

## Optimal Dosing of 5-Aminosalicylic Acid: 5 Decades of Choosing Between Politicians

*The right dose differentiates a poison and a remedy.*

—Paracelsus

5-Aminosalicylic acid (mesalamine) delivered to the colon by sulfasalazine (SASP) was advanced as therapy for ulcerative colitis (UC) in 1952.<sup>1</sup> Mesalamine and SASP are effective in the induction and maintenance of remission in UC; this is robustly supported by placebo-controlled trials. Unfortunately, however, the story of the mesalamine delivery systems and recommended doses from 1952 to the present time has not followed a logical, step-wise evolution to an ideal approach but rather resembles a series of political campaigns. As Otto von Bismarck, the Prussian statesman, stated in 1863, "Politics is not an exact science." It is common practice to lump mesalamine preparations together but to consider them separately from SASP. Within the mesalamine class, we have been presented with a variety of products: arrays of paired active molecules; prodrugs, custom-designed coatings; specialized granule design. Differences in the chemistry, delivery systems, and bioavailability of these specific products have made it difficult to sort out whether mesalamine is truly superior to SASP and more specifically whether a particular mesalamine delivery system is best.

"More is better" is a central theme and is based on the dose-response relationship observed with SASP in doses up to 4 g/day.<sup>2</sup> Many clinicians have used upward titration of SASP to the highest tolerated dose to induce remission followed by downward titration to a dose that minimized side effects for long-term maintenance therapy. In clinical practice, this strategy has been applied to various mesalamine preparations for which on careful scrutiny of the available data, a dose-response relationship may not be so clear.

A systematic review of mesalamine for the induction of remission in UC found only a trend to a significant dose response.<sup>3</sup> In the

PROBE trial examining type and dose of mesalamine for maintenance of remission in 388 patients with UC, mesalamine as Asacol 2 g/day and Salofalk 2 g/day showed equivalence, and no additional benefit was seen from higher dosing with 3.2 g of Asacol.<sup>4</sup>

In this issue of *Clinical Gastroenterology and Hepatology*, Kruis et al.<sup>5</sup> describe their experience in an international industry-funded investigation of one of the latest candidate mesalamine agents. They examined the efficacy of a new mesalamine pellet preparation administered as a sachet 3 times daily in equal doses for 8 weeks. These pellets are designed to offer both delayed and sustained release to target the colon. Three hundred nineteen patients were randomized to daily dosing with 1.5, 3.0, or 4.5 g. The primary end point was clinical remission rate at 8 weeks, and the study was powered accordingly. At 8 weeks, all groups had similar remission and improvement rates, with clinical remission ranging from 50% to 60%. They conclude that there is no significant dose response between 1.5, 3, or 4.5 g per day and suggest that the optimal dose for mesalamine is 0.5 g 3 times a day (1.5 g).

Kruis et al. are to be praised for controlling concomitant medications, choosing a primary end point, performing a power analysis, and then faithfully reporting the outcome of the study. Unfortunately, their conclusions do not end the debate over dose-response curves for this class of drugs. For example, in this particular trial, the clinician and patient will also be interested in more details of the median time to onset of action for each treatment arm. Most would concur that suffering 26 days of diarrhea (as was seen in the group randomized to 1.5 g per day) would be worse than the 15 days of diarrhea observed in the highest dose group. The study sub-

jects seemed to agree that this outcome was important; many voted with their feet, with 23% dropping out most often for "inefficiency of treatment" in the lowest dose group compared to 10% in the 4.5-g dose group. The 1.5-g dose group also suffered more adverse events than the higher dose groups, presumably because of classification of inefficiency of treatment as an adverse event. In addition, this study does not answer the question of whether patients treated with 1.5 or 3.0 g/day who fail to respond then subsequently respond if the mesalamine dose is escalated to 4.5 g/day.

How should the clinicians incorporate the information from this study into their practice? We suggest that they look at these data carefully. With further investigation of this agent, it is likely that there will be differences demonstrated between *efficacy*, where conclusions are made in the controlled construct of a study, and *effectiveness*, where conclusions are drawn from how an agent performs in clinical practice. For this particular delivery system (specialized pellets administered as a sachet) in a controlled trial setting (8-week observation period), the difference in clinical remission rates between doses was not significant. In practice, the relatively large number of pills required for the recommended dose of many of the commercial products in this class and the patient's inclination to opt for speedier (albeit more toxic) agents will also influence our perception of the candidate medication. In the meantime, this particular campaign reminds us to continue to question whether more is truly better. As we embrace information based on evidence, we should avoid falling into the trap of practical politics and heed the admonition of the U.S. historian

Henry Adams, "Practical politics consists in ignoring facts."

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