ABSTRACT: Constipation is the irregular and difficult stool passage associated with straining or sensation of incomplete evacuation. Irritable bowel syndrome (constipation dominant) and chronic idiopathic constipation are the two most common conditions which affect around half a billion of world's population as per stats. With medical advancement and technological aid, several new drugs have been brought into practice, plecanatide being the latest which was approved by food and drug administration (FDA) in January 2017 for CIC, followed by approval for IBS-C in January 2018.

Keywords: Plecanatide, bowel relaxation, evacuation

1 Introduction

Irritable bowel disease and chronic idiopathic constipation are two of the major diseases prevalent in today's era. Several studies have been done for evaluation of various treatment modalities for the same but majority of them couldn't suffice to the expected results and efficacy and not much of relief was noticed.

CIC and IBS are believed to affect a population of 25-45 million people worldwide [1]. IBS is a mix of belly discomfort or pain and trouble with bowel habits, can be diarrheal or constipation while CIC is a functional gastrointestinal disorder with features of chronic constipation without identifiable cause and no underlying physiology.

Osmotic laxatives were ranked as first line treatment for both CIC and IBS (constipation), followed by fiber supplements/bulking agents being second line of treatment. Lactulose is a FDA (food and drug administration) approved long term treatment of chronic constipation. Earlier, lubiprostone (amitizia, sucampo AG) which is a chloride channel activator, was the only approved therapy for both, while recently FDA has approved linaclotide(linzess,allegan) a guanylate cyclase C receptor agonist, giving a newer option, for short term treatment with improvement in stool frequency, constipation severity and abdominal pain and discomfort. But small response rates, higher cost and associated adverse effects make this as second line of treatment. Others include antispasmodics for symptomatic relief but their utility is limited to anticholinergic effect, serotonin agonist relieve abdominal discomfort but not much research data is available for the same.

In Jan 2017, FDA approved plecanatide (Trulance, synergy pharmaceuticals), another GC-C agonist for the treatment of CIC in adults, which was later approved for IBS-C in January 2018 [2].

2. Pharmacokinetics

Plecanatide, structurally related to human uroguanylin, is its first analogue and functions as guanylate-C agonist [3].

Plecanatide is a 16 amino acid peptide with molecular formula C65H104N18O26S4, molecular weight1682daltons the amino acid sequence:

H-Asn1-Asp2-Glu3-Cys4-Glu5-Leu6-Cys7-Val8-Asn9-Val10-Ala11-Cys12-Thr13-Gly14-Cys15-Leu16-OH

Plecanatide is acted upon by intestinal enzymes and is converted to its active metabolites. Both of them further bind to guanylate cyclase C (GC-C) receptors and acts as its agonist on the luminal surface of the intestinal wall [3]. This results in increase in cyclic guanylase
monophosphate (cGMP). Hence increase in cyclic GMP leads to further secretion of chlorides and bicarbonates into the intestinal lumen via cystic fibrosis Trans membrane conductance regulator (CFTR) channels. This leads to increase in intestinal fluid volume, further leading to an increase in intestinal movements [3]. Concentrations of Plecanatide and its metabolites are undetectable and minimally distributed in tissues following a dosage of 3 mg, thus AUC (area under curve); max concentration(C max) and half-life (t ½) cannot be calculated [4].

3. Pharmacodynamics

With respect to food, subjects who consumed plecanatide with meals, had more episodes of loose stools rather than that in fasting subjects within 24hrs [5].

No excretion studies have been conducted.

4. Clinical trials

Effect of plecanatide on CIC (chronic idiopathic constipation)

A STUDY WAS CONDUCTED in the United States on adults with chronic idiopathic constipation (CIC). This double-blind, placebo-controlled, phase III study evaluated the efficacy and safety of plecanatide versus placebo in CIC [6].

Subjects were to meet the modified Rome III CIC criteria and were randomized to plecanatide 3 mg (n = 443), 6 mg (n = 449), or placebo (n = 445). Subjects were to record bowel movement (BM) characteristics [spontaneous BMs (SBMs) and complete SBMs (CSBMs)] [6].

The primary endpoint was the percentage of overall CSBM responders (weekly responders for ≥9 of 12 treatment weeks, including ≥3 of the last 4 weeks). Weekly responders had ≥3 CSBM/week and an increase of ≥1 CSBM from baseline. Results showed a rise in percentage of overall CSBM responders resulted with each plecanatide dose compared with placebo (3 mg = 20.1%; 6 mg = 20.0%; placebo = 12.8%; p = 0.004 each dose). In a 12 week period, plecanatide significantly improved stool consistency and stool frequency, increases in mean weekly SBMs and CSBMs, maintained in the 12week duration in plecanatide-treated patients.

Adverse events were mild to moderate, diarrhoea being common (3 mg = 3.2%; 6 mg = 4.5%; placebo = 1.3%) [6].

Study concluded that Plecanatide had a significantly greater rate of durable overall CSBM responders and improved stool frequency and secondary endpoints.

5. TRULANCE Phase 3 IBS-C Program

Approval of plecanatide for IBS-C was based on two studies done on a total of 2100 patients which was randomised, of 12 weeks duration, double blind and placebo controlled [7].

Both trials included a baseline data of patients 2 weeks prior to starting the treatment, followed by that in 12 weeks treatment duration and that of two weeks of follow up post treatment.

One of the major inclusion criteria was patients who fulfilled ROME III IBS-C criteria related to abdominal pain and stool changes for at least 3 months [7].

Primary end point was change from baseline in complete spontaneous bowel movements and spontaneous bowel movements.

Efficacy of the drug was evaluated using responders analysis. Further responders had defined criteria in which a pt. should have had at least 3 CSBM in a given week. Furthermore increase in at least one CSBM from base line in the same week which should have occurred for at least 9weeks of total 12 weeks treatment. Efficacy response rate of 21% was observed with 3mg of plecanatide (n=453) which was 10% with placebo (n=452) [7].

Another study done using 6mg plecanatide did not show any additional benefit or response (19.6%) and incidence of diarrhoea was reported more with 6mg dose as compared to 3mg dose.

Most common adverse reaction noted was diarrhoea, noted in 0.6% of subjects who consumed plecanatide [7].

6. Adverse effects

The most common observed side effects of plecanatide are diarrhoea [6-8].

A phase 2 double blind, placebo controlled trial done in January 2017 done on 1733 subjects of CIC received 3mg of Trulcance or placebo once daily for 12 weeks; adverse reaction diarrhoa was observed in 2% of the cases, majority cases showed these in 4 weeks of treatment initiation out of which 0.6% cases had severe diarrhoea within first 3 days of treatment initiation [7].

These side effects may subside as your body gets adapted to the medicine [8].
Less common side effects noticed are

- body aches or pain, fever
- URTI
- sinusitis
- difficult, burning, or painful urination
- bloating and fullness in stomach
- headache
- muscle aches
- nausea
- passing gas
- tightness of the chest
- unusual tiredness or weakness [8]

The drug should be stored in a cool dry place away from moisture.

In case a dose is missed, skip the missed dose and take next dose on regular time.

Approval of plecanatide has given pharma industry a newer and much reliable drug for treatment of these conditions with lesser adverse effects. And it has been brought into practice in the health care industry in the US.

7. Contraindication

Plecanatide can cause severe dehydration in paediatric group, thus it is contraindicated for children less than 6 yrs. and should be avoided in age group 6-18yrs [9]. A nonclinical study done resulted in death of young juvenile mice (human age equivalent to 1 month and less than 2 years) post oral administration of plecanatide, due to increased intestinal expression of GC-C, causing diarrhoea.

Also patient with known or suspected mechanical GI obstruction shouldn’t be administered plecanatide [9].

8. Special population

As stated earlier, plecanatide is absorbed negligibly in the system. Plecanatide is not expected to result any birth defects and miscarriage as per available data on the same [2].

Also there is no available evidence of any effects or presence of the drug or its metabolites in breast milk or not seen to have any effects on breast fed infants [9].

No effects seen on fertility or reproductive function in male or female mice at oral dose of up to 600mg/kg/day [7].

Dose for geriatric age group should be administered with caution considering the reduced hepatic, renal and cardiac function [9].

9. Present status

Plecanatide was approved by Food and drug administration (FDA)) for treatment of CIC in January 2017 followed by approval for IBS (constipation dominated) in January 2018.

Plecanatide is accepted AND Efficient as per various clinical studies. The approved dose is of 3mg once daily, with or without food [11].
References


Competing Interests:
The authors declare that they have no competing interests.

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