The History of 5-ASA Compounds and their Use in Ulcerative Colitis – Trailblazing Discoveries in Gastroenterology

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5 aminosalicylates have had a dramatic effect on the management of patients with inflammatory bowel disease. Their success in reducing the frequency of flare-ups in ulcerative colitis laid the foundations of long-term disease control in gastroenterology. As a result the concept that medication should be taken to prevent disease episodes was present at the beginning of therapeutic gastroenterology. 5 aminosalicylates were amongst the first disease specific therapeutic agents of the twentieth century. They were conceived as drugs that could be targeted at the cause of disease. The original idea of dealing directly with infection and inflammation through the combining of sulphonamides and aspirin derivatives was a reflection of the growing belief of the 1930s that treatment should be targeted.

The demonstration in 1935 that sulphanilamide was the active component in Prontosil Rubrum led to the production of a large number of sulphonamides. The subsequent discovery that sulphonamides blocked a specific metabolic activity in bacteria due to competitive inhibition with naturally occurring PABA (para-aminobenzoic acid) confirmed their role as potential anti-bacterials [1]. May and Baker 693 (or sulphapyridine), which was developed by Jewins and Phillips, proved to be the most potent and broad spectrum [2, 3]. It was the agent that was to be combined with a 5 aminosalicylate to produce sulphasalazine. The stimulus to this development was the belief that rheumatoid arthritis was, at least in part, due to a bacterial infection.

Nanna Svartz was the first woman to become a professor of medicine at a state university in Sweden. As head of the medical clinic at the Karolinska Hospital she practiced as a rheumatologist. She was keen to develop a twin pronged approach to the management of rheumatoid arthritis and planned to capitalise on the penetration of connective tissue by 5 aminosalicylic acid. She hoped to use this molecule to carry sulphapyridine into the tissues [4]. Through a chance meeting with Phillip Willstaedt, Pharmacia, the Swedish pharmaceutical company, produced a number of candidate drugs of which salicylazosulphapyridine or sulphasalazine held the most promise. Almost through serendipity, sulphasalazine was found to be effective in the control of ulcerative colitis. A small study of 9 patients which depended upon clinical observation suggested that the drug was effective [5]. At this time there was no real alternative treatment and sulphasalazine spread around the world as the agent of choice for patients with ulcerative colitis. Its mechanism of action was unclear and it was associated with significant side effects.

As early as 1937, Dr. Arnold Bargen from the Mayo Clinic in Rochester, Minnesota started to investigate the potential role of sulfanilamide in the treatment of ulcerative colitis. Two deaths from acute yellow liver atrophy led to a search for a preparation which might “possess a therapeutic effect comparable to that of sulphanilamide without its toxicity”[6]. A number of potential agents were assessed, including azosulphamide and sulfathiazole. However, the most effective agent was to be salicylazosulphapyridine or Salazopyrin [7].

Despite these difficulties in 1965 the first placebo controlled trial of sulphasalazine treatment was conducted in the UK [8]. After one year of treatment with 2g of sulphasalazine, 24 of 34 patients with ulcerative colitis remained in remission. In 1972 Dissanayake and Truelove showed in a placebo controlled trial of 64 patients with objective end-points that long-term use of sulphasalazine suppressed disease activity up to 5 years in ulcerative colitis and introduced the concept...
that life-long therapy was central to the successful treatment of this condition [9]. With its role as a long-term preventive treatment the problem of side effects became one of the driving factors behind the search for which part of the molecule was responsible for sulfasalazine’s anti-inflammatory activity. This search identified 5 aminosalicylate (Mesalazine) and not sulfapyridine as the active component within sulfasalazine. Azad Khan and Sidney Truelove performed an elegant series of studies using three separate retention enemas in a blind clinical study over a period of two weeks. Sulfasalazine and 5 aminosalicylate (5-ASA) enemas produced a significant clinical improvement in 30% of patients compared with a 5% response in those who received sulfapyridine [10].

The problem with 5-ASA is its lack of stability. Solutions to this problem have centred around three main approaches: A. delivery directly to the colon as a retention or foam enema; B. encapsulating the drug within a pharmaceutical coating; C. binding the 5-ASA moiety to a carrier molecule.

Perhaps the most innovative approach was the use of 5-ASA as its own carrier molecule. Sidney Truelove’s group investigated the effect of two 5-ASA molecules linked back to back. The resulting compound was disodium azo-disalicylate or Olsalazine. Although effective, its role has been limited by the occurrence of diarrhea as a significant side effect.

During the 1980s John Rhodes and Brian Evans investigated the role of eudragit-S coating as a way of stabilising mesalazine. Their novel idea was to develop a product which would split open with the change in pH as intestinal content crossed the ileocaecal valve into the colon [11]. The rupture of the outer capsule released active mesalazine into the colon. The product was marketed as Asacol by Tillotts Laboratories Ltd. The role of entrepreneurs, such as David Slagel, in bringing these new products to market cannot be overemphasised.

Eva Paulsen was a civil engineer whose specialty laid in the development of production techniques for a range of pharmaceuticals. During the late 1970s she became interested in ways of stabilising 5-ASA so that it could be given as an oral medication [12]. Together with Soren Halskov, she developed a technique for encapsulating mesalazine within microgranules. These prolonged release through coating made from a polymer, alchyl-cellulose, which was independent of the pH. The product was marketed as Pentasa.

In 1980, Hugh Baron and John Lennard-Jones approached Siegfrid Gottfried and Lily Baxendale of Biorex Laboratories to investigate the possibility of linking the 5-ASA moiety to an inert carrier molecule. Dr. Rosalind Chan, a chemist, suggested four possible molecules with a diazo link to 5-ASA. This resulted in the production of two compounds with branch chains containing an amino acid [13]. In one case this was 4-amino-benzoyl-β-alanine or Balsalazide and the other was Ipsalazide which was based around a glycine chain [13 -15]. Balsalazide has been shown to be effective in a large number of clinical trials. The azo-bonds, which link the moieties, are split by azo-reductase present in bacteria in the large bowel. However, its mode of action cannot be simply attributed to the release of active 5-ASA from an inactive carrier molecule. Pharmacokinetic studies would suggest that it is metabolised and excreted in a distinct way. In 1988, 79 patients were treated in a comparative study with sulphasalazine [15]. Balsalazide proved effective and to have fewer side effects and again the entrepreneurial spirit of a relatively small developmental company had played a significant role in converting the ideas of practising gastroenterologists into prescribing reality.

During the early 1980s the search for better stability and less side effects led to an interest in 4-ASA rather than 5-ASA. It has been investigated in several clinical trials, but always as an enema. In general it appears as effective as 5-ASA but exhibits fewer side effects [16-18]. It is commercially available as Quadrara in a number of European countries.

In the 1990s the pharmaceutical industry took a more active interest in the development of 5-ASA products. One aspect of this interest centred around the need to improve long-term compliance with 5-ASA therapy. Clinical studies had been restricted to follow-up periods of no greater than 18 months and compliance with therapy was clearly an issue [19, 20]. One approach to such difficulties has been to develop a once daily preparation. In 2000, Villa et al filed a patent which had a three component matrix structure [21]. It described a structure which was formed by successive amphiphilics: lipophilic or inert matrices incorporated or dispersed in hydrophilic matrices. As a result, the dissolution rate of the active constituents could be controlled. Cosmo Pharmaceuticals SpA developed this Multi Matrix System (MMX) at Lainate in Italy. The combination of more than one release controlling mechanism prevents dissolution in the upper gastrointestinal tract and allows delivery of mesalazine uniformly throughout the colon. A study of 79 patients in Rome by Prantera et al demonstrated that this system was as effective but more acceptable than enema treatment [22].

It was during this period that interest focused on the potential of 5-ASA compounds to reduce inflammatory activity and so potentially to reduce the risk of colorectal cancer in ulcerative colitis. In 1994 sulfasalazine was first shown to reduce the risk of colorectal cancer by between 31% and 80%
amongst a cohort of 3,112 patients from Uppsala in Sweden [23]. Confirmation came from a study in Leicester UK where the risk was reduced by 28% [24]. A UK nationwide study of patients with ulcerative colitis who developed colorectal cancer in 2000 confirmed a reduction in risk of more than 70%, especially for those taking mesalazine [25]. These studies emphasised the importance of regular therapy with 5-ASA medication and raised the question of what was the minimum duration of treatment to achieve this benefit.

Conflicts of interest: No conflict to declare.

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