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A dynamic model of once-daily 5-aminosalicylic acid predicts clinical efficacy

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Abstract

New once daily mesalamine formulations may improve adherence to medication usage. Response to Asacol and other forms of 5-aminosalicyclic acid (5-ASA) is better correlated with tissue concentrations and best predicted by concentrations of the drug within the lumen of the colon. Our group used computer simulation to predict colonic 5-ASA levels after Asacol administration. In our study, the model simulated Asacol distribution in the healthy colon, and during quiescent and active ulcerative colitis. An Asacol dosage of 800 mg, three times a day, was compared to 2400 mg given once a day. Under ideal conditions, the predicted maximum drug in the total colon and individual colonic segments over 100 d differed by less than 3% between single and multiple doses. Despite changes in motility and defection rates, the predicted maximum and average 5-ASA concentrations in the total colon and individual colonic segments differed by less than 10% between dosing regimens. Asymmetric distribution of 5-ASA in the colon was influenced by frequency of bowel movements and colonic transit rate. In active colitis, sigmoid 5-ASA concentration becomes negligible. Our model supports once daily administration of Asacol as standard treatment for ulcerative colitis.

Key words: Ulcerative colitis; 5-aminosalicylate; Mesalazine; Asacol; Once-daily

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TO THE EDITOR

We read with a great interest the editorial by Lakatos[1] that summarizes the available literature on the short and medium term efficacy and safety of the new once-daily mesalazine formulations. Single dose regimens may improve adherence to medication usage. However, older forms of 5-aminosalicylic acid (5-ASA) may also be administered in a single daily dosage, apparently with adequate effects[2]. Most pharmacokinetic studies on

Asacol and other forms of 5-ASA are limited to data collected from serum, urine or fecal drug concentrations. However, response is better correlated with tissue than with plasma concentrations, and is best predicted by concentrations of the drug within the lumen of the colon[3,4]. A number of factors influence the concentrations of drugs in colon, such as 5-ASA. Our group[5] created a computer model to predict 5-ASA levels in colon after Asacol administration using STELLA software (Isee Systems, Inc., Lebanon NH, USA). This model divides the intestinal system into individual compartments-upper GI tract, right colon, transverse colon, descending colon and the recto-sigmoid colon, and predicts the movement of 5-ASA from one compartment to the other. Retrospective data for drug concentrations based on serum levels have been utilized[6,7]. In addition to local transfer of the drug, each colonic compartment loses a fraction of its drug concentration due to mass movements with defecation[8]. In our study, the model was run to simulate Asacol distribution in a healthy colon, and during quiescent and active ulcerative colitis. To achieve this, simulations were performed with increasing defecation rates up to 12 bowel movements daily along with variation of upper GI and colonic motility. One hundred 24 h cycles were studied. An Asacol dosage of 800 mg, three times a day, was compared to 2400 mg given once a day. Under ideal conditions, the predicted maximum drug in the total colon and individual colonic segments over 100 d differed by less than 3% between single and multiple doses. Despite changes in motility and defection rates, the predicted maximum and average 5-ASA concentrations in the total colon and individual colonic segments differed by less than 10% between dosing regimens. The model could also predict almost no drug within the lumen of the recto-sigmoid colon during severe disease activities[5].

Our model supports the once daily administration of Asacol, a concept catching on with new clinical trials. Asymmetric distribution of 5-ASA in the colon is influenced by frequency of bowel movements and the rate of colonic transit is an important factor in determining 5-ASA dosing in active ulcerative colitis.

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