METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLIDE ANTIBIOTICS

CLAIM FOR PRIORITY

This application claims the benefit of Provisional Patent Application Ser. No. 61/190,053, filed Oct. 15, 2008.

BACKGROUND

This application relates to methods allowing for the co-administration of colchicine together with one or more macrolide antibiotics for therapeutic purposes with less danger than is associated with prior methods of administration.

Colchicine:

Colchicine, chemical name (−)-N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is a pale yellow powder soluble in water in 1:25 dilution.

Colchicine is an alkaloid found in extracts of *Colchicum autumnale, Gloriosa superba*, and other plants. Among its many biological activities, colchicine blocks microtubule polymerization and arrests cell division. It has adversely affected spermatogenesis in humans and in some animal species under certain conditions.

Colchicine is a microtubule-disrupting agent used in the treatment of gout and other conditions that may be treated, relieved or prevented with anti-inflammatory treatment. Colchicine impairs the motility of granulocytes and can prevent the inflammatory phenomena that initiate an attack (or flare) of gout. Colchicine also inhibits mitosis, thus affecting cells with high turnover such as those in the gastrointestinal tract and bone marrow; therefore, the primary adverse side effects include gastrointestinal upset such as diarrhea and nausea.

Colchicine has a low therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of most other widely used drugs. Consequently, actions that result in increased colchicine levels in patients receiving colchicine therapy are particularly dangerous. Co-administration of colchicine to patients along with certain other drugs can have the effect of increasing colchicine levels. Such drug-drug interactions with colchicine have been reported to result in serious morbid complications and, in some cases, death.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

Gout:

Gout (or gouty arthritis) is a disease caused by a build up of uric acid. Such a build up is typically due to an overproduction of uric acid or to a reduced ability of the kidney to excrete uric acid. Gout is more common in certain groups of patients, including adult males, postmenopausal women, and hypertensives. Heavy alcohol use, diabetes, obesity, sickle cell anemia, and kidney disease also increase the risk of developing gout. The condition may also develop in people who take drugs that interfere with uric acid excretion.

In gout, crystals of monosodium urate (a salt of uric acid) are deposited in joints, e.g., on articular cartilage, as well as in and on tendons and surrounding tissues. These deposits correlate with elevated concentrations of uric acid in the blood

stream and are believed to provoke the painful inflammatory reaction that occurs in affected tissues. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as by swelling, redness, warmness, and stiffness in the affected joint. Low-grade fever may also be present. The patient usually suffers from two sources of pain. The patient experiences intense pain whenever an affected joint is flexed. The inflammation of the tissues around the joint also causes the skin to be swollen, tender and sore if it is even slightly touched. For example, a blanket or even the lightest sheet draping over the affected area could cause extreme pain.

A gout flare is a sudden attack of pain in affected joints, especially in the lower extremities, and most commonly in the big toe. In afflicted individuals, the frequency of gout flares typically increases over time. In this fashion, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain.

In acute gout flares, symptoms develop suddenly and usually involve only one or a few joints. The big toe, knee, or ankle joints are most often affected. The pain frequently starts during the night and is often described as throbbing, crushing, or excruciating. The joint appears infected, with signs of warmth, redness, and tenderness. Flares of painful joints may go away in several days, but may return from time to time. Subsequent flares usually last longer. Acute gout may progress to chronic gout flares, or may resolve without further attacks.

The chronic appearance of several attacks of gout yearly can lead to joint deformity and limited joint motion. Nodular uric acid deposits, called tophi, may eventually develop in cartilage tissue, tendons, and soft tissues. These tophi are a hallmark of chronic gout, which usually develop only after a patient has suffered from the disease for many years. Deposits of monosodium urate can also occur in the kidneys of gout sufferers, potentially leading to chronic kidney failure.

Use of Colchicine to Treat Gout:

Colchicine can reduce pain in attacks of acute gout flares and also can be used beneficially for treating adults for prophylaxis of gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and subsequent inflammatory responses.

The anti-inflammatory effect of colchicine is relatively selective for gouty arthritis. However, other types of arthritis occasionally respond. It is neither an analgesic nor a uricosuric and will not prevent progression of acute gout to chronic gout. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks as well as to relieve the residual pain and mild discomfort that patients with gout occasionally experience between attacks.

Macrolide Antibiotics:

Macrolide compounds are natural products and natural product derivatives characterized by the presence of a macrocyclic (large) lactone ring known as a macrolide ring. The macrolide antibiotics are important therapeutic agents. Commercially available macrolide antibiotics include azithromycin, clarithromycin, dirithromycin, erythromycin, and roxithromycin.

Clarithromycin is a semi-synthetic macrolide antibiotic with in vitro activity against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms, as well as most *Mycobacterium avium* complex (MAC) microorganisms. The drug is believed to exert its antibacterial