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EFFICACY AND NEUROLOGICAL SIDE EFFECTS OF PRUCALOPRIDE IN ADULTS WITH CHRONIC IDIOPATHIC CONSTIPATION

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ABSTRACT
Prucalopride is a 5 HT-4 receptor agonist used for the treatment of laxative resistant Chronic Idiopathic Constipation (CIC). CIC is a common condition defined by infrequent stools, difficulty in passing stools without any underlying cause and it was diagnosed based on Rome IV criteria. The clinical efficacy of Prucalopride was found to be > 3SCBMs (Spontaneous complete bowel movements)/ week over 4week treatment. The most common treatment associated side effects are head ache, nausea, vomiting, abdominal pain and cramps. The neurological side effects including suicidal ideation, visual hallucination, loss of memory are also reported and it was evaluated using PHQ (Patient health questionnaire) Questionnaire. This is an observational cohort study conducted over a period of 6 months in the gastroenterology department of a tertiary care hospital. A total of 100 patients satisfying inclusion criteria was analysed. Case records was prospectively reviewed for evaluating the efficacy of the treatment and the neurological side effects was evaluated using PHQ questionnaire. Data analysis was conducted using Python libraries including SciPy, Pandas, Numpy. The study was conducted to evaluate the efficacy of prucalopride and its possibility to develop neurological side effects. The 59 % of the total population has their SCBM increased more than 3 per week over 4week treatment and no evidence of neurological side effects were identified. Prucalopride can exhibit disease modifying properties (>3SCBM/week over 4week treatment) in patients with CIC when other laxatives are failed to produce the effect. This provides an important advancement in treating the disease. In our study the evidence of neurological side effects were not reported and further studies are needed to conduct in more sample size inorder to confirm the effect.

KEYWORDS: Prucalopride, Chronic Idiopathic Constipation (CIC), Spontaneous Complete bowel movement (SCBM), Laxatives.

INTRODUCTION
Chronic Idiopathic Constipation(CIC) is a common gastrointestinal problem results in infrequent stools, difficulty in passing stools with pain and stiffness that occur without any underlying cause.[1] The CIC is assessed by means of passing fewer than 3 spontaneous complete bowel movements(SCBM) per week for more than 6 months.[2] According to Rome VI criteria two or more of the symptoms for 12 weeks that defines constipation includes at least 25% of defecation, straining lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal blockage, manual maneuvers to facilitate defecations, fewer than three defecations per week.[3-5] The three subtypes of CIC includes Normal transit constipation(NTC), Slow transit constipation(STC), Disorders of defecation (DD).In normal transit constipation the stool become harder but it moves through the colon at a normal rate along with abdominal pain and bloating. In slow transit constipation the stool moves through the colon slowly along with abdominal bloating and pain. The disorders of defecation include rectocele, rectal prolapse, and dysynergic function.[5] The CIC can be caused by medications such as antacids, iron supplements, antidiarrheal agents, anti-parkinsonism agents, calcium channel blockers, tricyclic antidepressants etc and certain medical conditions includes cerebrovascular disease, autoimmune neuropathy, multiple sclerosis etc.[6]

The pharmacological treatment of CIC includes bulk laxatives, osmotic agents, stimulant laxatives etc. The 5 HT-4 receptor agonists are mainly preferred for the treatment of CIC. Cisapride is the first drug introduced in this class but withdrawn from the market in 2000 due to occurrence of cardiac arrhythmias.[7] It occurs due to the interaction of the drug with cardiac human ether a–go-go (hERG) encoded potassium channels results in the blocking of these channels leads to the prolongation of QT interval. Tegaserod is an another partial 5-HT 4

agonist was also withdrawn from the market in 2007 due to the occurrence of ischemic cardiac events.[8]

Prucalopride is a Dihydrobenzofurancarboxamide derivative from benzofuran family selectively stimulates 5 –HT4 receptors and promotes enterokinetic properties.[9] It was developed by Shire Development LLC and approved for use in Europe in 2009 in Canada on December 7, 2011. Then on December 14, 2018 the Food and drug administration (FDA) approved Prucalopride (trade name Motegrity) for the treatment of Chronic Idiopathic Constipation.[10] It was used in the condition were other laxatives failed to produce adequate relief and it does not interact with hERG encoded potassium channels. The primary efficacy end point of Prucalopride is calculated on the basis > 3SCBMs / week over 4week treatment.[11] The mechanism of action of Prucalopride enhances the propulsive motor actions by interacting with the 5 HT 4 receptors present in the gastrointestinal tissues and it has lesser affinity towards 5 HT 1,2 receptors so that there is no significant cardiac side effects. The most common treatment associated side effects are head ache, nausea, vomiting, abdominal pain and cramps. Increased risk of suicidal ideation and behavioral thoughts are also reported as warning drug information in patient taking Motegrity. The available strengths of Prucalopride are 1mg, 2mg and 4 mg which is administered once daily. It is contraindicated in Chron's disease and Ulcerative colitis.[12] The pharmacokinetic properties of Prucalopride shows that it has a bioavailability of >90%. It has a steady state volume of distribution of 567 litres after intravenous administration and a plasma protein binding of 30%. The plasma clearance is about 317 ml/min and the route of elimination was renal excretion.

Long term studies and post marketing data's reveals that Prucalopride is a promising compound or a new therapeutic alternative in the treatment of CIC in adults were other laxatives failed to produce prokinetic effects.[13] Hence Prucalopride is a clinically beneficial pharmacotherapy for the treatment of laxative resistant Chronic Idiopathic Constipation.[14]

MATERIALS AND METHODS

This was an observational Cohort study conducted at a tertiary care hospital, Ernakulam. Approval from Institutional Ethical Committee was obtained prior to the study. Patients diagnosed with Chronic idiopathic constipation and treated with the drug Prucalopride was identified from the gastroenterology department. A study population including all patients with chronic idiopathic constipation treated with Prucalopride from June 2019 to February 2020 are enrolled in the study. Case records was reviewed prospectively for evaluating the efficacy of the treatment and the occurrences of neurological side effects was evaluated by providing PHQ questionnaire. The efficacy was evaluated by considering spontaneous complete bowel movement greater than three per week over 4week treatment. Data analysis was conducted using Python libraries including SciPy, Pandas, Numpy. Statistical Analysis was done by using Exploratory data analysis, Mann-Whitney U test, Kruskal–Wallis test, Wilcoxan Signed Rank test.

RESULTS AND DISCUSSION

This observational cohort study was carried out for a period of 6 months in the gastroenterology department of a tertiary care hospital in Kerala. The study was conducted to evaluate the clinical efficacy of Prucalopride in adults with CIC were other laxatives failed to produce the effect and to identify the occurrence of neurological side effects. A total of 100 patients was selected for our study based on inclusion and exclusion criteria.

Exploratory Data Analysis (EDA) was used here that refers to the critical process of performing initial investigations on data so as to discover patterns, to spot anomalies, to test hypothesis and to check assumptions with help of summary statistics and graphical representation.

Here, the study of prucalopride efficacy will help to determine whether this drug administered over 3 weeks exhibits disease modifying properties (SCBM >3 per week) in CIC when other laxatives are failed to produce the effect.

The analysis is mainly divided into two parts

- Descriptive part
- Inferential part

In the descriptive part, we described the patient's age wise characteristics, gender wise characteristics and the duration of the treatment. In the inferential part, we compared the effect of drug in different age wise, gender wise and during different periods of treatment. The reports illustrates that most of the cases were reported between the age group 14- 47 including 42% youth, 34 % middle aged, 24 % elderly (Table:1). Among 100, 67 % of patients diagnosed in the study were males and the remaining 33% were females.

The 59% of study population has undergone the treatment only for 4weeks exhibits >3 SCBM /week and the remaining 27%, 14% for 6week and 8week treatment period respectively. The 59% of the patients achieved >3 SCBM/week over 4week treatment reveals primary efficacy endpoint of the drug (Table-1, Fig-1).

Table 1: Duration of treatment the study population undergone.

Duration of Treatment	Percentage
Over 4weeks	59
Over 6weeks	27
Over 8weeks	14

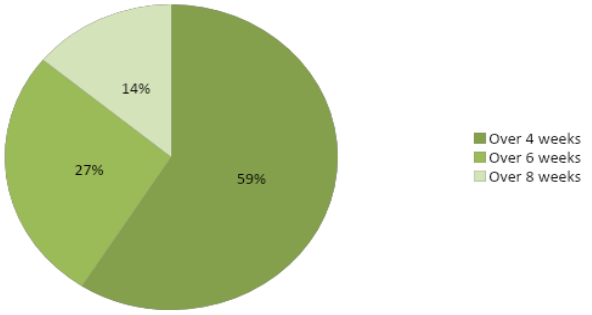

Figure 1: Duration of treatment the study population undergone.

The findings of the current study based on clinical efficacy of the drug was having a close resemblance with study conducted by Camilleri *etal*. To determine the clinical efficacy following statistical tests such as Mann-Whitney U test, Kruskal- Wallis test, Wilcoxon Signed rank tests are used. Wilcoxon signed rank test are conducted to evaluate the SCBM per week of the study population before administering Prucalopride is less than SCBM per week after 4 weeks of treatment (P Value <0.05). The results illustrates that after administering Prucalopride SCBM per week has increased. The effectiveness of the drug for 3 different duration of treatment was evaluated by performing Kruskal-Wallis H test suggests that the effect of the drug is different for at least one treatment period. The P value significance of Mann- Whitney U test suggests that the effect of Prucalopride over 6 weeks of treatment is not same as that of 8 weeks period. The administration of Prucalopride was found to be effective within 4 weeks of treatment for the study population. The 59% of the total population has their SCBM increased more than 3 per week. After 6 weeks 86% of the total population has their SCBM increased more than 3 per week. Then after 8 week the whole population has their SCBM increased more than 3 per week. Therefore, the administration of Prucalopride is found to be effective within 4 weeks of treatment for majority the study population (Table-2, Fig-2).

Table 2: SCBM per week over different durations of treatment.

Treatment Duration	Percentage of Population (scbm/week>3)	Percentage of Population (scbm/week <3)
Over 4week	59	41
Over 6week	86	14
Over 8week	100	0

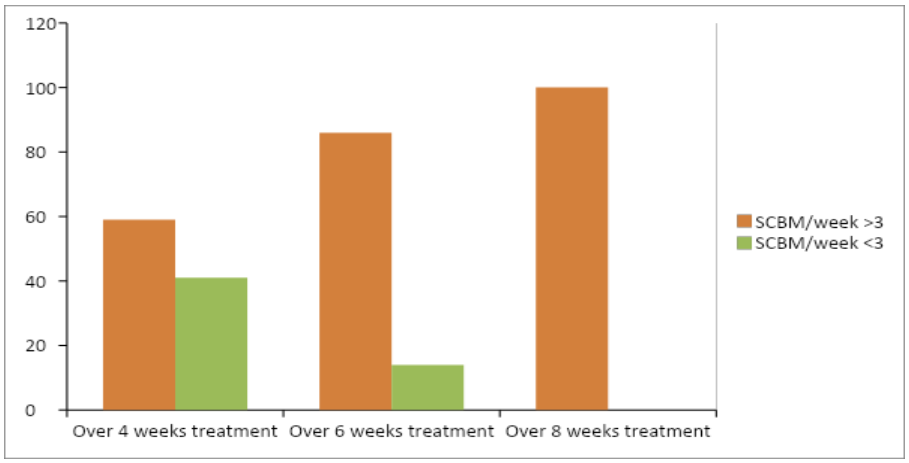

Figure 2: SCBM per week over different durations of treatment.

Determination of possibilities to develop neurological side effects provides a new safety profile for this drug. In this study no evidence of neurological side effects was identified.

CONCLUSION

Prucalopride is a selective, high affinity 5HT-4 receptor agonist used for the treatment of CIC in adults where other laxatives failed to provide adequate relief. A total of 100 patients was studied to evaluate the clinical efficacy, neurological side effects and quality of life. This study illustrates that the drug can exhibit disease modifying properties (>3 SCBM /week over 4week treatment) in patients with CIC when other laxatives failed to produce the effect. This provides an important advancement in treating the disease. The evidence of neurological side effects were not reported in this study. Thus detailed studies are required to conduct in more sample sizes inorder to confirm the occurance of neurological side effects.

Limitations of The Study

The main limitations that we encountered in our study was: -

- Limited time frame
- Few numbers of samples.

- Interrupted due to Covid -19 pandemic

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