Lack of effect of spironolactone on hair shaft diameter in hirsute females

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Summary: Because of its anti-androgenic activity spironolactone 50–200 mg daily is advocated widely for the management of female hirsutism but this practice lacks adequately controlled experimental support. In a double-blind placebo controlled study of the efficacy of spironolactone 100 mg daily in idiopathic hirsutism we were unable to demonstrate objective benefit from spironolactone treatment. The mean effect of spironolactone given over a 9 month period was to increase hair shaft diameter by + 15% with 95% CI (– 0.4% to + 29%). In addition there were no changes in circulating serum androgen concentrations.

Introduction

Spironolactone is an aldosterone antagonist in clinical use as a potassium sparing diuretic and antihypertensive agent. Its side effects of gynaecomastia in men and menstrual disturbance in females have been attributed to antiandrogenic activity probably mediated peripherally by competitive inhibition of the binding of dihydrotestosterone to cytosol receptors.^{1,2} Although not licensed for the treatment of hirsutes, there have been reports that this accessory property of spironolactone may be useful therapeutically in hirsutism of various aetiologies.^{3–15} However, all these studies had serious design flaws (Table I). Only one investigation⁵ included a 'control' group – but this was not matched with the spironolactone treated group for duration or severity of hirsutism and was not studied simultaneously, casting doubt on its validity. Accordingly we have conducted what we believe to be the first double-blind randomized placebo controlled study of spironolactone in hirsutism.

Methods

Thirty-eight females with a presumptive diagnosis of idiopathic hirsutism gave written informed consent for the investigation which was approved by the hospital ethical committee. The study was a double-blind parallel group comparison of spironolactone 100 mg daily and placebo, administered for 9 months. The patients were paired, one member of each pair being

randomized to active treatment and the other to placebo. Pairs were matched primarily for menstrual regularity (or irregularity) but also, as closely as possible, for duration and degree of hirsutism (Ferriman & Gallwey Index¹⁶), family history of hirsutism, age of menarche and presence of acne to ensure equal allocation to the treatment groups of any patients with unrecognized polycystic ovary syndrome. Patients in each pair were treated simultaneously to obviate the potential influence of seasonal variation on hair growth.

We used changes in hair diameter as an objective index of hair response to spironolactone since it is readily measurable and parallels changes in length.^{17,18} Other techniques for the assessment of hair growth are available including measurement of hair length,^{17,18} hair weight¹⁷ and incorporation of ³⁵S cystine into growing hairs,¹⁹ but these offer no advantage over hair diameter. Measurements were made before treatment and at 6, 12, 24 and 36 weeks of treatment. Hair shavings were taken from a 5 cm² patch delineated on the right thigh of each subject at the outset of the study; this area was otherwise untreated thereafter. The shavings were mounted on a microscope slide and shaft diameter measurements were taken from each of ten separate hairs (to minimize the influence of hair shaft diameter variation along each hair shaft). The measurements were made with a Wild M20 microscope with a drawing tube attachment and a digitising tablet coupled to an Apple IIe microcomputer. The lower limit of sensitivity at 10 × magnification was 0.01 mm with a coefficient of variation of 2.8%.

At the end of the study subjects were asked to evaluate subjectively the effect of treatment, specifically with regard to changes in texture and

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Table I Summary of studies reporting benefit from spironolactone in hirsutism

Reference	Type of hirsutism	n	Spironolactone Dose (mg/day)	Assessment Semi-objective	Objective	Control group included
Boisselle & Tremblay (1979) ³	mixed	31	50	–	–	–
Shapiro & Evron (1980) ⁴	mixed	30	200	b	–	–
Cumming <i>et al.</i> (1982) ⁵	mixed	11	200	b	1	+
Nielsen (1982) ⁶	mixed	21	50	a	–	–
Messina <i>et al.</i> (1983) ⁷	mixed	18	200–400	b	–	–
Milewicz <i>et al.</i> (1983) ⁹	PCOS	34	100	b	–	–
Spandri <i>et al.</i> (1984) ¹⁰	mixed	9	100	–	3	–
Lobo <i>et al.</i> (1985) ¹¹	idiopathic	30	100–200	–	1	–
Pittaway <i>et al.</i> (1985) ¹²	mixed	10	100–150	a	–	–
Dorrington-Ward <i>et al.</i> (1985) ¹³	idiopathic	14	150	b	1,2	–
Evans & Burke (1986) ¹⁴	mixed	48	200	a,b	–	–
Tremblay (1986) ¹⁵	mixed	379	50–75	a	–	–

Type of hirsutism: PCOS refers to polycystic ovarian syndrome, ‘mixed’ refers to probable inclusion of idiopathic hirsutism and PCOS.

Assessment: (a) frequency of hair removal; (b) hair distribution/density score; (1) hair shaft diameter; (2) hair length; (3) hair weight.

colour of the hair and any change in the frequency of epilation. They were also questioned about changes in acne (if present) and greasiness of the skin and hair.

Serum androgens, gonadotrophins, prolactin and plasma canrenone (a major metabolite of spironolactone) were assayed on each occasion that hair shaft diameter was measured. Testosterone (T) and androstenedione (A2) were estimated by radio-immunoassay (RIA) following ether extraction of serum. Dehydroepiandrosterone sulphate (DHAS) concentrations were measured by RIA without prior extraction. Sex hormone binding globulin (SHBG) capacity of serum was assessed by saturation with ³H-dihydrotestosterone in a modification of Rosner’s method.²⁰ Serum luteinising hormone (LH), follicle stimulating hormone (FSH) and prolactin were measured using conventional RIA. Gonadotrophin assays were standardized using the second international reference preparation MRC 78/549 for FSH and the first international reference preparation MRC 68/40 for LH. Prolactin assays were calibrated against MRC 75/504. Plasma canrenone was measured by high performance liquid chromatography. The between batch coefficients of variation for serum and plasma variables were 10–15%.

Results

Of the 19 pairs who entered the study 11 completed the protocol. Two pairs were withdrawn because of non-compliance in the actively treated subjects (as assessed by plasma canrenone concentrations). Three withdrawals were due to spironolactone-induced menorrhagia; the remainder opted out for personal reasons unrelated to drug therapy.

Hair diameter

Results for hair shaft diameter are presented in Figure 1. To simplify presentation, results are expressed for baseline, mean of 6 and 12 weeks treatment and mean of 24 and 36 weeks treatment. Hair diameter was not altered significantly by spironolactone. Compared to placebo, mean changes after spironolactone were +15% (95% CI –0.4% to +29%) where a positive sign denotes increase in hair diameter. Thus the benefit of spironolactone in reducing hair diameter is unlikely to exceed 0.4%.

Figure 1 Effect of spironolactone on hair shaft diameter (results expressed as mean, vertical bars s.e.m.).

Subjective responses

Subjective assessments of response to spironolactone and placebo are illustrated in Figure 2. A trend favouring benefit from spironolactone was noted – but this did not achieve statistical significance.

Serum hormone concentrations

Results are summarized in Table II. No significant changes in hormone concentrations were noted.

Plasma canrenone

Plasma canrenone concentrations exhibited considerable intra-patient and inter-patient variability but confirmed compliance in all but the two subjects mentioned above.

Discussion

Previous workers have reported that spironolactone 50–200 mg daily, for 3 months to 13 months, results in improvement in female hirsutism.^{3–15} These findings have depended on entirely uncontrolled observations^{3,4,6–15} and on a study where controls were clearly inadequate.⁵ Furthermore, assessment of hair growth has mainly been subjective^{3,6,8,12–14} or, at best ‘semi-objective’ relying on hair distribution or density scores, or frequency of hair removals^{4,6,7,9,12–15} (Table I). Three uncontrolled studies^{5,11,13} have reported benefit of spironolactone on the basis of hair

Figure 2 Subjective assessment of effect of spironolactone on hair growth.

diameter measurement but in this carefully controlled study using the same objective measurement we have shown that spironolactone is unlikely to have a clinically important effect on hair growth in hirsute females even when given for 9 months. Subjective assessment did show a trend towards improvement

Table II Effect of spironolactone on androgens, gonadotrophins and prolactin concentrations (results expressed as mean ± s.e.m.)

Variable (units)	Normal range	Group	Basal	Mean of 6 & 12 week assessments	Mean of 24 & 36 week assessments
T (nmol/l)	1.0–3.2	P	3.1 ± 0.2	3.0 ± 0.3	2.6 ± 0.3
		S	3.3 ± 0.3	2.7 ± 0.2	2.5 ± 0.2
A2 (nmol/l)	2.0–13.0	P	9.1 ± 1.0	8.2 ± 1.6	7.3 ± 0.9
		S	8.2 ± 1.0	6.5 ± 1.0	7.8 ± 1.0
DHAS (µmol/l)	2.0–11.0	P	6.6 ± 1.0	5.7 ± 1.0	6.3 ± 0.9
		S	7.0 ± 0.8	7.6 ± 1.0	6.6 ± 0.9
SHBG (nmol/l)	30–120	P	30.4 ± 3.7	32.1 ± 4.8	35.2 ± 5.5
		S	30.2 ± 4.9	36.9 ± 4.3	35.9 ± 5.2
LH (U/l)	<2–15	P	8.2 ± 1.6	11.4 ± 2.3	8.5 ± 1.6
		S	10.1 ± 1.9	12.8 ± 2.6	11.0 ± 2.4
FSH (U/l)	<1–92	P	3.7 ± 0.5	4.3 ± 0.8	4.6 ± 0.7
		S	6.2 ± 2.7	4.3 ± 0.5	3.9 ± 0.4
Prolactin (mU/l)	60–360	P	339.5 ± 62.5	303.6 ± 43.8	227.7 ± 71.1
		S	407.2 ± 130.8	357.3 ± 75.1	336.8 ± 109.3

Group: P = placebo, S = spironolactone treated.

with spironolactone but, in three patients who reported benefit, spironolactone was associated with reduced menstrual irregularity and, in four with favourable effects on acne or hair greasiness. These ancillary changes although 'antiandrogenic' may have influenced subjective judgement of overall outcome and emphasize the importance of objective criteria in the evaluation of therapy for hirsutism.

Plasma testosterone concentrations tended to fall during spironolactone treatment but this reduction was paralleled in the control group. Many previous reports have emphasized decreases in circulating testosterone levels^{3-5,9-11,13,14} in support of the concept of an antiandrogenic effect of spironolactone being responsible for the assumed benefit. Such findings are likely to be spurious arising from the lack of adequate control patients in these studies.

Although no objective benefit of spironolactone was

seen in our study, the drug was well tolerated. Menorrhagia was equally frequent in spironolactone and placebo treated patients and, in some, menstrual periods were more regular while taking the active agent. Spironolactone may be of benefit when used in combination with oestrogen or dexamethasone as suggested by uncontrolled observations¹² but this requires confirmation. Meanwhile our study provides no evidence to support the use of spironolactone as a single agent in the therapy of female hirsutism.

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