



## COMPARATIVE EVALUATION OF THE EFFICACY AND TOLERABILITY OF ITOPRIDE HYDROCHLORIDE AND DOMPERIDONE IN PATIENTS WITH NON-ULCER DYSPEPSIA AT JLNMC, BHAGALPUR, BIHAR

### Pharmacology

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### ABSTRACT

**Background :** Prokinetic drugs are widely used for treatment of non-ulcer dyspepsia (NUD).

**Aims and Objectives :** To assess the efficacy and tolerability of a new prokinetic agent, itopride hydrochloride in patients of NUD and compare it with domperidone.

**Methods :** Fifty-six patients who fulfilled the inclusion and exclusion criteria were enrolled in the study. Patients underwent upper gastrointestinal endoscopy to rule out organic pathology as a cause for their symptoms. The patient's symptoms were graded on a 4-point scale (0 to 3) at the beginning of treatment and at the end of Week-one and Week-two. Patients were randomly allocated to receive either one tablet of itopride hydrochloride 50mg three times daily or one tablet of domperidone 10mg three times daily for two weeks. Pre-treatment and post-treatment hemogram, liver function and renal function tests, prolactin level and ECG were done in all patients. The response to therapy was evaluated by assessing the relief of symptoms at the end of two weeks on a 5 -point scale. Statistical analysis was done using two-tailed paired t-test; Wilcoxon matched pairs ranks sum test, Mann-Whitney-U test and chi-square test as applicable.

**Results :** Of the fifty-five patients enrolled in the study (age range of 18-60 yrs, median age of 35yrs), 26 were males and twenty nine were females. They had a median duration of symptoms for 4 weeks. Twenty-seven patients received itopride and 28 received domperidone. One patient did not follow up in the domperidone group, thus 54 patients were evaluable for analysis. Moderate to complete symptomatic relief was observed in 22 (81%) patients in the itopride group and 19 patients (70%) in the domperidone group ( $p > 0.05$ , NS). Both the drugs were well tolerated and neither caused prolongation of QT interval nor any abnormality in any serum biochemistry values.

**Conclusion :** Therapy with itopride resulted in good symptomatic relief, was safe, well tolerated and comparable in efficacy to domperidone in relieving the symptoms of NUD. By virtue of its efficacy and tolerability, it could be an ideal choice for providing symptomatic relief to patients suffering from non-ulcer dyspepsia.

### KEYWORDS

#### INTRODUCTION

Prokinetic drugs like metoclopramide, cisapride and domperidone enhance gastric emptying, prevent retention and reflux of acid or food and relieve symptoms of dyspepsia. However, metoclopramide causes dystonic reactions and drowsiness, while domperidone has been reported to cause galactorrhoea and gynaecomastia. Cisapride has the potential to prolong the QT interval in the ECG, and rare but serious cardiac arrhythmias have been reported. This has prompted the search for newer agents with equal efficacy but lower side effect potential. Itopride hydrochloride, a new prokinetic drug, has been reported to improve gastrointestinal motility by a dual mode of action, i.e. by inhibiting the action of dopamine on the D<sub>2</sub> receptors on the post-synaptic cholinergic nerves and by stimulating the release of acetylcholine in the myenteric plexus. It also prevents the hydrolysis of the released acetylcholine by the enzyme acetylcholinesterase. Unlike cisapride, it has no affinity for the 5-HT<sub>4</sub> receptors in the heart that are implicated in the undesirable cardiac effects of cisapride.

#### AIM AND OBJECTIVES

The present study was undertaken to compare the efficacy and safety of itopride as compared to domperidone in patients suffering from non-ulcer dyspepsia.

#### MATERIALS AND METHODS

This study was conducted at Department of Pharmacology, Jawaharlal Nehru Medical College, Bhagalpur, Bihar. Patients selected from Medicine department of JLNMC.

Patients aged 18 to 60 years, and presenting with complaints of non-ulcer dyspepsia like epigastric distension or pain, nausea, heartburn, anorexia were screened for the study after taking their informed consent. Patients with endoscopic evidence of ulcer disease, severe oesophagitis, or with history of chronic intake of non-steroidal anti-

inflammatory drugs, anticoagulants, and acid suppressants were excluded from the study. Pregnant and lactating women and persons suffering from any systemic disease were not included in the study.

Patients were randomly allocated to receive either one tablet of itopride hydrochloride, 50 mg, three times daily or one tablet of domperidone 10 mg, (Nausidome) three times a day 15 - 30 minutes before food for 2 weeks. Concomitant medication with any other prokinetic drug, antacids, enzyme preparations, H<sub>2</sub>- blockers or proton-pump inhibitors was not permitted during the study period. They were advised to avoid alcohol and smoking during the study period.

Patients' symptoms were graded on a 4-point scale (0 to 3) as 0- no symptom, 1- mild symptoms, 2-moderate symptoms and 3-severe symptoms prior to treatment. Symptoms were re-evaluated one and two weeks later. Following treatment, relief of symptoms was assessed at the end of 2 weeks on a 5 -point scale (1 to 5) as: 1- marked or complete relief of symptoms, 2- moderate relief of symptoms, 3- slight relief of symptoms, 4- no relief, 5- worsening of symptoms.

A 12-lead ECG was done on each patient at the screening visit to exclude QT prolongation, and at the end of 2 weeks to detect any effect of itopride or domperidone on the QT interval. Biochemical investigation like complete hemogram, blood urea, serum creatinine, liver function tests, prolactin level were done at the screening visit and at the end of treatment. Clinical adverse events, if any, were recorded at the end of week 1 and week 2, along with their nature, intensity, action taken and outcome. Data are presented as Mean  $\pm$  SD. Scores for the symptoms are presented as median (range). Statistical analysis was done using two-tailed paired t-test, Wilcoxon-matched pairs rank sum test, Mann-Whitney test and chi-square test as applicable.

## RESULTS

Of the 55 patients enrolled in the study, 26 were males and 29 were females. Their median age was 35 years, median weight 50 kg and median duration of complaints, 4 weeks. Twenty-seven patients were assigned itopride and 28 received domperidone. One patient from the domperidone group was lost to follow-up. The patients were matched for age and body weight. Four patients in the itopride group and two in the domperidone group had a history of smoking. Six patients in the itopride group and two in the domperidone group had a history of alcohol intake. One patient in the itopride group and none in the domperidone group had a history of intake of ulcerogenic drugs. Dietary history revealed that diet was spicy in 14 patients in the itopride group and in 19 patients in the domperidone group. Only one patient in the itopride group had a history of intake of very spicy diet. The remaining patients in both the groups consumed a mild, non-spicy diet. Only one patient in the domperidone group had a history of TB lymphadenitis for which he was receiving therapy.

At baseline, the median scores were mild to moderate in both the groups. Following therapy the median scores for the individual symptoms declined significantly in both the groups. However, the difference in the decline of scores between the groups was not significant.

Symptomatic relief was moderate to complete in 22 (81%) patients on itopride and in 19 patients (70%) on domperidone group ( $P=0.52$ )

Two adverse events were reported by one patient in each group, fever by a patient receiving itopride, and drowsiness by one patient receiving domperidone. Both were mild and subsided without interfering with continuation of the treatment. Clinical tolerability was good to excellent in all the patients.

The mean values of serum biochemistry tests at baseline and at the end of two weeks therapy are depicted in Table 1. At baseline, all the patients in both the groups had a normal serum biochemistry profile. Therapy with both the drugs did not produce any abnormalities in serum biochemistry profile at the end of two weeks' therapy. At baseline, none of the patients showed any prolongation of the QT interval. Therapy with both the drugs was well tolerated and none of the patients showed any prolongation of QT interval in the post-treatment ECG from either group.

**Table 1 : Effect on therapy on serum biochemistry and QT interval**

Parameter	Itopride Group Pre-Rx	Itopride Group Post-Rx	Domperidone Group Pre-Rx	Domperidone Group Post-Rx
Hb (gm/dL)	12.2±1.76	12.0±2.05	11.55±2.05	11.49±1.98
WBC-T/C(umm)	8885±2412	8600±2158	8100±2827	8500±2479
BUN (mg/ml)	8.11±1.45	8.16±1.57	8.2±1.51	9.07±2.25
Creat. (mg/ml)	0.8±0.1	0.81±0.11	0.79±0.11	0.79±0.11
AST (U/L)	27.62±9.17	27.25±10.16	25.85±8.19	23.74±6.93
ALT (U/L)	30.11±9.02	29.92±10.16	30.67±8.19	29.11±6.93
$\gamma$ -GT (Units)	30.14±12.5	33.21±10.2	24.66±18.9	26.0±19.6
Alk. Phos. (U/L)	133±23.5	143±25.5	134.8±28.2	129.11±32.8
Bilirubin (mg/dl)	0.97±0.3	0.96±0.2	0.94±0.1	0.89±0.1
Prolactin (ng/ml)	10.6±5.4	10.7±5.1	9.2±3.0	8.4±3.1
Total chol. (mg/dl)	166.1±46.6	163.4±33.9	168.6±32.8	160.8±27.9
FBS (mg/dl)	81.8±18.1	85.96±8.3	82.1±9.2	81.8±8.2
QT interval (millisec.)	0.34±0.044	0.34±0.042	0.32±0.055	0.31±0.046

$P>0.05$  for all values in both groups. Test: 2-way paired t-test

## DISCUSSION

Itopride is a novel prokinetic drug with dual mode of action. In present study, efficacy of itopride (81%) was comparable to domperidone (70%) in relieving the symptoms of NUD. Both the drugs were clinically and biochemically well tolerated. We did not find any remarkable rise of prolactin level, or any changes in the QT interval in

both the study groups. Other investigators have reported similar efficacy without adverse cardiac side effects in patients treated with itopride.

Following the withdrawal of cisapride due to its cardiac side effects, mosapride is widely used and believed to be devoid of pro-arrhythmic potential. However in one case report, mosapride has been shown to give rise to torsades de pointes when used along with flecainide. Cisapride and mosapride share the same metabolic pathway (cytochrome P450 enzyme system) and have been reported to have drug interaction potential with other commonly used drugs like macrolides, antifungals, etc. On the other hand, itopride is metabolized by a different pathway (flavin mono-oxygenase system), and thus reported to be devoid of significant drug interaction potential. In the present study also we did not encounter any cardiac side effects with itopride. However, since we have not included any patient with QT abnormality and with concomitant drug ingestion, further studies with itopride in high risk groups would be needed.

## CONCLUSION

Thus, from our preliminary observations, we conclude that, therapy with itopride, a new prokinetic agent, resulted in good symptomatic relief in patients with NUD. It was comparable in efficacy to domperidone in relieving symptoms, was well tolerated and devoid of cardiac side-effects in the present study.

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