**Format for ANSWERING REVIEWERS**

November, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name ESPS Manuscript NO: 626)

**Title:** ISOLATED FEVER INDUCED BY MESALAMINE TREATMENT

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**Name of Journal:** *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 The format was adjusted according to theformat of case reports

2 The written language was edited by nature publishing group (npg) language group

3 As I mentioned in my discussion, the mechanism of fever induced by drugs, in our case the mesalamine is unknown.

4 PMID and DOI citations were added to references

5 The first page of the reference 6 ([Schroeder KW](http://www.ncbi.nlm.nih.gov/pubmed?term=Schroeder%20KW%5BAuthor%5D&cauthor=true&cauthor_uid=21960801)) is provided

**Review**

**Is Mesalamine Safe?**

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The aminosalicylates currently available for treating infla-mmatory bowel disease share a common ancestry with the development of sulfasalazine by Nana Svartz in the late 1930s and 1940s. This drug was the fortuitous result of the diazo bonding of an antibacterial agent, the sulfa moi­ety sulfapyridine, and a salicylate, 5-aminosalicylic acid, also known as mesalamine. Although the goal for this drug was treatment of inflammatory arthritis, subsequent clinical observations suggested that it provided particular benefit to patients with both arthritis and colitis.1 Clinical trials in the 1960s showed clear benefit for treatment of mildly-to-moderately active ulcerative colitis as well as for maintenance of remission in these patients.2-5 Although widely used for treatment of patients with Crohn’s disease, it was less certain that the drug was effective when studied in controlled trials. For years, the relative anti-inflamma­tory role of the parent molecule as compared to the sulfa moiety or the salicylate was unknown. Enema studies by Khan in the 1970s found that the benefit of sulfasalazine could be reproduced by 5-aminosalicylic acid, but not by sulfapyridine, in treating distal colitis.6 This led to the conclusion that the active ingredient in sulfasalazine was the 5-aminosalicylic acid and that sulfasalazine is a prodrug: this molecule passes unaffected through the gas­trointestinal tract until reaching the colon, where bacterial diazo reductase cleaves the diazo bond, releasing the two moieties. Much of the sulfa is absorbed in the colon and is responsible for many of the adverse effects associated with the parent molecule, whereas the 5-aminosalicylic acid appears to be the active agent and free of most of the adverse effects previously found with sulfasalazine.7 Many formulations, including delayed-release, sustained-release, and alternative prodrugs, have been developed to deliver the 5-ASA or mesalamine to the distal bowel, with the hope that most adverse effects of sulfasalazine can be avoided. Trials of mesalamine in the treatment of ulcerative colitis have shown efficacy in treating mildly-to-moderately active disease and in maintenance of remission.8,9 Studies in Crohn’s disease have shown less impressive benefit in treating mildly-to-moderately active disease and in maintenance trials.10

The mechanism of action of mesalamine prepara­tions is attributed to modulation of the arachidonic acid metabolism with inhibition of the cyclooxygenase and lipoxygenase pathways. Additionally, mesalamine inhibits inflammatory cell functions, natural killer cell activity, plasma cell antibody production, and tumor necrosis factor activity, decreases interleukin-1 production from macrophages, and acts as a free oxygen radical scavenger.11 Some of these mechanisms, though not all, are shared by sulfasalazine.

Types of adverse effects to sulfasalazine can be divided into those that are dose-related intolerance versus those that are non–dose-related idiosyncratic reactions. Dose-related problems include nausea, vomiting, headaches, malaise, and nonspecific abdominal pain, and may be related to the patient’s acetylator status, with regard to the sulfapyridine.12 Idiosyncratic reactions that are not dose-related are common as well and include hypersensitivity rash, male infertility, agranulocytosis, aplastic anemia, hemolytic anemia, hepatic dysfunction, pulmonary dys­function, and worsening bowel symptoms. Up to 30% of patients are intolerant to sulfasalazine at doses of 4 g daily, and few patients are able to tolerate more than this daily dose,13 which is equivalent to 1.6 g daily of mesalamine. Some of these adverse effects can be alleviated by dos­age reduction or gradual dose escalation. At least 80% of patients intolerant of sulfasalazine are able to tolerate mesalamine preparations.14 These sulfa-free preparations have been used in doses of mesalamine up to 4.8 g daily for treatment of gastrointestinal inflammation, usually with excellent tolerance and with a frequency of adverse events no more common than with placebo.15

Although mesalamine preparations are generally well tolerated, adverse reactions have been described with their usage.16 These include worsening colitis; renal toxic­ity such as interstitial nephritis and nephrotic syndrome; pulmonary toxicity such as interstitial lung disease and fibrosis, bronchiolitis obliterans, pulmonary granulo­matosis, and eosinophilic pleural effusion; pericarditis, pancreatitis, hair loss, and Stevens-Johnson syndrome. These reactions appear to be idiosyncratic in onset, though the mechanism remains unclear. It is possible that some of these effects are seen primarily with mesalamine as a result of the larger doses associated with this drug than with sulfasalazine. Generally, these adverse effects will occur in affected patients with any oral or topical preparations of delayed-release mesalamine or prodrug

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

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