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Spironolactone in Dermatology: A Mini Review

Jayakar Thomas [a*#], S. Soundarya [a≡] and S. Vaishnavi [aΦ]

[a] Department of Dermatology, Chettinad Hospital and Research Institue, Kelambakkam, Chennai, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Mini-review Article

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ABSTRACT

Spironolactone is a drug, similar in structure to aldosterone and acts as an aldosterone receptor antagonist with an anti-androgenic effect.
This drug has proven to be useful in several dermatological entities, however its use has not been well explored. Its use in diseases such as acne has opened the door to the possibility of new therapies depending on the clinical manifestations of the patients, as well as its possible to use it as a first line treatment. Other diseases associated with the use of spironolactone where its effects have been shown to be useful are hidradenitis suppurativa, hirsutism and female pattern androgenetic alopecia. In this review we discuss the use of spironolactone in different skin diseases that are common in our environment, dosage according to different studies, treatment recommendations and adverse effects; all of the above mentioned in order to use this drug in a daily clinical practice.

Keywords: Acne; hidradenitis suppurativa; hirsutism; polycystic ovary syndrome; spironolactone; androgenetic alopecia.

[#] Professor;
[≡] Assistant Professor;
[Φ] Senior Resident;
**Corresponding author: E-mail: jayakarthomas@gmail.com;*

1. INTRODUCTION

Spironolactone is a drug, similar in structure to aldosterone and acts as an aldosterone receptor antagonist.

The adrenal cortex produces 2 classes of steroids: androgens and corticosteroids which are further divided into mineralocorticoids and glucocorticoids. The main mineralocorticoid is aldosterone, the receptor for which is expressed in the kidney, colon, some glands and in the hippocampus. In the kidney it acts in the epithelium of the distal cortical tubule and cortical collecting tubule to reabsorb sodium and increase excretion of potassium (K+) and hydrogen (H+) and it has been studied that aldosterone is produced locally in the heart and its vasculature so it is considered to act as a local hormone.

Spironolactone is a competitive and reversible aldosterone receptor antagonist and inhibits androgen biosynthesis. This drug is minimally absorbed orally as it is rapidly metabolized in the liver via its active metabolites canrenoic acid and 6β-hydroxy 7α-thiomethyl spironolactone.

Spironolactone was first used in 1954 for the treatment of hyperaldosteronism and has also been used as a potassium-sparing diuretic. It reduces vascular fibrosis, inhibits angiogenesis, decreases vascular tone and reduces portal hypertension, which is why it has been used in liver cirrhosis, and has been shown to reduce the number of people hospitalized for heart failure, It has been shown to reduce hormone reactivation (aldosterone-escape) in patients with stable heart failure treated with angiotensin-converting enzyme inhibitors (ACE inhibitors) and finally there has been renewed interest in this drug because recent clinical studies have shown its potential use in acne, hirsutism, hidradenitis suppurativa, female pattern androgenetic alopecia and precocious puberty [1].

2. ANDROGENIC ACTION ON SKIN AND HAIR

Sex hormones, especially androgens, play an essential role in maintaining the normal function of reproductive organs, among other physiological and pathological functions of different tissues. They are synthetized in the adrenal glands, ovaries, testes, placenta and brain. Their function goes beyond this, as they act on the skin in different processes. The role of androgens and the androgen receptor (AR) have been studied for several years, however their molecular mechanisms in skin disorders remain largely unknown.

In the skin, androgens regulate hair growth, sebum production and secretion, aid wound healing, skin barrier formation and embryogenesis. Androgens in the skin are produced de novo from cholesterol or other circulating adrenal or gonadal precursors, mainly from dehydroepiandrosterone sulphate (DHEA-S). It should be remembered that the development of the skin adnexa, as well as sebum production, will be modified by physiological changes from birth to puberty in response to increased plasma androgen levels, especially DHEA, which is secreted by the adrenal glands, and which is increased exponentially in both sexes at any sign of puberty. Dihydrotestosterone (DHT) stimulation also plays an important role in inducing functional immature sebocytes to express androgen receptors (AR) for the process of lipogenic differentiation. Androgens also regulate the production of apocrine sweat glands which are shown to have elevated levels of 5α-reductase activity and increased DHT concentration; they are also involved in the regulation of multiple enzymes involved in cholesterol synthesis; and given the role of cholesterol as a precursor of pheromones, androgens are shown to play an important role in the synthesis and secretion of these hormones. DHT was also shown to increase the expression of apoprotein D (Apo D), a protein that carries axillary odor molecules [2].

The synthesis of steroid hormones is carried out in various tissues of which the adrenal glands, ovaries, testes, placenta and brain are classically involved. However, the skin constitutes an important peripheral steroidogenic tissue. Genes are expressed in the skin, which are intimately involved in the synthesis of sex hormones such as CYP11A1, CYP17A1, 3β-hydroxysteroid dehydrogenase (3β-HSD), CYP19A1 (aromatase) among others. It is well known that the skin synthesizes steroids de novo from endogenous cholesterol starting from the main precursor, adrenal DHEA-S which is hydrolyzed by steroid sulfatase located in sebaceous glands and dermal papilla cells in terminal hair follicles, while the enzymatic activity of 3β-HSD1 converts DHEA to androstenedione, and 17β-HSD3 converts androstenedione to testosterone. Regarding 17β-HSD3 and its 5 isoforms there is evidence of its high expression in the

keratinocytes of the internal or external root sheath, a pattern similar to that seen in the sebaceous glands especially in the face of over expression of 17β-HSD2; this gene is of great importance since it has been seen in higher proportion in its oxido-reductive function in skin that is not prone to acne compared to the usual topography of this entity [3].

Testosterone is reduced to DHT by the enzyme 5 α-reductase; which is considered the most potent androgen because it cannot aromatize to estrogens and has higher affinity to androgen receptors. The 5α-reductase enzyme presents three isotypes: 5α-reductase type 1, 2 and 3. Type 1 is predominantly expressed in skin and adnexa; because it is overexpressed in certain areas of hair follicles such as occipital hair follicles in hairy skin and beard area, on the other hand especially speaking of isotype 2 this will be expressed in the frontal biparietal and vertex areas, therefore this isoenzyme is involved in the pathophysiology of androgenetic alopecia. It is also expressed in epididymis, seminal vesicles, prostate and genital fibroblasts and type 3 in benign prostatic tissue and is overexpressed in advanced prostate cancer.

3. SPIRONOLACTONE

Spironolactone and two metabolites: 7α-thiomethyl-spironolactone and canrenone bind to cytoplasmic mineralocorticoid receptors and function as aldosterone antagonists [3].

It was introduced into clinical medicine in 1954 mainly for the treatment of hyperaldosteronism, but over time it has become an important drug for the treatment of various diseases as a diuretic and antihypertensive, especially in congestive heart failure, arterial hypertension, chronic renal disease, portal hypertension secondary to liver cirrhosis, among others. In the field of dermatology, spironolactone has been used for its anti-androgenic effects to diminish the effects of testosterone on women's skin and hair [4].

Spironolactone alters steroidogenesis in the gonads and adrenal glands by decreasing the testosterone/estrogen ratio which increases testosterone metabolism and subsequent serum clearance. It may also act peripherally by competing for cytosolic receptors with 5α-dihydrotestosterone whose deficiency results in feminization.

Androgens generate hyper seborrhea, promote follicular hyperproliferation and plugging, which contributes to abnormal desquamation of follicular epithelial cells with the consequent development of acne. In addition, sebaceous glands have more steroid enzymes to convert DHEA-S and androstenedione to testosterone and dihydrotestosterone, which increases sebaceous gland activity, and a nuclear receptor for androgens has been found to be more sensitive in women with acne [5,6].

It has a high oral availability, up to 90%, and for its distribution it is 98% bound to proteins. It has a mainly hepatic metabolism with a half-life of 12.5 hours and its metabolites are excreted in urine and bile [7,8].

The main adverse effects are hyperkalemia which is more frequent in patients with impaired renal function and those receiving potassium supplementation or concomitant therapy with ACE inhibitors. Dehydration and hyponatremia occur occasionally, especially when the drug is combined with other diuretics. Side effects such as hyperestrogenemia occasionally occur in patients receiving high doses including gynecomastia, decreased libido, and relative impotence in men; menstrual irregularities and abnormal breast tenderness in women.

The uses of spironolactone include [9-10,7]:

- Acne of adolescent female
- Hidradenitis suppurativa
- Female pattern androgenetic alopecia
- Hirsutism

4. CONCLUSIONS

The diseases mentioned in this review have multifactorial origin where the androgenic effect plays an important role and is the main trigger. Spironolactone is an aldosterone antagonist diuretic and is considered an underused therapeutic alternative in the various diseases mentioned above, it is a low-cost drug with a good safety profile. This review was carried out in order to consider this drug as a first-line therapy for female pattern acne where it could reduce the use of antibiotics, avoiding resistance to them as well as new alternatives for the treatment of androgenetic alopecia, hirsutism, among others.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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