METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a Divisional of U.S. application Ser. No. 12/372,046, filed Feb. 17, 2009, which claims priority from U.S. Provisional Application Ser. Nos. 61/138,141 filed Dec. 17, 2008 and 61/152,067 filed Feb. 12, 2009, all of which are hereby incorporated by reference in their entirety.

FIELD OF THE DISCLOSURE

This disclosure relates to methods allowing for the co-administration of colchicine together with one or more second active agents for therapeutic purposes with improved safety compared to prior methods of administration.

BACKGROUND

Colchicine, chemical name (–)-N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is an alkaloid found in extracts of *Colchicum autumnale, Gloriosa superba*, and other plants. It 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, resulting in effects in cells with high turnover rates such as those in the gastrointestinal tract and bone marrow. The primary adverse side effects of colchicine therapy include gastrointestinal upset such as diarrhea and nausea.

Colchicine has a narrow therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of many 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 (or gouty arthritis) is a disease caused by a build up of uric acid in the joints. 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 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. 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 manner, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain.

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.

Cytochrome p450 (CYP) enzymes are agents of drug metabolism that are found in the liver, the gastrointestinal tract and other locations in the body. CYP enzymes occur in a variety of closely related proteins referred to as isozymes and different CYP isozymes may preferentially metabolize different drugs. The 3A family of CYP isozymes, particularly CYP3A4, is also known to be involved in many clinically significant drug-drug interactions, including those involving colchicine and second active agents. While drugs are often targets of CYP-mediated metabolism, some may also alter the expression and activity of such enzymes, thus impacting the metabolism of other drugs. The biotransformation of colchicine in human liver microsomes involves formation of 3-demethylchochicine and 2-demethylcolchicine. As shown by experiments using antibodies against CYP3A4 and experiments using chemical inhibition of CYP3A4, this transformation is correlated with (and thus apparently mediated by) CYP3A4 activity.

P-glycoprotein (P-gp) is an ATP-dependent cell surface transporter molecule that acts as an ATPase efflux pump for multiple cytotoxic agents, including colchicine. P-gp actively pumps certain compounds, including drugs such as colchicine, out of cells. P-gp is encoded by the Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene, also referred to as the multiple drug resistance 1 gene (MDR1).

Since colchicine acts intracellularly, the combined effects of CYP3A4 inhibition and P-gp inhibition by second active agents that also interact with CYP3A4 and P-gp can cause colchicine toxicity in patients taking what would be a safe dose of colchicine in the absence of concomitant second agent administration. Various studies of adverse reactions from exposure to multiple drugs have found that 6.5-23% of the adverse reactions result from drug-drug interactions. Unfortunately, each year a number of deaths occur as the direct result of patients adding a concomitant prescription pharmaceutical product to their existing medication regimen.

There accordingly remains a need for improved methods for administering colchicine to individuals who are concomitantly being treated with second active agents so as to reduce the possibility of colchicine toxicity while maintaining the sometimes life-saving advantages of being able to administer the two (or more) agents concomitantly. The present disclosure addresses this need and provides further advantages.

SUMMARY

In one embodiment, a method of treating an individual in need of treatment with colchicine comprises concomitantly administering to the individual colchicine and another drug, for example, ketoconazole or ritonavir or cyclosporine, wherein the colchicine is administered as a dosing regimen with a starting colchicine dose of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg. According to another embodiment, the other drug is, for example, verapamil or diltiazem, and the starting colchicine dose during coadministration with the other drug is no more than about 1.2 mg colchicine,