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(54) Title: COMPOSITIONS FOR TREATMENT OF CHRONIC INFLAMMATORY DISEASES

(57) Abstract

This invention defines novel compositions which can provide a basis for clinical teatment of several chronic inflammatory diseases, said diseases including varieties of arthritis, ileitis, colitis and other inflammatory disorders, as well as trauma resulting from ischemia and subsequent reperfusion. Increased lipid peroxidation is a common to the etiology of all of the clinical disorders addressed herein. Such increased lipid peroxidation generates carbonyl substances which are cytotoxic and additionally serve to perpetuate and disseminate the inflammatory process. This invention involves use of orally administered amine derivatives of benzoic acid as carbonyl trapping agents. These primary therapeutic agents act by chemically binding to and sequestering the aldehyde and/or ketone products of lipid peroxidation. p-Aminobenzoic acid (or PABA) is an example of the primary agent of the present invention. PABA has a small molecular weight, is water soluble, has a primary amine group which should react with carbonyl-containing metabolites under physiological conditions and is tolerated by the body in relatively high dosages and for extended periods. The method of the present invention includes administration of a composition comprising (1) a therapeutically effective amount of at least one carbonyl sequestering primary therapeutic agent, (2) optionally one or more co-agent such as, for example, an anti-oxidant free radical trapping substance, and (3) at least one medicament recognized as effective to treat said chronic inflammatory disease, so as to produce an additive or synergistic physiological effect of an anti-inflammatory nature.

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COMPOSITIONS FOR TREATMENT OF CHRONIC INFLAMMATORY DISEASES

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the clinical treatment of chronic inflammatory diseases, including chronic gingivitis; chronic periodontitis; chronic autoimmune gastritis; ileitis; inflammatory bowel disease, including colitis; interstitial cystitis; psoriasis; arthritis; tendinitis; carpel tunnel syndrome and other cumulative trauma disorders; lupus erythematosus; pneumoconiosis; chronic obstructive pulmonary disease; inflammatory myopathies; inflammatory neuropathies, including Alzheimer's disease, myasthenia gravis and multiple sclerosis; epilepsy; as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke, kidney ischemia or myocardial infarction.

2. Description of Prior Art

The logic and potential value, even *synergistic* value, of using two or more therapeutic agents in combination for treatment of chronic inflammatory diseases has been recognized previously (Calhoun and coworkers, 1992; Hirschelmann and coworkers, 1991; Brooks and Schwarzer (1991); Wright and coworkers, 1977).

The present disclosure describes the inventive concept of using the therapeutic technology of US Patent Application 07/906,909 in combination with pharmaceutical agents having some medicinal value for treatment of the disease entities noted above. The inventive concept embodied in my earlier US Patent Application 07/906,909 filed 30 June 1992 is the use of compositions consisting of a primary agent which sequesters carbonyl products in combination with co-agents that have known anti-oxidant properties. The primary agents of the present invention, such as p-aminobenzoic acid (PABA), contain

a primary amine group, so as to enable reaction with carbonyl groups of disease-related substances. No pharmacological treatment of comprehensive effectiveness is currently available for any of the chronic inflammatory disorders discussed herein. However, a variety of pharmaceutical agents have been described which may offer at least some degree of symptomatic relief from the clinical effects of these diseases.

Clinical use of the drug sulfasalazine (SAZ) represents a well documented example of the use of a benzoic acid derivative as a trapping agent for the hydroxyl radical and other free radicals in the treatment of a chronic inflammatory disease. In the colon SAZ undergoes reductive cleavage to liberate 5-aminosalicylic acid (5-amino-2-hydroxybenzoic acid, or 5-ASA), which is the therapeutically active agent. Ahnfelt-Ronne and coworkers (1990) presented research findings which docoment the use of SAZ for successful treatment of chronic inflamatory bowel disease (CIBD), also known as ulcerative colitis. SAZ is also recognized for use in treatment of ileitis (Budavari and coworkers, 1989, pg. 1412). Ahnfelt-Ronne (1990) compared their in vivo 5-ASA metabolic products to products observed after in vitro hydroxylation of 5-ASA by the Fenton reaction and tentatively identified 5-ASA metabolites as being hydroxylated derivatives. They never attempted to look for evidence of in vivo trapping of carbonyl products. Under the brand name *Asacol* and the generic name mesalamine, 5-amino-2-hydroxybenzoic acid in delayed-release tablets has also been marketed in the United States for use in treatment of CIBD (Dowd and coworkers, 1993, pgs. 1868-1869). Dull and coworkers (1987, pg. 2469) used mass spectrometry to definitively identify two of the several hydroxylation/oxidative deamination products which result from in vitro incubation of 5-ASA with activated human mononuclear cells. They identified these products as gentisic acid (2,5-dihydroxybenzoic acid) and salicylic acid (2-hydroxybenzoic acid), while five other 5-ASA metabolic products remained unidentified (pg. 2470).

Ahnfelt-Ronne and colleagues, Dull and coworkers, and earlier investigators never recognized the possibility of using a therapeutic agent to scavenge carbonyl products of

inflammation. Hence they never recognized the possibility of intentionally using a composition consisting of a primary agent which sequesters carbonyl products in combination with co-agents that have known anti-oxidant properties.

Further distinctions should be noted between the invention disclosed in US Patent Application 07/906,909 and previously recognized clinical use of SAZ. SAZ releases sulfapyridine, a somewhat toxic substance, into the body (Peppercorn, 1984, pgs. 377-379 and 383), while the invention of US Patent Application 07/906,909 does not. In addition, use of sulfasalazine depends on intestinal bacteria for activation of the drug, while the primary agents of the present invention do not. Besides use in treatment of CIBD, SAZ has been recognized, at least at the experimental level, for treatment of ileitis, radiation bowel disease, scleroderma, dermatitis herpetiformis and rheumatoid arthritis (Peppercorn, 1984, pgs. 380-381).

Other examples of amine drugs recognized as having anti-inflammatory properties include para-substituted *N*-benzenesulfonyl derivatives of anthrilic acid (Borne and coworkers, 1974), 4-amino benzoic acid anilides (Thiele, 1971; Deutsche Gold- und Silber-Scheideanstalt vorm. Roessler, 1972), tinoridine (Shimada and Yasuda, 1979) and benzothiazolinone derivatives (Takashima and coworkers, 1972). The chemical structures of these agents lie beyond those of the primary agents of the present invention. They are not presently recognized as carbonyl sequestering therapeutic agents. They have not been used in multiple ingredient compositions analogous to those of the present invention.

Several drug products containing PABA have been marketed for human use in the United States. However, it is believed that none have been proposed as effective for the treatments claimed herein. Potassium p-aminobenzoate has been marketed as *Potaba* (R) in the pure form as an antifibrotic, that is, skin softening, agent (Drug Information for the Health Care Professional, 8th ed., 1988, pgs. 111-113). As such it has been recognized for treatment of Peyronie's disease; diffuse systemic sclerosis; morphea and linear scleroderma; and dermatomyositis. For such purposes, *Potaba* is taken orally in

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