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Clinical Pharmacology of Spironolactone

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ABSTRACT

Spironolactone and two of its metabolites (7a-thiomethyl-spironolactone) and canrenone are aldosterone antagonists that bind to cytoplasmic mineralocorticoid receptors in the distal tubules of the kidney and promote sodium and water excretion as well as potassium retention. Spironolactone, after oral tablet intake, reaches a maximum concentration in 2.6 hrs and an active metabolite (canrenone) reaches a maximum concentration in 4.3 hrs. When taken with food, its bioavailability increases to ~95%. Spironolactone has a half-life of 1.6 hrs, while its metabolite, canrenone, has a half-life of 16.5 hrs, thus prolonging the biological effects of spironolactone. Spironolactone and eplerenone compete with aldosterone for binding to intracellular receptors, causing decreased gene expression and reduced synthesis of protein mediator that activates Na+ channels in the apical membrane and decreased the number of Na+ / K +ATPase pumps in basolateral membrane. Side effects of spironolactone can cause side effects, such as fluid and electrolyte imbalance (hyperkalemia, hyponatremia), mild acidosis, and transient elevation of serum urea nitrogen. Spironolactone used as diuresis in congestive heart failure, ascites, oedema, and nephritic syndrome reduction of hypokalemia induced by other diuretics or amphotericin; primary hyperaldosteronism. Coadministration of diuretics (spironolactone) with non-steroidal anti-inflammatory drugs escalated the pitfall of nephrotoxicity and non-steroidal anti-inflammatory drugs deescalate the hypotensive effect of diuretics.

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Introduction

Spironolactone and two of its metabolites (7a-thiomethyl-spironolactone) and canrenone are aldosterone antagonists that bind to cytoplasmic mineralocorticoid receptors in the distal tubules of the kidney and promote sodium and water excretion as well as potassium retention. As such, these compounds are considered potassium sparing diuretics [1, 2]. Spironolactone is a synthetic steroidal anti-mineralocorticoid agent with a structure resembling that of the natural adrenocorticoid hormone, aldosterone. Spironolactone competes with aldosterone on aldosterone-sensitive Na+ /K+ channels in the distal tubule of the nephron, thereby increasing the secretion of water and sodium while decreasing the excretion of potassium [3-5]. Spironolactone effects both gonadal and adrenal steroidogenesis to elevate plasma gonadotrophin levels in children and to act as antiandrogen at the target tissue level [6].

Pharmacokinetics

Spironolactone is absorbed partially (~65%), is metabolized extensively (even during its first passage through the liver), undergoes enterohepatic recirculation, and is highly protein-bound. It is rapidly and extensively metabolized in the liver to at least 17 metabolites, with canrenone, 7-alphamethylthiospironolactone (two pharmacologically active spironolactone metabolites, and 6-beta-hydroxy- 7- alpha-methylthiospironolactone as the main ones. Spironolactone, after oral tablet intake, reaches a maximum concentration in 2.6 hrs and an active metabolite (canrenone) reaches a maximum concentration in 4.3 hrs. When taken with food, its bioavailability increases to ~95%. Spironolactone has a half-life of 1.6 hrs, while its metabolite, canrenone, has a half-life of 16.5 hrs, thus prolonging the biological effects of spironolactone [7-9].

Mechanism of Action

Spironolactone is a mineralocorticoid receptor antagonist, specifically an antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. Spironolactone is a synthetic steroid that competes for the cytoplasmic aldosterone receptor. It increases the secretion of water and sodium, while decreasing the excretion of potassium, by competing for the aldosterone sensitive Na+/K+ channel in the distal tubule of the nephron. Approximately 5% of the filtered Na+ load is ultimately excreted in the urine or spironolactone and eplerenone compete with aldosterone for binding to intracellular receptors, causing decreased gene expression and reduced synthesis of protein mediator that activates Na+ channels in the apical membrane and decreased the number of Na+ / K +ATPase pumps in basolateral membrane [6,10,11].

Indications

Initially, spironolactone was considered and employed as a potassium-sparing diuretic, but it was subsequently shown to

be a very effective adjunctive agent in the treatment of heart failure. Spironolactone has a primary role in managing patients with heart failure with reduced ejection fraction by halting the disease progression, with significant beneficial effects on morbidity and mortality, across the spectrum of heart failure with reduced ejection fraction, including patients after a myocardial infarction. Furthermore, spironolactone has an important role in patients with resistant hypertension [12-16]. Spironolactone is an androgen receptor antagonist that is an effective treatment for hormonally mediated acne [17]. Spironolactone is therefore interesting in the treatment of primary hyperaldosteronism or for the management of heart failure in both adults and infants. This drug is also used to treat refractory edema reducing, for example, lung congestion in premature infants. In neonates like in adult having swallowing difficulty (mostly in neurology, gastroenterology, geriatric and reanimation departments), oral medication is given through a nasogastric tube making liquid formulations preferable. These liquid formulations should preferably have a minimal spironolactone content of 3 mg/ml to minimize the extra water-load to kidneys. Presently, this synthetic aldosterone antagonist has achieved unparalleled significance as a therapeutic agent effective against various diseases such as pediatric, edema, cirrhosis of the liver, malignant, nephrosis and primary hyperaldosteronism. Spironolactone in association with thiazide diuretics is used to treat hypertension and in association with furosemide for the treatment of bronchopulmonary dyspepsia [18-24]. Generally spironolactone used as diuresis in congestive heart failure, ascites, oedema, and nephritic syndrome reduction of hypokalemia induced by other diuretics or amphotericin; primary hyperaldosteronism.

Adverse Drug Reactions

Side effects of spironolactone can cause side effects, such as fluid and electrolyte imbalance (hyperkalemia, hyponatremia), agranulocytosis, tachycardia, paraesthesia, weakness, hypotension, oliguria, mental disturbances, hirsutism, menstrual irregularities, mild acidosis, and transient elevation of serum urea nitrogen. Importantly, hyperkalemia can be fatal and patient's potassium level needs to be checked while on spironolactone. As an anti-androgenic agent, it may produce loss of libido, gynecomastia/mastodynia and menstrual irregularities [25-31].

Contraindications

Spironolactone is contraindicated for anuria (absence or defective excretion of urine), hyperkalemia, acute or progressive renal insufficiency, addison's disease (a destructive disease marked by deficient adrenocortical secretion and characterized by extreme weakness, loss of weight, low blood pressure, gastrointestinal disturbances, and brownish pigmentation of the skin and mucous membranes) [23].

Drug Interaction

The label states that spironolactone and its metabolites interfere with radioimmunoassays for digoxin and increase the apparent exposure to digoxin while it is unknown to what extent, if any, spironolactone may increase actual digoxin exposure. Use of a digoxin assay is advised that does not interact with spironolactone. Aspirin inhibit the sodium excretion effect of spironolactone if administered concomitantly. Concurrent administration of spironolactone and barbiturates perhaps escalate the risk of orthostatic hypotension. Coincident administration of potassium sparing diuretics and angiotensin converting enzyme inhibitors exacerbate hyperkalemia since angiotensin converting enzyme inhibitors perhaps cause hyperkalaemia. Spironolactone increases the risk of lithium toxicity if administered coincidently. Coadministration of diuretics (spironolactone) with non-steroidal anti-inflammatory drugs escalated the pitfall of nephrotoxicity and non-steroidal anti-inflammatory drugs deescalate the hypotensive effect of diuretics [32-38].

Conclusion

Spironolactone is a synthetic steroidal anti-mineralocorticoid agent with a structure resembling that of the natural adrenocorticoid hormone, aldosterone. Spironolactone is absorbed partially (~65%), is metabolized extensively (even during its first passage through the liver), undergoes enterohepatic recirculation, and is highly protein-bound. Generally spironolactone used as diuresis in congestive heart failure, ascites, oedema, and nephritic syndrome reduction of hypokalemia induced by other diuretics or amphotericin; primary hyperaldosteronism. Side effects of spironolactone can cause side effects, such as fluid and electrolyte imbalance (hyperkalemia, hyponatremia), mild acidosis, and transient elevation of serum urea nitrogen. Coadministration of diuretics (spironolactone) with non-steroidal anti-inflammatory drugs escalated the pitfall of nephrotoxicity and non-steroidal anti-inflammatory drugs deescalate the hypotensive effect of diuretics.

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Data Sources

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Availability of Data and Materials

The datasets generated during the current study are available with correspondent author.

Competing Interests

The author has no financial or proprietary interest in any of material discussed in this article.

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