CASE REPORT

Indacaterol-induced severe constipation and abdominal pain: is there a role for colonic β_3 -adrenoceptors?Miguel F Carrascosa,¹ M Isabel Lucena,² Inmaculada Bellido,² José Ramón Salcines-Caviedes¹¹Internal Medicine Department, Hospital of Laredo, Laredo, Cantabria, Spain²Clinical Pharmacology Department, School of Medicine, Virgen de la Victoria University Hospital, University of Málaga, Instituto de Investigación Biomédica de Málaga (IBIMA), Centro de Investigación Biomédica en Red en el Área temática de Enfermedades Hepáticas y Digestivas (CIBERehd), Málaga, Spain**Correspondence to**

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SUMMARY

Indacaterol is an ultra-long-acting β_2 -adrenoceptor agonist that is indicated for the maintenance treatment of chronic obstructive pulmonary disease. We present a patient with severe chronic constipation and abdominal pain most probably induced by this medicament. Symptoms rapidly disappeared within 2 days after the drug withdrawal. As far as we know, no reports describing severe chronic constipation associated with indacaterol have been published. The Naranjo algorithm score and the Edwards and Aronson scale for causality assessment of suspected adverse drug reactions indicated a probable relationship between indacaterol use and constipation. Indacaterol-induced constipation is an unusual event that could be accounted for the high intrinsic activity of the drug on colonic β_3 -adrenoceptors, resulting in an inhibitory control of smooth muscle function and intestinal secretion. Clinicians should monitor such a possibility when prescribing this drug and maybe avoid its use in patients with a history of difficult bowel evacuation.

BACKGROUND

Indacaterol maleate is an ultra-long-acting β_2 -adrenergic agonist (LABA) intended for maintenance treatment of chronic obstructive pulmonary disease (COPD).¹ The add-on therapy with indacaterol has shown beneficial effects on lung function, exercise tolerance and quality of life in COPD patients.² Compared with the other commonly used LABA, formoterol or the anticholinergic tiotropium, indacaterol provides a fast onset and a sustained duration of action, allowing for once-daily inhaled administration.¹⁻³ This drug shows a good overall safety and tolerability profiles,¹⁻⁴⁻⁵ being mild cough not associated to bronchospasm, the most frequent adverse event.⁶ We describe a case of severe chronic constipation and abdominal pain most likely induced by indacaterol, which required hospitalisation and quickly resolved after the drug withdrawal. In addition, we suggest a possible mechanism to elucidate this untoward effect.

CASE PRESENTATION

Early in February 2011, a 66-year-old man with moderate COPD (stage II, GOLD classification of COPD⁷) presented to our emergency department because of worsening constipation and generalised abdominal pain. His medical history was otherwise unremarkable. He had been taking tiotropium bromide (18 µg

daily) and budesonide/formoterol (320/9 µg twice daily) until October 2010, when he was shifted to indacaterol (150 µg once daily) and budesonide/formoterol combination stopped (tiotropium bromide therapy was maintained, figure 1). A physician confirmed that the patient took the new medication properly, that is, inhaled via a low-resistance dry powder inhaler. Although he experienced a moderate improvement on exercise capacity, he began to develop progressive constipation and continuous abdominal pain after 7 days on indacaterol.

On admission, the patient complained of no deposition during the last 10 days and looked ill. His blood pressure, heart rate, temperature and respiratory rate were within normal limits. Physical examination was remarkable only for distended abdomen with diffuse tenderness and hypoactive bowel sounds.

INVESTIGATIONS

He was face-to-face interviewed by a clinician about his gastrointestinal complaints through a history-taking description of symptoms. Questions regarding episodes of abdominal pain or discomfort, bloating, stool irregularity, diarrhoea, stool appearance or chronic constipation prior to starting indacaterol treatment, were made by the attending physician. The patient's answers were unremarkable concerning all of them. Moreover, the patient was requested to fill in a validated questionnaire in order to register his symptoms and to define the stool output by using the Bristol Stool Scale.⁸ This clinical tool is based on nine variables (diarrhoea, constipation, abdominal pain/discomfort, bloating, flatulence, weight loss, nausea, vomiting and tenesmus) which are scored from 0 (no symptoms) to 3 (severe). The scale provides a global symptomatic score that is calculated as the sum of all symptom scores, with a final value ranging from 0 to 30. The patient scored 11 on this scale (constipation, 3; abdominal pain/discomfort, 2; bloating, 3; flatulence, 3). A psychosocial screening including stressors (work, family), current emotional state (depression, anxiety) and fear of disease was also performed showing normal results. The possible influence of other drugs, food or natural products hypothetically linked to the development of constipation was discarded by specific questioning.

Laboratory investigations included the following: complete blood cell count; haemoglobin concentration, mean corpuscular volume and erythrocyte sedimentation rate; serum C reactive protein; blood

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Figure 1 Temporal relationship between drugs administration and symptoms.

glucose, urea, creatine, glomerular filtration rate and electrolytes (Na, K and Ca^{2+}); serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ -glutamyl transferase and bilirubin; international normalised ratio and activated partial thromboplastin time; serum thyroxine and urinalysis. All these determinations were within normal limits. ECG, chest x-ray and abdominal ultrasonography imaging showed no abnormalities. Plain abdominal radiograph disclosed increase of the intestinal gas without signs suggestive of bowel obstruction. No other diagnostic tests were requested (abdominal CT scan, colonoscopy or opaque enema) given that there were neither clinical signs nor complementary findings supporting the existence of an underlying serious or life-threatening disease.

TREATMENT

Lactitol was added and he was discharged on the third hospital day.

OUTCOME AND FOLLOW-UP

Then, an outpatient 'watchful waiting' attitude was adopted, with regular clinical and laboratory evaluations. However, since

constipation and abdominal pain worsened even under laxative therapy and appropriate diet alteration, indacaterol was stopped early in March 2011, and the combination budesonide/formoterol was restarted at the same dose previously taken. Forty-eight hours after indacaterol discontinuation, he passed a large volume of normal appearance stools, with simultaneous resolution of abdominal pain (figure 1). The patient refused a rechallenge test for indacaterol because of his 'very unpleasant experience' while on the drug. Abdominal complaints have not recurred since then and at 3, 12 and 24 month follow-ups, he remained symptoms free.

DISCUSSION

A literature search was performed using the online version of MEDLINE, the Cochrane Database of Systematic Reviews, the US Food and Drug Administration-Drugs safety section (<http://www.fda.gov/Drugs/DrugSafety/default.htm>), the European Medicines Agency-New and event section (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_and_events.jsp&mid=), EMBASE, Scopus and Google Scholar to identify any experimental or clinical article that

Table 1 Pharmacodynamic and pharmacokinetic profile of indacaterol versus formoterol (summarised from references^{13 14 16 17})

		β-Agonist drug	
Parameters	β-Adrenoceptor type	Indacaterol	Formoterol
Pharmacodynamics			
pK _i	β ₁	6.21±0.12	6.12±0.09
	β ₂	7.36±0.06	7.84±0.05
	β ₃	5.48±0.14	5.49±0.08
pEC ₅₀ (absolute value of isoprenaline)	β ₁ (7.46±0.05)	6.60±0.24	6.96±0.12
	β ₂ (7.22±0.01)	8.06±0.02	8.58±0.02
	β ₃ (7.91±0.07)	6.72±0.13	7.56±0.14
E _{max} (% isoprenaline)	β ₁ (99±2)	16±2	29±2
	β ₂ (98±1)	73±1	90±1
	β ₃ (99±2)	113±7	103±4.7
Pharmacokinetics			
Median time to reach peak serum concentrations		≈15 min	≈10 min
Accumulation factor for the area under the serum concentration-time curve from 0–24 h		2.9–3.5 h*pg/ml	1.4–1.8 h*pg/ml
Absolute bioavailability after an inhaled dose		43–45%	21–37%
Systemic exposure from pulmonary absorption		75%	46%
Urine excreted unchanged drug		<2%	8–13%
Renal clearance		0.02 l/min	1.4 l/min
Terminal half-life after repeated dosing		126 h	17 h
Effective half-life after repeated dosing		52 h	24 h

The table shows indacaterol and formoterol binding affinity (dissociation constants, pK_i), functional potency (pEC_{50} related to isoprenaline absolute maximal response) and intrinsic efficacy (maximal effect (E_{max}) in percentage with respect to the maximal isoprenaline-induced cAMP production). Intrinsic efficacy is determined by measuring cAMP production in cells stably transfected with human β_2 -adrenoceptors.

Data are expressed as mean $\pm$ standard error of mean. Isoprenaline values are disclosed in parentheses.

reported (1) the coexistence of indacaterol or other LABA treatment and constipation and (2) the suggested hypothetical mechanism to explain such an association. As far as we are aware, this is the first case of indacaterol-induced constipation severe enough to require hospitalisation and drug withdrawal. Mild, transient upper abdominal pain has been rarely described in asthmatics taking indacaterol 300–600 µg once daily.⁴ On the other hand, a recent controlled clinical trial with patients randomised to two commonly used doses of indacaterol, showed a low frequency, dose-dependent constipation incidence (2/114 patients on 150 µg dose and 4/116 patients on 300 µg vs 1/117 on placebo dose).⁹ The need for hospitalisation and/or drug withdrawal in individuals taking indacaterol was not mentioned in these studies. We believe three facts strongly suggest that indacaterol caused our patient's disorder—the temporal relationship between starting of indacaterol treatment and the onset of abdominal complaints; the quick resolution of symptoms after drug discontinuation and a biological plausibility in the absence of other alternative explanations. In this regard, the Naranjo algorithm score¹⁰ and the Edwards and Aronson scale for causality assessment of suspected adverse drug reactions¹¹ indicated a probable relationship between indacaterol use and the development of constipation.

The fact that the patient condition improved when formoterol was substituted deserves commentary. It seems unlikely that the pharmacokinetic differences between these drugs, mainly related to the higher dose administered for indacaterol and the longer duration of its biological effects, could by itself account for the constipation, given the symptomatic abatement seen after switching to formoterol.⁸

Adrenergic β_2 -receptors are known to be present on the gastrointestinal system and it has also been demonstrated that β_3 -adrenoceptors are expressed in both the gastrointestinal smooth muscle and the cholinergic neurons of the myenteric and submucosal plexuses of the human colon.¹² Stimulation of β_2 -adrenoceptors decreases gastrointestinal motility and β_3 -adrenoceptors agonists inhibit muscle contraction of the colon and decrease intestinal secretion.¹² We hypothesise that the β_2/β_3 -adrenoceptor agonist indacaterol¹³ would have caused abdominal pain through inhibition of intestinal motility and secretion with subsequent constipation and bowel dilation. Besides, the fact that our patient was unresponsive to lactitol, an osmotic laxative, indirectly supports the presence of an intestinal motility disorder.

Interestingly, although indacaterol and formoterol are LABA, they exhibit different pharmacodynamic profile.^{13–15} Formoterol and indacaterol are very weak β_1 -adrenergic agonists and display similar β_2/β_3 binding affinity and agonist activity, as shown by their respective dissociation constant (pK_i) and functional potency (pEC_{50} related to isoprenaline absolute maximal response) at the human β_2 and β_3 adrenoceptors (table 1).^{13–15} However, formoterol has higher intrinsic activity (maximal effect (E_{max}) in percentage with respect to the maximal isoprenaline-induced cAMP production) at human β_2 -adrenoceptors and it is a much more selective β_2 -adrenoceptor than β_3 -adrenoceptor (640-folds).^{13–14} On the contrary, indacaterol is only 22-fold more selective β_2 -adrenoceptor than β_3 -adrenoceptor agonist,^{13–14} and it shows higher intrinsic activity at β_3 -adrenergic receptors when compared with formoterol (E_{max}) (table 1).^{13–14–16–17} Unfortunately, we were unable to find published data comparing pharmacodynamic parameters of indacaterol with other LABA on β_2 -gut adrenoceptors and β_3 -gut adrenoceptors.

The differential efficacy profile of indacaterol could translate in an efficacious bronchodilator effect with reduced

cardiovascular side effects. On the other hand, activity on gut motility could be explained by an indacaterol-specific effect owing to its higher intrinsic activity for β_3 -adrenoreceptors as compared with other drugs of the same class. Of note, a down-regulation of the inhibitory β_3 -adrenergic control of colonic smooth muscle function has been shown in an experimental model of colitis.^{17–18}

Advanced age and tiotropium coadministration could have also increased our patient's susceptibility to develop severe constipation. Indeed, a gradual increase in the risk of constipation has been linked to ageing.^{18–19} Tiotropium typical expected anticholinergic effects such as dry mouth, gastrointestinal disorders and urinary difficulties have been widely reported.^{19–20} However, a pooled analysis of adverse event reporting from 26 phase III and IV clinical trials involving 9149 patients treated with tiotropium has shown that dry mouth is by far the most common adverse event than constipation.^{19–20} In addition, constipation had been absent prior to indacaterol use in our patient, disappeared after indacaterol withdrawal, and did not recur despite the continuation of tiotropium treatment (figure 1).

The adverse reaction described is unusual for its nature and severity and brings new information to enhance the current knowledge about the safety profile of indacaterol. We suggest clinicians should bear in mind that indacaterol-induced severe constipation can occur, particularly in susceptible populations such as the elderly, and should monitor such a possibility when prescribing the drug and possibly avoid its use in patients with a history of difficult bowel evacuation.

Learning points

- ▶ Indacaterol is an ultra-long-acting β_2 -adrenoceptor agonist that is indicated for the maintenance treatment of chronic obstructive pulmonary disease.
- ▶ This drug shows a good overall safety and tolerability profiles, being mild cough not associated to bronchospasm the most frequent untoward event.
- ▶ However, indacaterol may cause chronic constipation and abdominal pain at the usual recommended dose.
- ▶ This adverse reaction could be accounted for the high intrinsic activity of the drug on colonic β_3 -adrenoreceptors, resulting in an inhibitory control of smooth muscle function and intestinal secretion.
- ▶ Clinicians should monitor such a possibility when prescribing this drug and perhaps avoid its use in patients with a history of difficult bowel evacuation.

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