

# Salazopyrin and Its Newer Analogues in the Treatment of Inflammatory Bowel Disease

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Salazopyrin has been in use for over 40 years now and various clinical studies during the last two decades have proved its efficacy in the treatment of both ulcerative colitis and Crohn's disease. Salazopyrin is a conjugate of 5 amino salicylic acid and sulphapyridine, linked by an azo bond. About 1/3 of the drug is absorbed from the upper G.I. tract and usually less than 10% of the total administered dose is excreted unchanged in the urine. The remaining absorbed portion is excreted as such in the bile and along with non-absorbed portion reaches the distal small intestine and colon<sup>1</sup>.

In the colon, bacterial reduction splits the drug into its two constituents.<sup>2</sup> Sulphapyridin is absorbed, partially metabolised and excreted in the urine, whereas 5 amino-salicylate remains largely in the colon, only a small portion being absorbed, and is probably the therapeutically active moiety of salazopyrin<sup>3</sup>.

Several studies including randomized controlled trials have shown marked improvement in the patients's clinical condition and sigmoidoscopic appearances with salazopyrin compared to placebo and other drugs.<sup>4-6</sup> However in one study,<sup>7</sup> steroid therapy was judged to be more prompt and overall more effective than that with salazopyrin, suggesting a combined treatment to be more effective. One group of investigators<sup>8</sup> suggested early use of salazopyrin in patients with severe ulcerative colitis after a response to systemic steroids had been obtained.

Further studies have established a role of maintenance therapy with salazopyrin in ulcerative colitis.<sup>9</sup> Subsequent studies<sup>10-13</sup> have convincingly shown a better prophylactic effect of salazopyrin as compared to high-fibre diet or mast cell stabilisers such as cromoglycate and it seems that Salazopyrin therapy continued beyond one year is likely to confer continued prophylaxis against relapse. The optimum dose for maintenance therapy, which is effective and yet gives lesser side effects, has been determined to be 2 gms daily in divided doses.<sup>14</sup>

Several studies have suggested the usefulness of salazopyrin in the treatment of Crohn's disease<sup>15-17</sup> and a controlled double blind study found 3 gm/day of salazopyrin to be significantly more effective than placebo in active Crohn's disease.<sup>18</sup> Subsequent studies confirmed these findings but no beneficial effect was noted in patients with ileitis alone<sup>19</sup>. Again salazopyrin was less effective than prednisone alone in active Crohn's disease,<sup>20</sup> and unlike the case in ulcerative colitis, it has not been shown to be of benefit in maintaining remission in Crohn's disease<sup>19</sup>. A study which evaluated the prophylactic effect of salazopyrin post-operatively, did not find it to have a significant beneficial effect in preventing recurrence of Crohn's disease<sup>21</sup>

Metabolic studies of salazopyrin have indicated that 5-aminosalicylate may be the active moiety of the drug and that sulphapyridine is responsible for the drug's toxicity. A study in which either salazopyrin, 5-aminosalicylate or sulphapyridine was administered as retention enemas in a blinded controlled fashion, over a 2 week period to patients. With active, mild to moderate ulcerative colitis, made the authors conclude that 5-aminosalicylate is the active component of salazopyrin.<sup>22</sup>

In other studies, suppositories containing 5 aminosalicylate were found to be as effective as salazopyrin given either as a suppository or orally and was more effective than either sulphapyridine or placebo given similarly.<sup>23</sup> 5-amino-salicylate and salazopyrin enemas were effective in inducing clinical and sigmoidoscopic remission in patients with proctitis or left sided colitis.<sup>24</sup> A related agent-4-

aminosalicylate also appears to be effective as an enema for treating distal colitis.<sup>25</sup>

As enemas are a rather inconvenient form of treatment especially as maintenance therapy, preparations that could deliver intact 5-amino-salicylate to the lower intestine, as does salazopyrin, were sought. One such compound is disodium azodisalicylate which links 5-aminosalicylate to itself through an azo bond. A small uncontrolled trial has suggested its efficacy in the enema form.<sup>26</sup> Another useful formulation is a watersoluble polymer that links 5-aminosalicylate by an azo bond to an inert polysulfanilamide. In an open protocol several patients with mild to moderate ulcerative colitis responded to this polymer. Similarly three other analogues of salazopyrin have been synthesised and suggested as potential therapeutic agents.<sup>27</sup>

To counter the need for bacterial cleavage of the azo bond, specially in the treatment of Crohn's ileitis, sustained release forms of 5-amino-salicylate have been developed. In an open trial, 92% of patients with Crohn's ileitis and ileocolitis improved after 6 weeks of therapy with this agent.<sup>26</sup>

All available experience suggests salazopyrin as the initial therapeutic choice in ulcerative colitis. Four gms/day is the maximum dose tolerated by most patients. Therapy should be continued as prophylaxis in patients who go into remission on a standard maintenance dose of 2 gms/day. Similarly salazopyrin is a reasonable initial choice in patients with acute Crohn's disease. The drug does not appear to have a prophylactic role in patients with Crohn's disease once remission has been achieved. In future, newer oral forms of 5-aminosalicylate should emerge as safe and clinically useful forms of therapy.

Though salazopyrin crosses the placenta, it has not been found to be harmful to the foetus<sup>28</sup> or to the new born being nursed by a mother taking the drug. Salazopyrin has also been used in other disorders such as radiation bowel disease, scleroderma, dermatitis herpetiformis and rheumatoid arthritis.<sup>29,32</sup>

The mechanism of action of salazopyrin remains unclear. A possible antibacterial mode of action has been suggested because of its sulphamide component. Possible effect of salazopyrin on systemic and local immunity have been studied. Inhibition of prostaglandin synthesis by salazopyrin has been suggested, however findings indicate that prostaglandins may not be important mediators of inflammation in inflammatory bowel disease.<sup>33</sup> An alternative hypothesis suggests that salazopyrin or 5-aminosalicylate may work by increasing local levels of prostaglandins, which may act in a cytoprotective manner, inhibition of potent chemotactic agents, which recruit inflammatory cells into sites of inflammation, may account for some of the anti-inflammatory effects of salazopyrin.<sup>34</sup> Salazopyrin has been shown to interact with folic acid and by competitive inhibition of folate conjugase cause folate malabsorption.<sup>35</sup> Metabolism of salazopyrin has been shown to be markedly reduced by the concurrent administration of cholestyramine, a nonabsorbable anion exchange resin.<sup>36</sup> A similar interaction has been reported between ferrous sulphate and salazopyrin.<sup>37</sup> Administration of broad-spectrum antibiotic concurrently, diminished salazopyrin metabolism probably due to a diminution in gut flora,<sup>3</sup>

The commonest but least severe adverse reactions due to salazopyrin include nausea, vomiting, anorexia and headache. Heart burn epigastric distress and diarrhoea are seen occasionally.<sup>38,39</sup>

More serious reactions include various skin eruptions and a blue discoloration resembling cyanosis. Bloody diarrhoea with fever and rash has been reported. Reversible pancreatitis and a spectrum of hepatotoxicity has emerged. Pulmonary complications include one report of subacute fibrosing alveolitis, tracheo-laryngitis and eosinophilic pneumonia. Acceleration of heart rate has been confirmed and is postulated to be due to the salicylate moiety. Suppression of haemopoiesis, megaloblastic and hemolytic anaemia have been described. Newly described, potentially important adverse effect is male infertility, which is reversible.<sup>40</sup>

Minor side-effects and mild allergic reactions can be overcome by dosage reduction or desensitization. As serious side effects are rare, salazopyrin remains a useful therapy for inflammatory bowel disease.

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