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The Potential Role of Racecadotril in the Treatment of Diarrhea Associated With Roflumilast^{*}

Potencial papel de racecadotril en el tratamiento de la diarrea asociada a roflumilast

Dear Editor,

Roflumilast is a new inhibitor of phosphodiesterase-4 (PDE4) that is marketed for the treatment of chronic obstructive pulmonary disease (COPD). The PDE4 enzyme hydrolyzes and selectively inactivates cyclic adenosine monophosphate (cAMP). This inhibition increases cell levels of cAMP, reducing most pro-inflammatory processes, and remodeling that are dependent on these cells.¹

A recent group analysis has demonstrated that roflumilast can be used to reduce exacerbations and improve dyspnea and lung function in patients with COPD who receive concomitant treatment with long-acting β_2 agonists (LABA), without increasing adverse effects.² In this study, the distribution of the adverse effects was similar in patients with or without concomitant treatment with LABA. Nevertheless, the study shows an association between roflumilast and the appearance of diarrhea with an incidence between 7.7% and 19.1%. Although the average duration of this adverse period is 11–12 days,³ the intensity of the diarrhea should be evaluated in each case in order to decide if the treatment should be maintained or not. Due to the temporary nature of this adverse effect and the benefits of the use of roflumilast, it is possible that some cases may benefit from receiving treatment for diarrhea. The mechanism of action of this diarrhea has been associated with higher levels of cAMP in intestinal epithelial cells, and this increase causes an imbalance between the concentrations of Na^+ and K^+ , which in turn promotes intestinal hypersecretion.

Racecadotril is a powerful selective inhibitor of enkephalinase, which is active orally. Enkephalinase is an enzyme that is responsible for the degradation of the enkephalin that is abundant in the intestinal villi, where the electrolyte exchange takes place. Curiously, enkephalins have antisecretory effects in the intestine by inhibiting the production of cAMP. Thus, racecadotril quickly resolves the acute diarrhea and has an incidence of adverse effects that is similar to placebo,⁴ without inducing the proliferation of bacteria.⁵ Unlike opioids, this drug does not have central or peripheral side effects, such as respiratory depression or the inhibition of the intestinal transit.

The anti-diarrheal effects of racecadotril have been studied in several assays, both in acute as well as chronic diarrhea, in adults, and in children, and a good effectiveness/safety profile has been found with a quick start time within the first 24 h. The dosage in adults is an initial 100-mg capsule followed by 1 capsule 3 times a day, preferably before meals. The treatment should not last more than 7 days.

Due to the mechanism of action, it is plausible to hypothesize that racecadotril can have an effect on diarrhea induced by roflumilast by counteracting its effects on the cell levels of cAMP. Unfortunately, to date there have been no clinical assays dealing with the efficacy and safety of this medicine for treating this potential new clinical indication, and, as far as we know, there are none presently underway (clinicaltrials.gov). With this letter, we would like to raise interest in this potential effect and promote the creation of clinical assays studying the use of racecadotril in the treatment of diarrhea associated with roflumilast.

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