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Mea culpa

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I started working on the development of aminosalicylates in 1983. At that time it was determined that sulfasalazine—5-aminosalicylic acid (5-ASA) linked to sulfapyridine by an azo bond—was primarily a prodrug that delivered 5-ASA into the colon to treat ulcerative colitis. At about the same time preliminary evidence suggested that delivery of 5-ASA into the small bowel could be therapeutic for Crohn's disease. In either case, the key was luminal delivery that minimized systemic absorption, since the effect of 5-ASA appeared to be topical on the epithelium and absorbed 5-ASA seemed to be inactivated by *N*-acetylation and urinary excretion.

Concern was expressed regarding the systemic effects of high doses of 5-ASA because aspirin (acetylsalicylic acid) and related salicylates have a well-recognized potential to cause nephrotoxicity in both animals and humans. In animal studies the nephrotoxic dose of 5-ASA approximated the 4–5 g dose potentially used in humans, and there was a single case of nephrotoxicity reported in a Danish patient treated with 3 g of a sustained-release mesalazine formulation. Thus, in advisory meetings on the development of mesalazine, Europeans, in particular, were concerned about using a dose of mesalazine higher than that delivered by full-dose sulfasalazine (sulfasalazine is approximately 40% 5-ASA, hence 4–6 g of sulfasalazine delivers the equivalent of 1.6–2.4 g of mesalazine into the colon). Further concern existed over the increased levels of mesalazine absorption associated with small-bowel delivery.

The subsequent development programs for both delayed-release (pH-sensitive) and sustained-release (ethylcellulose) formulations of mesalazine extensively explored the risk of nephrotoxicity for doses up to 4–4.8 g. Large clinical trials in patients with ulcerative colitis or Crohn's disease failed to demonstrate evidence of dose-related nephrotoxicity and numerous book chapters and journal articles described mesalazine as safe for the kidneys. Nevertheless, sporadic cases of nephrotoxicity continued to occur in patients treated with mesalazine, most often reported by nephrologists, while the preponderance of gastrointestinal literature continued to proclaim the safety of mesalazine and the absence of dose-related renal effects.

…I recommend that prescribers should be aware of the small risk of idiosyncratic nephritis attributable to any 5-ASA product, assess the patient's baseline renal function, and monitor their blood urea nitrogen and creatinine concentrations within the first 6 months of therapy and yearly thereafter.

Nevertheless, the US FDA placed a warning within the prescribing information for mesalazine products that stated "It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment.", but the warning did not state how frequently renal function should be assessed (Lialda® [http://www.lialda.com/Professional/pdf/pi.pdf] © 2007 Shire US Inc.; Pentasa® [http://www.pentasaus.com/PDF/pentasa_pi.pdf] © 2007 Shire US Inc.; Asacol® [http://www.asacol.com/pdf/us-asacol.pdf] 2007 Procter & Gamble Pharmaceuticals, Inc.).

Unfortunately, my own writings have reflected the general message that mesalazine was safe for the kidneys at doses up to 4.8 g necessary to treat patients with IBD and failed to emphasize the small, but well-described risk of idiosyncratic interstitial nephritis and renal failure, as outlined by others (*Inflamm Bowel Dis* [2007] 13: 629–638). A number of malpractice cases in the US have pertained to the prescriber's failure to monitor renal function in patients who developed nephrotoxicity secondary to 5-ASA treatment. So, despite the general safety of aminosaliyclates and the lack of dose-related nephrotoxicity, I recommend that prescribers should be aware of the small risk of idiosyncratic nephritis attributable to any 5-ASA product, assess the patient's baseline renal function, and monitor their blood urea nitrogen and creatinine concentrations within the first 6 months of therapy and yearly thereafter.

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Competing interests
The author has declared associations with the following companies/organizations: Ferring, Procter & Gamble, Salix and Shire. See the article online for full details of the relationships.

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