METHODS FOR CONCOMITANT TREATMENT OF THEOPHYLLINE AND FEBUXOSTAT

RELATED APPLICATION INFORMATION

This is a continuation of U.S. patent application Ser. No. 13/227,828, filed on Sep. 8, 2011, which claims priority to U.S. Provisional Patent Application No. 61/381,482, filed on Sep. 10, 2010, the contents of all of which are herein incorporated by reference in their entirety.

FIELD

The present disclosure relates to novel methods for treating hyperuricemia in patients also requiring treatment with theophylline. Specifically, the invention is directed to a method of administering theophylline in conjunction with one or more xanthine oxidoreductase inhibitors, whereby the xanthine oxidoreductase inhibitors do not cause alterations in the plasma concentrations of theophylline.

BACKGROUND

A substantial number of patients are affected with diseases of the respiratory system, including asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, and neonatal bradycardia. One of the primary treatments for respiratory diseases is the use of theophylline

Theophylline is a useful medicine frequently used as an agent for treating symptoms of bronchial asthma. It is known in the art that effective blood concentrations range from about 10 to 20 μg/ml. However, if the concentration of theophylline in the blood exceeds 20 μg/ml, serious side effects sometimes appear with regard to the cardiovascular system and the central nervous system. Further, there is a large difference in blood levels among individuals. Various conditions (e.g., cardiac insufficiency, liver and kidney disease, etc.), age differences, smoking, etc. also have large effects. Additionally, theophylline has a short biological half-life of about 6 hours for adults. In order to maintain the effective blood level, four doses per day have been considered necessary. However, such frequent dosing is troublesome to patients, reduces patient compliance, and causes the state of the disease to become worse. In particular, attacks of bronchial asthma often occur at daybreak. It is not possible to sufficiently prevent such attacks with ingestion of theophylline just before going to bed, and therefore, repeat ingestion close to daybreak is necessary. Thus, in the past, continuous effort has been made to develop a sustained release type theophylline formulation. Several formulations are already available on the market.

Another disease that affects a substantial number of patients is gout. Gout affects 3 to 5 million individuals in the United States of America (USA) and is increasing in incidence and prevalence. Gout is a serious health condition characterized by flares of acute arthritis, chronic gouty arthropathy, tophi, and uric acid urolithiasis, and is associated with a broad range of comorbidities, including cardiovascular disease, chronic kidney disease, and metabolic syndrome. At the joint level, a gout flare is best characterized as an acute monoarthritis arthropathy process with proliferative bone reaction that can affect any joint and that can later develop into chronic polyarthritis. Gout attacks tend to occur mostly in the lower extremities and over time additional joints can be involved.

The underlying metabolic aberration in gout is hyperuricemia, which is a condition defined as an elevation in serum

urate (sUA) level ≧6.8 m/dL. Hyperuricemia develops into gout when urate crystals are formed from supersaturated body fluids and deposited in joints, tophi, and parenchymal organs due to a disorder in the urate metabolism. Uric acid is the end product of purine metabolism and is generated in the cascade of hypoxantine→xanthine→uric acid.

Urate-lowering therapy (ULT) is used to treat hyperuricemia in subjects with gout. The goal of ULT is to reduce sUA to 6.0 mg/dL or less, below the concentration at which monosodium urate saturates extracellular fluid. Using ULT to reduce and maintain sUA levels <6.0 mg/dL ultimately improves the clinical symptoms of gout by reducing the frequency of gout flares, decreasing size and number of tophi, and improving quality of life. One alternative that may be used for the treatment of gout is the administration of xanthine oxidase inhibitors, such as allopurinol. Generally, allopurinol is considered one of the primary treatments of gout and has developed wide usage as a treatment for gout.

However, clinicians have few treatment options for hyperuricemic patients also suffering from respiratory diseases, such as chronic obstructive pulmonary disease, asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, and neonatal bradycardia. One of the primary treatments for these respiratory diseases is the administration of theophylline, a bronchodilator. Although theophylline provides a treatment for the respiratory diseases described herein, the therapeutic range of theophylline blood concentrations is thought to be very narrow, ranging from about 10 to about 20 μg/ml. As such, if the theophylline dosing does not provide a minimum blood concentration of 10 μg/ml, the patient is not provided significant relief from the respiratory condition, and at blood concentrations greater than 20 μg/ml, the patient may be susceptible to adverse effects such as abdominal pain, headache, muscle cramps, tremors, tachycardia, and seizures. Therefore, clinicians must exercise caution in determining treatment options for patients requiring theophylline treatment, and must closely monitor the potential for drug interactions that may increase or decrease theophylline blood concentrations.

It is further known within the art that the administration of allopurinol interacts with the metabolism of theophylline, causing the theophylline to be metabolized slowly, and leading to increased blood concentrations. As discussed in the art, the area under the curve (AUC) for theophylline in patients co-administered allopurinol and theophylline has been reported to increase by up to 27%, the half-life increased by approximately 25%, and the clearance of theophylline may be decreased by 21% (Manfredi B A, et al., *Clin. Pharmacol. Ther.,* 1981; 29(2), pp. 224-229). Accordingly, clinicians are required to alter the theophylline dosing and/or the allopurinol dosing in hopes of establishing a therapeutic dose for both disease states, while avoiding unwanted adverse effects that may result from increased theophylline concentrations.

Thus, in view of these considerations, there exists within the art a need to develop a treatment option for hyperuricemic patients that also suffer from respiratory disorders, whereby the clinician can administer typical dosing of theophylline without adjusting for adverse drug interactions.

SUMMARY

The present disclosure is directed to methods for treating hyperuricemia in patients requiring treatment with theophylline. The methods of the current invention avoid the drug interactions typically associated with theophylline administration and concomitant treatment with xanthine oxidase inhibitors.