Therapeutic Evaluation of Spironolactone and Finasteride in the Treatment of Acne Vulgaris

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ABSTRACT:

BACKGROUND:

Antiandrogens have been developed to treat acne; spironolactone, an androgen receptor blocker, and finasteride, 5 alpha reductase inhibitor, are two antiandrogens that can be used to treat acne vulgaris.

OBJECTIVES:

To evaluate the effectiveness and safety of spironolactone , finasteride, and combination of both drugs in the treatment of acne vulgaris.

PATIENTS&METHODS:

This single blinded uncontrolled clinical therapeutic trial was done in the Department of Dermatology and Venereology – Baghdad Teaching Hospital- in a period from December 2004 to October 2006.

The patients were classified according to the number of inflammatory lesions as having mild, moderate and severe acne. Severe acne was excluded from the study. History & close examination were performed to all patients regarding all points related to the disease. Sixty-nine patients with acne were divided into three groups and were instructed to take the following drugs for two months; group A: spironolactone 100 mg/day, group B: finasteride 5 mg/day, and group C: combination of both drugs.

The clinical assessment was done by counting the number of inflammatory lesions every two weeks for two months, recording any local or systemic side effects, & comparison between the number of inflammatory lesions before and after treatment was done.

RESULTS:

Sixty patients had completed this work, whose mean± SD of their ages of the three groups totally was 18.8 ± 2.3 years and for group A, group B, and group C as follow : 19 ± 2.6, 19.3 ± 1.9, and 18.1 ± 2.4 respectively, with 20 patients in each group.

Spironolactone was statistically significant in reducing the number of inflammatory lesions, finasteride was beneficial but did not reach a statistically significant level as spironolactone, and combination of both drugs was more effective in the treatment of acne vulgaris than spironolactone alone but did not reach a statistically significant level.

CONCLUSION:

Spironolactone is a good alternative drug to be used in patients with acne singly or in combination therapy with finasteride.

KEY WORDS: acne vulgaris, spironolactone, finasteride.

INTRODUCTION:

Acne vulgaris is a chronic inflammatory disease of pilosebaceous units, which is characterized by the formation of comedons, erythematous papules and pustules on the face, neck, upper trunk, and upper arm. It occurs primarily in the oily (seborrheic) areas of the skin. [1, 2]

It is a disease of adolescents with 90% of all teenagers being affected by some degree. The following factors are involved in the pathogenesis of acne enhanced sebum secretion; pilosebaceous duct obstruction, micro-organisms, and hormonal factor. [1]

Androgens are the main stimulants for sebum excretion. In acne, the sebaceous glands respond excessively to what are normal levels of these hormones (increased target organs sensitivity). This may be caused by *5α-reductase* activity being higher in target sebaceous glands than other parts of the body [3].

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A combination of the effects of circulatory androgens and the effects of their metabolism at the hair follicle modulate sebum production and acne severity. Androgens free testosterone, dihydroepiandrosterone sulfate [DHEAS] are the most important hormones in pathogenesis of acne [4].

There are many modalities of therapy; including both topical like benzoyl peroxide, adapalen, and topical antibiotics and systemic like oral antibiotics, retinoids, & anti-androgen therapy. [1]

Anti-androgen therapy is an option of treatment when acne is not responding to conventional therapy. If there are signs of hyperandrogenism, an endocrine evaluation is indicated. Although one indication for hormonal therapy is hyperandrogenism, women with normal serum androgen level also respond well to treatment.[1]

Hormonal therapy choices consist of androgen receptor blockers, androgen production blockers, & androgen metabolizing enzyme inhibitors.

Androgen receptor blocker like Cyproterone acetate, Flutamide, & spironolactone. Spironolactone is potassium sparing diuretic and aldosterone antagonist. It is used in edema associated with congestive heart failure (CHF), treatment of hypokalemia or prevention of it, essential hypertension, and others such as: hirsutism and acne [6]. Spironolactone is a steroidal androgen receptor blocker and has been used in the treatment of androgen mediated cutaneous disorders such as acne, hirsutism, and androgenic alopecia [7].

It can be used with antibiotics or oral contraceptives or as a single therapy. Therefore it can be used when the source of androgen is either adrenal or ovarian or when screening for serum androgen is normal [4].

Studies show that spironolactone at a dosage of 200 mg/day suppresses sebum production by 75% and can reduce lesion counts by up to 75 %. [8].

Side effects of spironolactone are dose related. The incidence is high, but the severity is generally mild and well tolerated. Menstrual irregularities are most common, breast tenderness or enlargement and decrease libido are infrequent. Other effects include mild hyperkalemia, headache, dizziness, drowsiness, confusion, nausea, vomiting, anorexia, and diarrhea [4].

Adrenal androgen production blocker like Glucocorticoids & Oral contraceptives. [2]

Enzyme inhibitors:

Certain enzymes in the skin produce androgens locally, specifically the *5-α reductase* enzyme which converts testosterone to dihydrotestosterone and it has 2 iso enzymes [9]. The conversion of testosterone to dihydrotestosterone is a key reaction for androgen activity. The type 1 isoenzyme is found in scalp skin, while the type 2 isoenzyme is found in prostate [10].

Finasteride, an androgen hormone inhibitor, selectively blocks the production of dihydrotestosterone by a competitive inhibition of *5-α reductase*. It is a potent inhibitor of the type II isoenzyme and is less effective against the type I isoenzyme. So, it will selectively block androgen activity in the prostate and skin and is potentially useful in the treatment of male pattern baldness, hirsutism, and acne. [11]

Finasteride has been shown to be similar in effectiveness to other well established antiandrogen therapies such as cyproterone acetate [12] or spironolactone [13].

Finasteride is generally well tolerated and safe, and the adverse reactions are mild and transient. Patients treated with the recommended dose `of 5mg daily reported impotence and ejaculation disorder.[14] It has no adverse hormonal effect in healthy men.[15] The drug is contraindicated in pregnancy because it may cause abnormalities of the external genitalia of the male fetus.[11]

The aim of the study is to re-evaluate the effectiveness, safety of spironolactone & finasteride singly and in combination in the treatment of acne vulgaris.

PATIENTS & METHODS:

This is a single – blind therapeutic clinical trial that was conducted in Department of Dermatology and Venereology in Baghdad Teaching Hospital during the period from December 2004 through October 2006. The number of enrolled patients with acne vulgaris was 69.

Full history was taken from each patient including age, sex, duration of the disease, previous treatment and ensured that every patient had stopped any systemic and topical treatment at least 2 months before starting the present therapy. Grading the severity of acne was chosen according to following score [6]:

1- Mild acne in which the count of papules is less than 10 and the count of pustules is less than20

2-Moderate acne in which the count of papules is ranging between 10-30 and the count of pustules is ranging from 20-40.

3- Sever acne in which the count papules are more than 30 and the count of pustules is more than 40.

  Severe acne and nodulo-cystic types were excluded from the present study.

Patients were divided into three groups according to the type of therapy:

1- Group A

In this group 23 patients were treated with spironolactone tablet(alctone.medico labs-Homs-Syria)100mg/day, patient were instructed to take

the tablet daily for 2 months and clinical evaluation was done every 2 weeks .The assessment carried out by counting the inflammatory lesions (papules and pustules) and recording any local or systemic adverse effects.

2- Group B

Including 22 patients who were treated with finasteride tablet(prostacare.Hayat pharmaceutical industries Co.Ltd-Amman-Jordan) 5mg/day. Evaluation & follow up were done in similar manner to group A

3 - Group C

Twenty-four patients were treated with a combination of spironolactone tablet 100 mg and finasteride tablet 5 mg daily for 2 months .An assessment & follow up was done to the patients as in group A & group B.

Consent was taken from each patient before using the therapy regarding nature of disease, its course, and duration to take drugs, & their side effects.

Response of patients to treatment is classified into:

1- Good response in which the reduction in the count of inflammatory lesions (papules and pustules) is 50% and more.

2- Partial response in which the reduction in the count of inflammatory lesions (papules and pustules) is less than 50%.

3- No response in which there is no change in the count of inflammatory lesions (papules and pustules).

Statistical analysis:

All data were coded and entered to the computer by using Epi-info version 6.Comparison between all groups was done by using analysis of variance (ANOVA). Comparison before and after treatment in each group was done by using paired t-test, comparison of the patient response to treatment in the three groups done by chi square, and p –value <0.05 was considered as level of significance.

RESULTS:

Sixty –nine patients enrolled in this work, 60 of them had completed the course of treatment [9(13%) patients did not complete treatment and considered defaulters for unknown reasons], their ages ranged between 13–26 years with a mean of 18.8 ± 2.3 years, with 20 patients in each group as follows:

Group A

It included of 11 females and 9 males, their ages ranged from 16-26 with a mean± SD of 19 ± 2.6 years.

Group B

It consisted from 13 females and 7 males, their ages ranged from 17-25 with a mean± SD of 19.3 ± 1.9 years.

Group C

It composed from 12 females and 8 males, their ages ranged from 13-23 with a mean ± SD of 18.1 ± 2.4 years

Comparison between the three groups regarding their ages, number of papules & pustules before therapy showed that there was no statistical significant difference as shown by table 2

The assessment of mean ± SD of papules and pustules count before and after treatment was as follows:

Group A

The mean ±SD of papules before treatment was17.2 ± 6.3 reduced to 9.7 ± 7.2 after treatment .This reduction was statistically significant (P= 0.001).

The mean ±SD of pustules before treatment was 25.5 ± 6.8 reduced to 13.4 ± 8.8 after treatment. This reduction was also statistically significant (P= 0.00001).

Group B

The mean ± SD of papules before treatment was 15.8 ± 5.8 reduced to 13.1 ± 7.5 after treatment. This reduction was statistically not significant (P= 0.21).

The mean ± SD of pustules before treatment before treatment was 23.5 ± 6.3 reduced to 19.8 ± 10.3 after treatment. This reduction was also statistically not significant (P= 0.25).

Group C

The mean ± SD of papules before treatment was 13.8 ± 5.3 reduced to 7.0 ± 5.1 after treatment. This reduction was statistically significant (P=0.0001).

The mean ±SD of pustules before treatment was 21.1 ± 6.3 reduced to 11.0 ± 7.5 after treatment. This reduction was statistically significant (P= 0.00004)**.**

The assessment of the patients' response to treatment in the 3 groups was as follows:

Table 1 : The assessment of the patient's response to treatment in the three groups.

Group	Good response No.	%	Partial response No.	%	No response No.	%	Total No. %
A	11	55	3	15	6	30	20 100
B	4	20	2	10	14	70	20 100
C	13	65	4	20	3	15	20 100

Chi square between group A&B was 6.67 with p=0.035.
Chi square between group A&C was 1.31 with p=0.51.
Chi square between group B&C was 12.55 with p=0.001.

When the three groups compared with each other, it was shown that both group A&C are statistically more significant than group B, and group C was more effective than group A but it did not reach a statistically significant level.

The assessment of side effects:

Group A

In this group 4(36.36%) female patients had menstrual irregularities, 3(15%) patients had headache, 4 (20%) had dizziness, and 2(22.22%) male patients had breast tenderness.

Group B

In this group 7(35%) patients had headache, 5(25%) had dizziness, 1 (14.28%) male patient had breast tenderness, 3(42.77%) male patients had mild breast enlargement, 2 (28.57%) male patients had decreased libido, and 1(14.28%) male patient had testicular pain.

Group C

This group showed that 5(41.66%) female patients had menstrual irregularities, 8(40%) patients had headache, 6(30%) had dizziness, 3(37.5%) male patients had breast tenderness, 2(25%) male patients had mild breast enlargement, and only 1 (12.5%) male patient had decreased libido.

Table- 2: The difference among treatment groups before and after therapy (ANOVA) used for comparison.

F-test		P-value
AGE	1.301	.280
Papules before	1.695	.193
papules after	4.116	.021
Pustules before	2.272	.112
Pustules after	5.165	.009

DISCUSSION:

Acne vulgaris is an extremely common skin disorder among adolescents, it can persist for years and result in disfigurement, dyspigmentation, and permanent scarring and it can have serious adverse effects on psychosocial development, resulting in emotional problems, depression, & withdrawal from society. [16]

Many therapies had been introduced to control acne vulgaris which are based on multiple etiological factors such as microbial, hormonal, these drugs are either topical such as erythromycin,clindamycin ,benzoyl peroxide and retinoic acid or systemic which include antibiotic such as tetracycline ,erythromycin and co-trimoxazole or oral retinoid like Isotretinoin or hormonal therapy like cyproterone acetate [17].

Androgens play a key role in the etiopathogenesis of acne vulgaris. In most patients excessive androgen production may be demonstrated [18]. While in the remaining patients who have normal circulating androgens, enhanced peripheral androgen metabolism has been found, either the androgen receptors are high or the target organs were hypersensitive to the circulating androgens. Thus many agents used to target hyperandrogenism have been shown to improve skin lesion [12].spironolactone has been used in the treatment of acne vulgaris and reported to be effective [7] but in a dose of 200 mg/day &longer duration of therapy while in the present study, spironolactone was effective in a dose of 100 mg/day with shorter duration of therapy.

Finasteride has been used by a single study and shown to be beneficial in the treatment of acne vulgaris and reach a statistical significant level [19], while the present work used a higher number of patients & the duration of therapy was longer, still was beneficial but did not reach a statistical significant level and finasteride was more effective in controlling papules rather than pustules.

Combination of drugs, spironolactone & finasteride, has been shown by the present work to be more effective than spironolactone alone but did not reach a statistical significant level.

The side effects of spironolactone were well tolerated, comparable to what had been published [7] and did not need to stop therapy in any patient. Also some side effects were seen in patients using finasteride and were similar to what has been published. [13, 19]

Multiple drug regimens have been introduced to patients with acne vulgaris mainly to increase the effectiveness of therapeutic agents, to minimize the side effects of drugs, and might shorten the duration of therapy [20]. So, according to the results of present work, we encourage to use spironolactone and finasteride in combination with other topical and/or systemic therapies of acne vulgaris.

CONCLUSION:

That spironolactone was statistically significant mode of therapy in treatment of acne vulgaris. Although finasteride did not reach a statistical significant level, it had some beneficial effect. However combination of both drugs was more effective than spironolactone alone.

REFERENCES:

1. Cunliffe WJ. And Simpson NB. Disorder of the Sebaceous Glands. In: *Rook's Text Book of Dermatology*, Burns T, Breathnach S, Cox N, Griffiths C. vol 2, 7th ed.Blackwell Scientific Publication, 2004; 43: 1927-1984.
2. Odom RB, James W, Timetly BG. Acne. In: *Andrews Disease of the Skin, Clinical Dermatology,* 9th ed. WB Sounder Company Philadelphia 2000; 13: 284-306.
3. Hunter JAA, Savin JA, Dahl MV. *Sebaceous and Sweat Gland Disorder.* In*: Clinical Dermatology*, 3rd ed., Blackwell Publishing Company 2002; 21:148-162.
4. Habif TP. *Acne, Rosacea and Related Disorder.* In*: Clinical Dermatology, A color Guide to Diagnosis and Therapy*, 4th ed. Mosby 2004; 7: 162-194.
5. Shaw JC. Hormonal therapies in acne. Expert Opin Pharmacother 2002; 3: 865-874.
6. Karch AM. *Lippincott's Nursing Drug Guide*. Lippincott, William and Wilkins 2003; 522-523.
7. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenetic alopecia.*Br J Dermatol* 1985; 112: 124-125.
8. Carmina E., Lobo RA. Hirsutism, Alopecia and Acne. In: *Principles and Practice of Endocrinology and Metabolism*, 3rd Ed, JB Lippincott, Philadelphia 2001; 991-1008.
9. Thibutot DM. Bayen E. Immunlocalization of *5α. Reductase* isoenzymes in acne lesion and normal skin. *Arch Dermatol* 2000; 136: 1185-1189.
10. Eicheler W, Dreher M, Hoffmann R. Immunohistochemical evidence for differential distribution of *5-α reductase* isoenzyme in human skin. *Br J Dermatol* 1995; 133: 371-376.
11. Rittmaster RS. Finasteride. *N Engl Med* 1994; 330: 120-5.
12. Venturoli S, Marescalchi O, Colombo FM, Macrelli S, Ravaioli B, Bagoli A, Paradisi R, Flamigni C. A prospective randomized trial comparing low dose flutamide, finasteride, ketoconazole and cyproterone acetate-estrogen regimens in the treatment of hirsutism. *Journal of Clinical Endocrinology and Metabolism* 1999; 84: 1304-10.
13. Fruzzetti F, Bersi C, Parrini D, Ricci C, Genazzani AR. Treatment of hirsutism :comparisons between different antiandrogens with central and peripheral effects. *Fertility and Sterility* 1999; **71**: 445-51.
14. Gormely GJ, Stoner E, Bruskewitz RC. The effect of finasteride in men with benign prostatic hyperplasia. *N Engl J Med* 1992; 327:1185-91.
15. Rittmaster RS, Lemay A, Zwicker H. Effect of finasteride on serum gonadotropins in normal men. *J Clin Endocrinol Metab* 1992; **75**: 484-8.
16. Koo JY, Smith LL. Physiological aspect of acne. *Pediatr Dermatol* 1991; **8**:185-8.
17. Brown S, Shalita A. Acne vulgaris treatment. *The Lancet* 1998; 351:1872-1875.
18. Slayden SM, Moran C, Sans WM, Boots LR, Azziz R. Hyperandrogenemia in patients presenting with acne. *Fertility and Sterility* 2001; **75**: 889-92.
19. Carmina E, Lobo RA. A comparison of the relative efficacy of antiandrogens for the treatment of acne. *Clinical Endocrinology* 2002; **57** :231-4.
20. Faure M, Faure ED. Hormonal treatment of acne. *Ann Dermatol Venereol* 2003; 130: 142-7.