POTASSIUM-BINDING AGENTS FOR TREATING HYPERTENSION AND HYPERKALEMIA

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/581,698 filed Dec. 23, 2014 which is a continuation of PCT Patent Application No. PCT/US2013/063921, filed on Oct. 8, 2013 which claims the benefit of U.S. Provisional Patent Application Ser. No. 61/711,184, filed on Oct. 8, 2012. The entire content of the above applications are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention generally relates to methods of treating hypertension (HTN) in patients in need thereof wherein the patient optionally further suffers from chronic kidney disease (CKD) or Type II diabetes mellitus (T2DM). The invention also relates to methods of treating kidney disease in a patient in need thereof, wherein the patient is optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The invention also relates to methods of treating hyperkalemia in a patient in need thereof, wherein the patient suffers from CKD, T2DM or HTN and are optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The methods can comprise administering an effective amount of a potassium-binding agent to the patient to lower the patient's blood pressure and/or increase or stabilize the patient's kidney function.

BACKGROUND OF THE INVENTION

Normal kidney function is critical for the maintenance of potassium homeostasis. The ability of the kidney to maintain potassium homeostasis depends on several factors, including the normal production of aldosterone, sodium delivery to the distal nephron, and adequate sodium-potassium exchange in the cortical collecting duct (Palmer, B. F., N. Engl. J. Med. 2004, 351:585-92). Of these factors, aldosterone production and action is closely regulated by the renin-angiotensin-aldosterone system (RAAS), a cornerstone of the regulatory components controlling blood pressure, blood volume and cardiovascular function. RAAS inhibition, designed to limit aldosterone production and function, is therefore an important treatment strategy for hypertension, diabetes, chronic kidney disease and heart failure. Several studies have demonstrated the renal protective effects of angiotensin receptor blockers (ARBs) such as losartan or irbesartan (Brenner, B. M. et al., N. Engl. J. Med. 2001, 345:861-869; de Zeeuw, D. et al. Kidney Intl. 2004, 65:2309-2320; Miao, Y. et al., Diabetologia 2010; Lewis, E. J. et al., N. Engl. J. Med. 2001, 345:851-860; Atkins, R. C. et al., Am. J. Kidney Dis. 2005, 45:281-287), while studies using dual blockade of the RAAS with an aldosterone antagonist (spironolactone or eplerenone), added to either angiotensin converting enzyme inhibitor (ACEI) or ARB therapy, were shown to substantially reduce cardiovascular endpoints in heart failure or post-myocardial infarction patients (Pitt, B. et al., N. Engl. J. Med. 1999, 341:709-717; Pitt, B., Molecular & Cellular Endocrinol. 2004, 217:53-58; Zannad, F. et al., European J. Heart Failure 2010).

Despite the demonstrated clinical benefits of RAAS inhibitors, the fundamental mode of action of the drugs

disturbs the exchange of sodium for potassium in the kidney tubule. As a result, potassium retention can precipitate hyperkalemia, defined as a serum potassium value >5.0 mEq/L. This is particularly problematic in patients with reduced renal function resulting from chronic kidney disease and common co-morbidities such as hypertension, diabetes and heart failure. In this situation, the combination of RAAS inhibition and reduced renal function can aggravate the nascent positive potassium balance and trigger a hyperkalemic event. The discontinuation or reduction in the dose of RAAS inhibitors is a common intervention for patients taking RAAS inhibitors who show abnormally elevated serum potassium levels, which deprives patients of the benefits of RAAS inhibitors. Thus, there is a need to control blood pressure in patients and treat hyperkalemia.

SUMMARY OF THE INVENTION

One aspect of the invention is a method of treating hypertension in a patient in need thereof. The method comprises administering an effective amount of a medication that controls the serum potassium of a patient in need thereof into the normal range. The method comprises administering an effective amount of a medication that controls the serum potassium of a patient in need thereof into the normal range within two days of treatment, and in particular with chronic dosing, and further with such chronic over a period of at least one month, more specifically at least 3 months, preferably at least 6 months and more preferably at least 9 months. More specifically, the method comprises administering an effective amount of a potassium binding agent, such as 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form, to the patient.

Another aspect is a method of treating hypertension in a chronic kidney disease patient in need thereof. The patient is optionally treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent and the method comprising administering an effective amount of a potassium binding agent, such as 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form, to the patient to control the patient's serum potassium into the normal range.

A further aspect is a method of treating hypertension in a heart failure patient in need thereof. The patient is optionally treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent and the method comprises administering an effective amount of a potassium binding agent, such as 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form, to the patient to control the patient's serum potassium into the normal range.

Yet another aspect is a method of treating hypertension in a type 2 diabetes mellitus patient in need thereof. The patient is optionally treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent and the method comprises administering an effective amount of a potassium binding agent, such as 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form, to the patient to control the patient's serum potassium into the normal range.

Yet a further aspect is a method of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The method comprises administering an effective amount of 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form to the patient to increase or stabilize the