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ORIGINAL RESEARCH

A real-world retrospective study of omeprazole–domperidone combination in managing acid peptic disease with PRoton-pump Inhibitors in patients with type 2 DiabEtes mellitus (PRIDE-2)

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Abstract

Background: Proton-pump inhibitors, along with a prokinetic agent, are widely used to provide symptomatic relief amongst patients with acid peptic disease (APD). This article evaluates the effectiveness and safety of the omeprazole–domperidone combination amongst patients with type 2 diabetes mellitus for the management of APD.

Methods: PRIDE-2 (PRoton-pump Inhibitor in patients with type 2 DiabEtes mellitus) is a retrospective study reviewing electronic medical records of patients with type 2 diabetes mellitus and APD who were receiving the omeprazole–domperidone combination and visiting multiple Indian healthcare settings between March 2018 and April 2021. The effectiveness outcome of the therapy was evaluated in terms of resolution of APD symptoms at visit 5 (120 days after baseline visit) compared with visit 1 (baseline visit). Safety was determined in terms of reported adverse events (AEs) during the treatment period (120 days).

Results: A total of 174 patients were included in the study. The mean age of the patients was 51.5±9.6 years, with the majority (59.8%) being men. A significant proportion of patients reported relief from APD symptoms, including abdominal pain (91.6%), epigastric burning (68.7%), nausea (89.5%), flatulence (100.0%), loss of appetite (93.6%), and altered bowel movements (94.7%) (p<0.001 for each) at visit 5 compared with visit 1. No serious AEs were reported.

Conclusion: Omeprazole–domperidone combination was beneficial in providing symptomatic relief to patients with diabetes and APD. The combination therapy was well tolerated, with few reports of minor AEs.

Keywords: acid peptic disease, domperidone, omeprazole, proton-pump inhibitors, symptomatic relief, type 2 diabetes mellitus.

Citation

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Introduction

Acid peptic disease (APD) encompasses a group of gastrointestinal tract disorders, majorly including gastroesophageal reflux disease (GERD), peptic ulcer disease and dyspepsia. It eventuates either due to compromised mucosal defences or enhanced acid secretion.[1] APD is a common disorder afflicting millions of people globally and a major cause of mortality and morbidity.[2] Type 2 diabetes mellitus (T2DM) is also an eminent public health problem that is escalating at an unprecedented rate. According to International Diabetes Federation, 537 million adults are currently living with diabetes mellitus (DM) worldwide.[3] In addition to well-established risks for microvascular and macrovascular complications

amongst patients with DM, DM has also been recognized as a risk factor for complicated APD.[4] Damage to the enteric nervous system due to irreversible autonomic neuropathy or oxidative stress is believed to be the causal or contributing factor for gastrointestinal dysfunction amongst patients with DM.[5] The remarkable changes that are frequently observed in patients with DM are decreased gastric secretion and motility.[6] Nearly 75% of patients with DM confront some form of gastrointestinal dysfunction due to altered gut motility.[7] The prevalence of oesophageal dysmotility and GERD symptoms in patients with DM is reported to be as high as 63% and 41%, respectively.[8,9]

Acid-related diseases significantly impact patient quality of life and productivity.[1] Common APD complaints encompass acid reflux, regurgitation, chest pain, cough and dysphagia.[10] Other frequent symptoms include headache, dizziness, diarrhoea, abdominal pain, constipation, nausea, vomiting and flatulence.[11,12]

Proton-pump inhibitors (PPIs) are the preferred therapy for acid-related diseases, as they are potent inhibitors of gastric acid secretion.[1] PPIs specifically inhibit H^+/K^+-ATPase pumps, leading to irreversible inhibition of gastric acid secretion.[13] Omeprazole is the first congener of PPIs, and its effectiveness in the management of acid-related diseases is well recognized.[14] Further, coadministration of a prokinetic agent along with PPIs allows their swift passage to the upper intestine, thus preventing impaired acid suppression by avoiding the retention of PPIs in the stomach. Amongst prokinetic agents, domperidone has fewer side-effects, a better cardiac safety profile[15] and significantly improves gastrointestinal tract symptoms.[16] Besides managing gastric complications related to DM, PPIs have also exhibited their role in improving glycaemic control probably by increasing the serum gastrin concentration, thus affecting glucose metabolism through the promotion of β-cell regeneration/expansion and enhancement of insulin secretion.[17,18]

Although PPIs in combination with prokinetic agents have been widely used in patients with APD, studies assessing the effectiveness and safety of these agents in patients with DM when prescribed along with antidiabetic medications are limited. Therefore, the PRIDE-2 study was conducted to envisage the safety and effectiveness of the omeprazole–domperidone combination in managing APD amongst patients with T2DM on fixed antidiabetic therapy in real-world Indian settings.

Methods

This retrospective, observational study included patients who visited outpatient settings of healthcare setups located in three Indian states between March 2018 and April 2021. Data from electronic medical records (EMRs) of patients with T2DM and APD were collected from these healthcare settings.

Study population

Patients with T2DM aged ≥18 years with newly diagnosed APD and who were receiving fixed oral hypoglycaemic agents (OHAs) for a minimum of 3 months before visit 1 (baseline visit) were considered. Patients who were prescribed omeprazole–domperidone combination for APD for a minimum of 4 weeks were included in the PRIDE-2 study. Patients with type 1 DM or gestational DM, patients receiving insulin or other injectables, and patients with T2DM prescribed H_2-receptor antagonists or other PPIs for treatment of APD were excluded.

Study outcomes

The study outcomes were evaluated at visit 0 (90 days before visit 1), visit 1 (index visit), and visits 2, 3, 4 and 5 (i.e. at 30, 60, 90 and 120 days post-index period, which is the period after the index visit). The primary outcome of the study was to evaluate the clinical improvement, defined as symptomatic relief or the resolution of symptoms of APD (e.g. pain in the abdomen, epigastric burning, nausea, flatulence, loss of appetite and altered bowel movements) at visit 5 compared with visit 1. Safety was evaluated by determining the number of adverse events reported during the study period. The secondary outcome was the impact of omeprazole–domperidone combination on glycaemic control. The effect of therapy on glycaemic control was determined in terms of the mean percentage reduction in glycaemic parameters, including HbA1c, fasting blood sugar (FBS), post-prandial blood sugar (PPBS) and random blood sugar, at visit 1 compared with visit 0, and at visit 5 compared to visit 1.

Statistical analysis

Data were analysed using R studio 1.2.1335. Continuous variables (like age and duration) were described as mean and compared using the *t*-test/Mann–Whitney *U* test. Categorical variables (e.g. sex and city/state) were presented as percentage/proportions and compared using the χ^2 test/Fisher's exact test. A p value of ≤0.05 was considered statistically significant.

Ethics

Patient confidentiality was retained using anonymized and de-identified data at the source level. Data collection was conducted as per the protocol and applicable ethical and regulatory guidelines, including the Declaration of Helsinki, Schedule Y, Indian GCP, and ICH-GCP. The PRIDE-2 study was approved by Royal Pune Independent Ethics Committee (on 18 August 2021, Approval Letter No. RPIEC 150821).

Informed consent

Being a retrospective study, only anonymized and de-identified data were used. Therefore, as per the Declaration of Helsinki, the study does not necessitate the obligation to obtain informed consent because the study does not involve identifiable individuals. Patient informed consent waiver was obtained from the Royal Pune Independent Ethics Committee.

Results

Baseline characteristics

A total of 174 patients with T2DM and APD were included in the study. Mean age was 51.5±9.6 years, and the majority were men (104; 59.8%). Other baseline characteristics of patients included in the study are provided in Table 1. Several patients were known to have multiple comorbidities; most had cardiovascular comorbidity (53.3%). Further, some concomitant medications were also reported to be taken by the patients during the study period. Cardiovascular drugs (56.0%) were the most-often used concomitant drugs, followed by endocrine drugs (40.0%) and diuretics (4.0%). Additionally, patients were taking fixed OHAs, including the combination of metformin and glimepiride (62.6%), metformin and vildagliptin/sitagliptin (23.6%), and metformin monotherapy (13.8%).

Table 1. Baseline characteristics (*n*=174).

Parameter	Variable
Age, years	51.52±9.60
Height, cm	165.27±9.56
Weight, kg	73.18±11.89
Pulse, bpm	80.86±7.11
Body temperature (°C)	36.6±0.50
Systolic blood pressure, mmHg	126.76±11.81
Diastolic blood pressure, mmHg	79.12±6.74
Sex	
Men	104 (59.80%)
Women	70 (40.20%)
State	
Gujarat	80 (46.00%)
Maharashtra	68 (39.10%)
Madhya Pradesh	26 (15.00%)
Oral hypoglycaemic agents	
Metformin + glimepiride	109 (62.64%)
Metformin + vildagliptin/sitagliptin	41 (23.56%)
Metformin	24 (13.79%)
Comorbidities	
Cardiovascular	57 (53.27%)
Respiratory	3 (2.80%)
Neurological	2 (1.86%)
Orthopaedic	2 (1.86%)
Others	43 (40.18%)
Concomitant medications	
Cardiovascular	28 (56.00%)
Endocrine	20 (40.00%)
Diuretic	2 (4.00%)

Effectiveness

Symptomatic relief

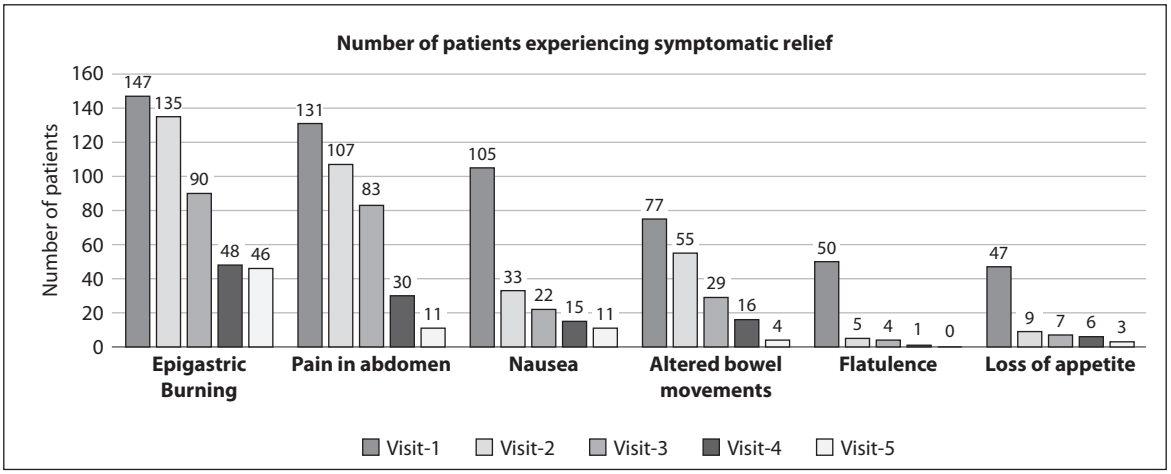
The effectiveness outcome of the omeprazole–domperidone combination was assessed by determining the number of patients who experienced resolution of symptoms at visit 5 in relation to visit 1. Patients chiefly complained about epigastric burning (84.5%) and pain in the abdomen (75.3%) at visit 1. Some patients also complained about nausea (60.3%), altered bowel movements (43.1%), flatulence (28.7%) and loss of appetite (27.0%).

The number of patients experiencing epigastric burning was decreased from 147 (at visit 1) to 46 (at visit 5), with 68.7% of patients having symptomatic relief ($p<0.001$). Pain in the abdomen was reported by 131 patients at visit 1, and the number gradually reduced to 11 at visit 5, demonstrating that the symptom was resolved in 91.6% of patients ($p<0.001$). The number of patients who reported nausea declined from 105 (at visit 1) to 11 (at visit 5), indicating that 89.5% of patients achieved relief ($p<0.001$). The number of patients complaining about altered bowel movements declined from 75 to 4 at visit 5 compared to visit 1; 94.7% achieved symptomatic relief ($p<0.001$). Flatulence was resolved in all the patients (100.0%) at visit 5 ($p<0.001$). Symptomatic resolution of loss of appetite was reported in 93.6% of patients, as the number of patients experiencing loss of appetite was reduced from 47 to 3 at visit 5 compared to visit 1 ($p<0.001$) (Figure 1).

Glycaemic control

The percentage decrease in mean HbA1c levels was noted to be 9.47% from visits 0 to 1, that is, before initiating the omeprazole–domperidone combination, whilst patients were receiving only OHAs ($p<0.001$). A further significant reduction of 6.8% (from visits 1 to 5; $p<0.001$) was observed whilst patients were taking OHAs along with the omeprazole–domperidone combination.

Figure 1. Effectiveness of omeprazole–domperidone combination with regards to symptom relief.



Similarly, the percentage reduction in mean FBS level was found to be 16.8% from visits 0 to 1 (p<0.001) with a subsequent reduction of 11.5% from visits 1 to 5 (p<0.001). A marked reduction of 22.4% was observed in mean PPBS levels from visits 0 to 1 (p<0.001), followed by a further decrease of 11.5% from visits 1 to 5 (p<0.001). The reduction in random blood sugar levels was recorded to be 17.8% from visits 0 to 1 (p<0.001) with an ensued reduction of 9.7% (visit 1 to 5; p<0.001).

Tolerability

Omeprazole–domperidone combination was well tolerated in patients with T2DM and APD as, out of a total of 174 patients, only 2 (1.1%) patients reported side-effects, including muscle and bone pain.

Discussion

The findings of the PRIDE-2 study demonstrated that the omeprazole–domperidone combination provides significant relief for APD-associated symptoms like epigastric burning, pain in the abdomen, nausea, altered bowel movements, flatulence and loss of appetite in patients with T2DM. These findings aligned with the evidence available in the literature that exhibited the omeprazole–domperidone combination to be well tolerated and effective in acid-related diseases. In a randomized controlled study, treatment with omeprazole–domperidone combination for 8 weeks provided significant reduction in heartburn severity amongst patients with GERD (n=60) as the Visual Analogue Scale (VAS) score was observed to decline from 77.9±11.7 (before treatment) to 1.7±3.30 (after treatment) (p=0.000). Further, complete cupping of reflux symptoms (83.3%) and healing of oesophagitis (92%) was found after treatment amongst these patients.[19] Another study demonstrated the effectiveness of the omeprazole–domperidone combination by significantly improving the VAS scores of clinical symptoms like swelling, pain, burning sensation and sour regurgitation of the upper abdomen amongst patients with chronic gastritis (n=48) after a treatment period of 3 weeks.[20] Similarly, a meta-analysis (16 studies) including 1,446 patients reported that the combination of PPIs and prokinetics resulted in a noteworthy reduction in global symptoms of GERD irrespective of the prokinetic type.[21]

During the current study period, no major side-effects were observed; hence, the omeprazole–domperidone combination was stated to be relatively safe when prescribed with OHAs. These findings were consistent with the observations of a phase IV study that the combination of omeprazole and domperidone was well tolerated as only minor side-effects, like breast swelling and headache, were reported amongst patients with GERD.[19] Further, various studies have demonstrated a good safety profile of both drugs individually.[22,23] In a pooled data study of published trials including 2,812 patients, omeprazole was stated to cause only minor side-effects like headache, diarrhoea, nausea, and rash.[22] Similarly, a retrospective review of nearly 100 patients suffering from gastroparesis and receiving domperidone summarized the drug to be well tolerated.[23] Further, domperidone is reported to possess a better cardiac safety profile as compared to other prokinetics; all the prokinetics are classified as prescription-only drugs in most countries, including India, due to concerns regarding cardiac adverse effects.[15]

In the present study, a significant reduction was observed in glycaemic parameters from visits 0 to 1, which

can be attributed to the action of OHAs. However, the reason behind the subsequent improvement in glycaemic parameters (from visits 1 to 5) might be the addition of omeprazole to the existing drug regimen of OHAs. In consonance with the findings of the present study, a study also reported a pronounced improvement in glycaemic parameters like HbA1c, FBS and PPBS in patients with T2DM after receiving a PPI for 24 weeks.[24] Likewise, a retrospective study demonstrated significantly lower values of average HbA1c (7.0%) amongst patients taking concurrent PPIs as compared to patients who had not (7.6%).[25] Although some findings have indicated the role of PPIs in improving glycaemic control, further randomized controlled studies including a large number of patients are indispensable to confirm their clinical effect.

Limitations

Due to its retrospective nature and small sample size, the scope of the present study was limited to the information available in existing database records.

Conclusion

The omeprazole–domperidone combination demonstrated significant effectiveness in providing relief from symptoms associated with APD amongst patients with T2DM. The combination was observed to be well tolerated and can be safely used in patients with T2DM and APD receiving OHAs. Further, an improvement in glycaemic parameters was also observed in these patients, which has to be validated by further randomized controlled studies.

Contributions: The authors' responsibilities were as follows: Authors from Dr. Reddy's Laboratories (AUP, KCV, CSP, AM, RR and BK) contributed towards conceptualizing the study hypothesis, design of the study, data analysis and interpretation of study outcomes, and compiling the manuscript. BS and NM significantly contributed to revising the manuscript critically for important intellectual content and final approval and review. All authors read and approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: AUP, KCV and CSP are the Medical Advisor, Team Lead and Clinical Research Specialist, respectively, at Medical Affairs Department, Dr. Reddy's Laboratories Ltd, Hyderabad. AM, RR and BK are Medical Cluster Head, Head Ideation & Clinical Research and Head Medical Affairs, respectively, at the Medical Affairs Department, Dr. Reddy's Laboratories Ltd, Hyderabad. BS and NM have no conflicts of interest to disclose. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2023/01/dic.2022-10-3-COI.pdf

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