



Prucalopride and Varenicline (Champix): Case Report of a Possible Drug Interaction at Enteric Serotonin (5-HT) Receptors

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Abstract

Background: Prucalopride is a highly selective, high affinity agonist of serotonin (5-HT)₄ receptors on cholinergic motor neurones, and stimulates gastrointestinal motility through enhanced release of acetylcholine. Prucalopride is approved for the treatment of Chronic Constipation (CC) in adult women, for whom standard laxative use has failed to provide adequate relief.

Varenicline (Champix), prescribed as a smoking cessation aid, prevents nicotine stimulation of the mesolimbic dopamine system associated with nicotine addiction. Varenicline is a highly selective, high affinity partial agonist at neuronal $\alpha 4\beta 2$ nicotinic receptors. It displays full agonism on $\alpha 7/5$ -HT₃ nicotinic acetylcholine receptors and is a potent agonist of the human 5-HT₃ receptor.

Case Presentation: Prucalopride treatment for an adult white female produced a marked, sustained improvement in her chronic constipation. The benefit disappeared rapidly after commencing varenicline, but was restored equally rapidly, once the varenicline was discontinued.

Conclusion: This case suggests a possible drug interaction between prucalopride and varenicline at enteric 5-HT receptors. An interaction between these two medications has not previously been described.

Keywords: Prucalopride; Varenicline; Serotonin; Receptors; Interaction; Case report

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Introduction

Prucalopride stimulates the peristaltic reflex, colonic mass movements and colonic transit and improves patient-reported outcomes in the treatment of Chronic Constipation (CC), namely bowel movement frequency, bowel movement consistency, constipation-related quality of life (QOL) and symptom scores and global assessments [1,2]. The improvement in patient satisfaction with bowel habit and treatment is maintained during treatment for up to 24 months and prucalopride therapy is generally safe and well tolerated in all age groups [1-3]. The National Institute for Health and Clinical Excellence (NICE) Guidance [3] states that:

“Prucalopride is recommended as an option for the treatment of chronic constipation, only in women for whom treatment with at least two laxatives, from different classes, at the highest tolerated recommended doses, for at least six months, has failed to provide adequate relief, and invasive treatment for constipation is being considered”.

Varenicline (Champix), prescribed for smoking cessation, interrupts signals of reward and reinforcement of smoking by blocking the effect of nicotine on the mesolimbic dopamine system [4]. The recommended dosage regime is 1mg twice daily for twelve weeks, following an initial titration regime within the first week, starting at 0.5 mg once daily. A date for cessation of smoking is scheduled by the user within the first two weeks of the treatment period [4]. In a meta-analysis of 101 studies of therapies for smoking cessation, varenicline proved more effective than bupropion (odds ratio 1.40) and nicotine replacement therapies (odds ratio 1.56) [5].

An interaction between these drugs has not previously been described. A review of the pharmacology and pharmacokinetics of both drugs indicates a potential for an interaction at enteric 5-HT receptors.

Case Presentation

A 57 year old white female presented with a 40 year history of refractory CC with distressing

straining, bloating and nausea. She had tried many laxatives over the years, and required 60 mg senna daily to open her bowels once per week. Examination revealed mild abdominal distension. She was commenced on prucalopride 2 mg daily. At review, four weeks later, she reported an increase in bowel frequency from once per week to opening her bowels every two to three days. Overall, she reported approximately 75% improvement in her symptoms, describing it as "a life-changing experience". Prucalopride 2 mg daily was continued.

Ten weeks later, she was prescribed varenicline as a smoking cessation aid, following a standard twelve week regime. Within 24-48 hours of starting the course, her symptoms of straining, bloating and nausea returned, and within a week, her bowel frequency decreased, virtually to the same frequency as prior to commencing prucalopride. Two weeks later, she stopped smoking, but her symptoms persisted, despite continuing prucalopride throughout. Since she was so symptomatic, she discontinued varenicline after eight weeks but continued to abstain from smoking.

Within 24-48 hours of stopping varenicline, her symptoms and bowel frequency rapidly improved and the prucalopride effect was fully restored. This improvement has been maintained from discontinuation of varenicline until the present day.

Investigations

Routine investigations were ordered prior to making a diagnosis of CC. These included a full blood count, C-reactive protein, urea and electrolytes, thyroid function tests, serum calcium, blood glucose, liver function tests and tissue transglutaminase, which were all within normal range.

Outcome

Prucalopride produced an improvement in bowel frequency and a marked improvement in the symptoms and quality of life of our patient. Following the discontinuation of varenicline, this has been maintained until the present day.

Once a potential drug interaction was considered, an extensive literature search of prucalopride, varenicline and their mechanisms of action was conducted to determine if there was a previously reported pharmacological basis for an interaction between the two drugs.

Discussion

Approximately 90% of the human body's total 5-HT is located in the enterochromaffin cells in the gastrointestinal tract, where it plays a key role in the regulation of gastrointestinal motility and secretions. Disruption of 5-HT release within the gut can lead to alterations in gut motility and is implicated in the pathogenesis of gastrointestinal motility disorders, such as irritable bowel syndrome and CC [6].

Seven types of 5-HT receptors and numerous subtypes have been described. 5-HT₄ receptors are G-protein-coupled proteins, expressed both in smooth muscle cells and in enteric neurones in the myenteric plexus, which supplies motor innervation to both layers of the tunica muscularis. Activation of these receptors both enhances acetylcholine release in the longitudinal muscle layer and inhibits spontaneous activity in the circular muscle layer. This contemporaneous action enhances prokinetic pathways within the colon and leads to synchronised, effective colonic propulsion [6,7]. Prucalopride is a 5-HT₄ agonist and its observed effects are exerted via highly selective action at 5-HT₄ receptors on cholinergic motor neurones, with 150-fold higher affinity for 5-HT₄ receptors than it does for other

receptors [7,9,10]. *In vitro* data indicate that prucalopride has a low interaction potential, and therapeutic concentrations of prucalopride are not expected to affect the CYP-mediated metabolism of co-medicated medicinal products [10]. Prucalopride is a weak substrate for P-glycoprotein, but not an inhibitor at clinically relevant concentrations [10,11].

Varenicline is a neuronal α 4 β 2 nicotinic receptor partial agonist. It has a higher affinity than nicotine for this receptor and thus blocks the nicotinic effect on the mesolimbic dopamine system and thereby, the signals for reward and reinforcement of smoking [4]. It also displays full agonism on α ₇/5-HT₃ nicotinic acetylcholine receptors, and *in vitro*, at clinically relevant concentrations, binds to human 5-HT₃ receptors, where it acts as a potent agonist [9]. 5-HT₃ receptors are found throughout the gut on vagal and mesenteric afferents. They mediate visceral signals from the intestine to the central nervous system, fast excitatory neurotransmission within the enteric nervous system and stimulation of mucosal terminals of myenteric intrinsic primary afferent neurons [6]. 5-HT₃ antagonists inhibit the increase in colonic tone after a meal in healthy humans and are efficacious in the treatment of IBS-D (Diarrhoea-predominant Irritable Bowel Syndrome) patients [12,13]. In addition, 5-HT₃ antagonists can be used to inhibit nociceptive signals transmitted to the central nervous system as a result of visceral hypersensitivity, and are utilised in the treatment of nausea and vomiting in patients undergoing chemotherapy [6].

Prucalopride and varenicline both possess low pharmacokinetic interaction potentials. They both have high affinity and selectivity for their receptors and minimal effect on cytochrome P450 enzymes. Varenicline and prucalopride are both well absorbed following oral administration, their bioavailability unaffected by concomitant intake of food and they are both excreted largely unchanged in the urine [4,10,11,14].

Intriguingly, varenicline, as a 5-HT₃ agonist, has also been demonstrated to have an occasional anti-motility effect, being associated with reports of constipation. A meta-analysis demonstrated that, when used for more than 6 weeks at a dose of 1 mg twice daily, there is an association between varenicline and constipation (numbers needed to harm: 24) [15]. More understandable is the significant association between varenicline and nausea (numbers needed to harm: 5) [15]. Furthermore, 5-HT₄ receptor agonists have been shown to reduce nociceptive signals from the gastrointestinal tract through mechanisms that are unclear [6,16].

Prucalopride and varenicline both have potential effects on enteric nicotinic receptors. Acetylcholine release from the activation of 5-HT₄ receptors in the myenteric plexus in turn activates α ₇/5-HT₃ nicotinic acetylcholine receptors on activated resident macrophages within the sub-serosal and circular smooth muscle layers, to inhibit their inflammatory reactions in the muscle layer of the intestine. Under normal conditions in a healthy individual, these macrophages are largely dormant and have been found to become activated under certain conditions, such as following intestinal manipulation. Varenicline displays full agonism on α ₇/5-HT₃ nicotinic acetylcholine receptors and it is therefore unlikely that the antagonistic effect proposed in this case would be a result of interaction on nicotinic receptors [17].

In the present case, prucalopride treatment for our patient produced a marked, sustained improvement in her chronic

constipation. The benefit disappeared rapidly after commencing varenicline, but was restored equally rapidly, once the varenicline was discontinued. The effect of prucalopride on bowel movements and symptom relief has been maintained long term. While this case could represent previously reported varenicline-associated constipation, we know that varenicline is a potent 5-HT₃ agonist and would therefore be expected to cause diarrhoea. Furthermore, prucalopride would be expected to enhance the pro-kinetic effect of varenicline, through its action on 5-HT₄ receptors. However, this is not the case in our patient and leads to an interesting potential for a competing interaction or modulation of the effect of these drugs on enteric 5-HT receptors.

Conclusion

This case highlights the importance of post-marketing vigilance and surveillance of new medications. At the time of this potential interaction, prucalopride was a new medication, acting via a novel mechanism. This case explores the pharmacological and pharmacokinetic mechanisms, in particular those related to gastrointestinal 5-HT receptors, which are not as well recognised as cholinergic or adrenergic mechanisms, in addition to the dual enzyme systems, CYP-mediated and cytochrome P450, in the metabolism of medicinal products.

We can only speculate as to whether this apparent antagonist effect, with its rapid onset and offset, could have been due to an interaction of prucalopride and varenicline on enteric 5-HT receptors. Future clinical and pharmacological studies of the effects of 5-HT, prucalopride and varenicline on gastrointestinal motility may help to clarify the potential mechanisms of action of both drugs.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor of this journal.

Competing Interests

Declaration of personal interests: Dr Moriarty has served as an advisory board member, or received lecture fees or travel grants from SHIRE (manufacturers of prucalopride), Almirall, AstraZeneca, GlaxoSmithKline, Janssen, Johnson & Johnson and Warner Chilcott.

Authors' Contributions

M. Jakeman: First draft of the manuscript and subsequent revisions.

K. Moriarty: Patient selection and revisions to the manuscript.

S. Schneider: Review of the pharmacological literature and contribution to manuscript revisions.

All authors approved the final version of the manuscript.

Authors' Information

KM is a Consultant Gastroenterologist, who has pioneered internationally-recognised, Gastroenterology, Liver, Psychiatry, Psychology, Pain Specialist holistic care, especially for socioeconomically-deprived, vulnerable patients with alcohol problems and disabling Abdominal Pain/Irritable Bowel Syndrome (IBS). He has published more than 100 papers, including many on bowel disorders, and written an Understanding Irritable Bowel Syndrome Patient Self-help Book (7th Edition 2013), which is sold worldwide.

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