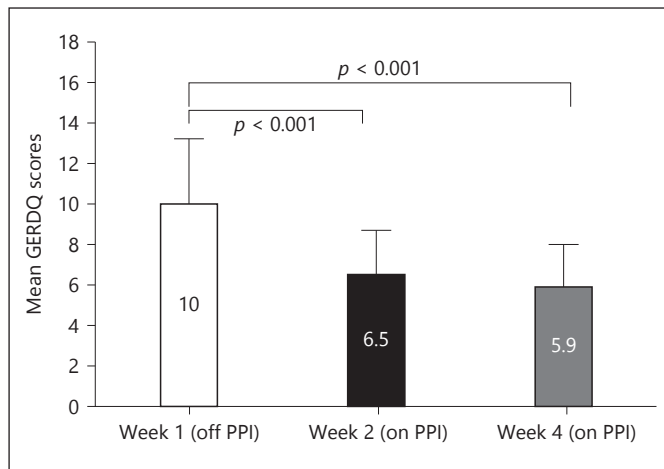


Fig. 4. Mean GERDQ scores on week 1, 2, and 4. GERDQ, gastroesophageal reflux disease questionnaire; PPI, proton pump inhibitor.

meal (62.5% of patients reported regular consumption) did not appear to impact the frequency of heartburn during week 1. Based on pill counts at day 14 and 28, all patients were adherent to treatment (>80% of pills consumed as instructed). There were no significant adverse events noted. One patient (3.1%) reported nausea at week 3.

Discussion

Around 1.8 billion Muslim adherents are estimated to constitute around 24% of the world's population [4]. Every year, during the month of Ramadan, observant Muslims fast for around 28–30 days (1 lunar month) that results in significant changes in both lifestyle and diet. GERD is reported to affect around 10–20% of the world population [4, 5] and around 6% had clinically troublesome heartburn symptoms [4]. These estimates make GERD a burden not only in the general population but also in Muslims planning to fast during the month of Ramadan. Although PPIs are well established in the treatment of heartburn [4], there have been no studies that document its effect during Ramadan.

In this study, we show that dexlansoprazole has a significant effect in reducing heartburn symptoms during the Ramadan month. The rapid onset of relief shortly after starting treatment in the second week of Ramadan is evidenced by significant improvement in mean 24FH% compared to baseline. This rapid response was more pronounced in patients with high probability of GERD, that

is, those with GERDQ scores ≥ 8 . Furthermore, patients who continued to have heartburn during week 2 reported significant improvement in the severity of their symptoms. Importantly, the response to dexlansoprazole continued to improve over time shown by further benefit in week 4 compared to week 2. These results support the role of a PPI with an advanced mode of action and release in patients who suffer from gastroesophageal reflux during the Ramadan month. Moreover, the reduction in GERDQ scores after the initiation of dexlansoprazole is indicative of an improvement in a number of patient-related symptoms inherent to the GERDQ questionnaire, namely heartburn, regurgitation, disrupted sleep, and the need to take additional medicine for symptom relief. However, we did not specifically collect information on improvement in quality of life during the trial.

Our study has some key strengths and few limitations. The screening of eligible subjects and the careful baseline assessment, including the validated GERDQ questionnaire, improved the identification of subjects with GERD. In support of this is the small number of subjects with low probability GERDQ scores < 8 (25%) and the high prevalence of heartburn at baseline assessment and during the first non-intervention week of the study (only 1 patient reported no episodes of heartburn during that week). An important strength of the study is the close follow-up of study subjects via daily SMS reminders and diary feedback using a web-based application with live dashboard monitoring of response resulting in daily assessment of symptoms without recall bias or missing data. This is further demonstrated by the high adherence rate. The study limitations include the small sample size, open-label nature of the study, and the lack of a placebo arm and/or investigator blinding which may increase the risk of bias and inflate the response rate. However, the time-sensitive nature of the study and the limited window of recruitment made difficult the identification of a large number of healthy subjects with frequent heartburn willing to participate in a randomized placebo-controlled trial. Moreover, no placebo medication was given to patients during their first week. Instead, patients were just asked to start their medication on the 8th day of the fasting month. Further, the limited period of study (1 month in this case) restricted the baseline observation period to 1 week (week 1 of Ramadan) and the active therapy period to 3 weeks, and which unlike most GERD intervention studies, lead to a restricted weekly assessment of response. Another limitation is the recruitment of patients based primarily on the presence of heartburn, the cardinal symptom of GERD, without baseline endoscopic or pH-

metric assessment of GERD. This in fact was the reason for the selection of the dose of dexlansoprazole approved for the treatment of erosive esophagitis (60 mg) in order to avoid undertreating patients. Lastly, certain confounding factors including, but not limited to, the duration of prior PPI therapy was not measured or accounted for and this could have affected the results. Despite the absence of other similar studies on GERD in Ramadan, it is conceivable that other PPIs could be as effective as dexlansoprazole in this setting.

In conclusion, despite being an open label trial subject to placebo effect, this study demonstrates the efficacy of dexlansoprazole 60 mg in the treatment of gastroesophageal reflux during the fasting month of Ramadan. The rapid onset of symptomatic relief and the continued and sustained improvement during the treatment period support the use of dexlansoprazole in such patients.

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Disclosure Statement

The authors have no conflict of interest to disclose.

Authors' Contributions

H.H.R., L.B.O.R., M.A.R., R.H.S., and H.C.: Study planning, advertisement logistics, patient enrollment, regulatory administration, critical review of the manuscript. H.R. and L.B.O.R.: Data entry and analysis, drafting of the manuscript. A.I.S.: Study conception, design and supervision; oversight of data collection and interpretation of data; review of literature; drafting of the manuscript.