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CONTENTS

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SPIRONOLACTONE IN THE PRESURGICAL THERAPY OF MALE TO FEMALE TRANSSEXUAL PHILOSOPHY AND EXPERIENCE OF THE VANCOUVER GENDER DYSPHORIA CLINIC

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SUMMARY

Vancouver General Hospital has had, for approximately 5 years, a number of individual specialists working together in the care of transsexual patients. For the past year, a formal multidisciplinary clinic has been in operation. In March, 1986, the provincial medical plan recognized the Gender Dysphoria Clinic by agreeing to fund gender reassignment surgery for patients who were approved by the program.

The philosophy of the clinic is to support or assist each person who meets the criteria for transsexualism - belief that he/she is in a body of the wrong sex - to fulfill the chosen gender role. A new endocrine therapy was developed to facilitate this transition. This treatment regime evolved from experience with spironolactone, an antiandrogen, in treating female hirsutism.

Sixty-one men with true transsexualism were referred to the clinic. The ten who had previous castration or reassignment surgery and one who discontinued therapy were omitted from further analysis. Twenty-three patients (SPS group) had not received any form of hormonal treatment for their transsexualism. Twenty-seven subjects were initially on some form of conventional therapy (CT group) prior to the initial clinic visit.

The CT group had an average serum testosterone (T) level of 169 ± 193 ng/dl (normal female: 20-80; male: 300-1000 ng/dl). Nine of the CT patients had hypertension ($\geq$ 140/90 mm Hg).

All fifty patients were begun on spironolactone (100-300 mg/day), conjugated estrogen (0.625-5.0 mg/day, 21 days out of 28) and medroxyprogesterone (10-20 mg/day). Initially the progestogen was given during the last two weeks of a 28-day cycle, but subsequently was given daily. For psychological reasons, 10 of the CT group remained on synthetic estrogen, sometimes in greater than physiological doses.

The CT group experienced a drop in T to 87.4 ± 110.0 ng/dl and SPS subjects had reductions from 642 ± 236.2 to 49.2 ± 41.1 ng/dl by 12 months of therapy. Both groups experienced decreased beard and body hair, rapid loss of morning erections and male sexual response, and increased breast development. Systolic blood pressure decreased significantly in both groups (CT group, 129.2 ± 17.3 to 121 ± 14 mm/Hg, $p < 0.002$; SPS group, 127.8 ± 13.6 to 120.5 ± 14.1 mm/Hg, $p=0.05$). Only 1 of the CT patients continued to have BP 140/90. Neither group had a significant weight gain.

Antiandrogen therapy, combined with physiological female steroid therapy, improved the presurgical care of male to female transsexuals making possible a more rapid and safe transition to full-female living.

INTRODUCTION

Within the last decade, the number of transsexuals in the Vancouver area seeking help from the medical profession appears to have increased. In response to this need, a new, multidisciplinary evaluation and treatment program has been developed at Vancouver General Hospital.

This report has two purposes: 1. to share the philosophy and experience of the Vancouver Gender Dysphoria Clinic; and 2. to outline the rationale and clinical experience with spironolactone, an antiandrogen, in the endocrine management of the male to female transsexual.

PHILOSOPHY OF THE VANCOUVER GENDER DYSPHORIA CLINIC

The approach of the clinic is to facilitate the transsexual in achieving full life as a person in the opposite gender role. The program is divided into four phases: 1. Diagnosis; 2. Transition to full cross-gender living; 3. Surgical reassignment; and 4. Long-term follow-up.

The diagnosis is made by two psychiatrists after extensive interviews, with the help of corroborating histories and psychological testing if necessary. Only true transsexuals begin the second or transition phase.

The transition phase is, in essence, a living experiment. The individual experiences the realities of life as the opposite sex, and the clinic personnel observe the transformation in dress, mannerisms, speech, social functioning and emotional stability. It is the time when the full resources of the clinic are used. Social service assists with economic support, vocational testing and training, and job skills. Psychiatric counselling is a necessary and continuing aspect of therapy. Endocrinological management results in the early anatomical and sexual changes. The goals of endocrine therapy are listed in Table 1.

Table 1: Endocrine Therapy of the Male to Female Transsexual

GOALS

1. Feminize body shape and subcutaneous tissue
2. Eliminate male pattern body hair
3. Decrease male sexual responses
4. Do no harm

Given a successful transition phase, the decision concerning reassignment surgery, made by consensus of team members, is very easy. The judgment of the team is based on the firm and demonstrated desire of the individual to be accepted as a person of the opposite sex. There are no arbitrary occupational,relationship or personality barriers to reassignment surgery. If there are any doubts about the transsexual's readiness for surgery, the transition perio is extended and continuing psychotherapy offered.

The follow-up phase of the transsexual's program includes on-going psychiatric counselling. The endocrine management following castration consists of balanced physiological hormone replacement. Follow-visits are rarely required more often than once per year.

ENDOCRINE MANAGEMENT OF THE MALE TRANSSEXUA

Antiandrogens with near-physiological femal hormone therapy

The literature concerning male to female transsexuals has concentrated on the psychological and social well being of thes patients (1-3). Hormonal management has tended to follow the recommendations for high-dose estrogen therapy proposed by Benjamin in early pioneering work (4). Ver little scientific evaluation of hormonal therapy exists. No carefully controlled study has looked at the efficacy, side-effects or long-term safety of the usual forms of therapy i.e., high-dose exogenous estrogen administered orally or parenterall (5), or moderate-dose oral contraceptive pill (6). Endocrine management is further complicated by the tendency of patients to obtain pharmacological doses of hormones from other physicians or illegally. This tendency to self-medicate may be less in a positive therapeutic environment.

Estrogen therapy is associated with dose-related effects on the coagulation and vascular system, and with increased risk of breast and endometrial cancer. In men treated with high-dose estrogens, there is an approximately two-fold increase in thrombophlebitis (7), and an increased risk of myocardial infarction and stroke (8 Four single case reports of estrogen complications in transsexuals are in the current literature, documenting thrombotic cerebrovascular (9), cardiovascular (10), pulmonary vascular (11) lesions and prostatic metaplasia (12).

The Vancouver Gender Dysphoria Clinic has initiated a rational, effective endocrine management program utilizing the anti-hypertensive medication, spironolactone. This drug has powerful hormonal and anti-androgen effects including: 1. decreased

androgen formation in the gonad and adrenal by reduction of cytochrome P-450; 2. inhibition of 11 and 18 hydroxylation; and 3. competition with dihydrotestosterone (DHT) for 8S cytosolic receptors in androgen-responsive tissue, especially the hair follicle (13).

When spironolactone is given to produce a medical castration (reduction of serum T to prepubertal male or female levels) and to interfere with DHT action on the male-type pilo-sebaceous unit, nearly physiological doses of female sex steroids can be used. Low-dose estrogen therapy (usually conjugated estrogen, 1.25 to 2.5 mg/day), given cyclically (three weeks out of four) and always with medroxyprogesterone, 10-20 mg/day, produces feminization without apparent side-effects.

Progesterone, an antiandrogen in its own right, competes with T for binding to the 5-alpha-reductase enzyme which converts T to DHT. Progesterone has trophic effects on the breast, counters any mitotic potential of long-term estrogen as well as suppressing gonadotrophin concentrations (14). Combining physiological doses of cyclic estrogen with cyclic or continuous progestogen is a safe and efficacious way of managing the male to female transsexual. The following report details our preliminary experience with this combined therapy.

METHODS

All biologically normal males with the diagnosis of transsexualism referred for endocrine management between 1980 and 1986 are presented. Standard radioimmunoassay methods were used to measure serum luteinizing hormone (LH), follicle stimulating hormones (FSH) and T (15). Hormone therapy is given as the prescribed dose or, if there is discrepancy, the patient-reported ingested dose. Blood pressure, weight and height were recorded. Where possible, photographic documentation of breast, facial and body hair changes was obtained when subjects were not using electrolysis treatments.

Analysis of data by non-paired t-test was used for between-group comparisons, while paired t-testing was used to compare changes over time in the same individuals. All results are two-tailed. An alpha less than 0.05 is considered significant.

Subjects

Sixty-one men met the criteria for true transsexualism. Ten subjects had post-reassignment surgery or castration and were excluded. One person discontinued therapy after 9 months. The remaining 50 men were divided into two groups based on previous endocrine therapy. Those patients on hormone treatment were considered to have "conventional therapy" (CT group). Their hormone therapy is detailed in Table 2. Patients not previously treated were a prospectively-evaluated spironolactone and physiological steroid (SPS) group. Demographic characteristics of the two groups are presented in Table 3.

Therapy

All subjects on parenteral therapy were switched to oral medications. All estrogen therapy was prescribed cyclically (Fig. 1). Conjugated estrogen (Premarin R) was the preferred type, but those on other preparations were sometimes continued on the same drug. The dose of estrogen was reduced to an equivalent of the full female replacement therapy, 0.625 to 1.25 mg BID. Occasionally, it was not possible to lower the estrogen dose due to resistance from the patient. Medroxyprogesterone (Provera R), 10 to 25 mg/day, was given for two out of four weeks to cover the "estrogen gap" (Fig. 1).

RESULTS

At the initial visit, men on high-dose estrogen therapy had significantly higher T levels after one year of conventional therapy than did the SPS group after 12 months treatment with spironolactone, cyclic estrogen and progestogen (Table 4). The T level was within the normal female range in the SPS group (49.2 ± 41.1; female range 20-80 ng/dl). There were no significant differences in the adrenal androgen, dehydroepiandrosterone sulfate (DHEAS), prolactin or LH serum levels. The mean FSH level, however, was higher and nearly reached significance (p=0.06).

The SPS group had lower high-density lipoprotein cholesterol (HDL) although

Table 2: Conventional Therapy in 27 Previously Treated Subjects

Therapy	N *	Mean Dose
Injectable estrogen (Estradiol Valerate)	8	20-40 mg (every 2 wks)
Injectable progesterone (Hydroxyprogesterone)	6	50-150 mg (every 2 wks)
Synthetic estrogen	16	7.1 ± 7.2 mg
Conjugated estrogen	15	3.9 ± 2.3 mg
Provera	5	13.0 ± 5.7 mg

*Most patients on injectable hormones were also taking oral preparations.

Table 3: Demographic Data of Two Transsexual Study Groups at Their First Endocrinology Vis

Variable*	Conventional	Spironolactone
Number	27	23
Height (cm)	173.4 ± 6.3	172.6 ± 10.0
Weight (kg)	72.4 ± 14.8	70.3 ± 12.9
Age (yrs)	34.4 ± 10.5	30.7 ± 6.2
Systolic BP	129.2 ± 17.3	127.8 ± 13.6
Diastolic BP	77.7 ± 10.1	79.8 ± 10.4

*None of the variables are significantly different by non-paired t-testing.

Table 4: Initial Visit For The Conventional Therapy Group vs 1 Year Visit For Spironolactone Treated Group

Variable*	Conventional		Spironolactone
Testosterone	169.0 ± 193.3	p=0.03	49.2 ± 41.1
DHEAS	2725.4 ± 1852.4	NS	2508.6 ± 993.9
Prolactin	15.1 ± 9.6	NS	10.9 ± 5.5
LH	8.6 ± 7.4	NS	9.4 ± 3.8
FSH	3.9 ± 4.7	p=0.06	8.4 ± 5.2
HDL	64.2 ± 17.4	p=0.02	48.8 ± 4.9
HbA1c	5.4 ± 1.0	p=0.08	4.7 ± 0.3

*Normal female ranges for hormonal and metabolic data are: Testosterone 20-80 ng/dl; Dehydroepiantrosterone (DHEAS) 820-3380 ng/ml; Luteinizing hormone (LH) 4-20 mIU/ml; Follicle stimulating hormone (FSH) 0.6-11.0 ng/ml; Prolactin 3-20 ng/dl; High density lipoprotein cholesterol (HDL) 35-85 mg/dl; Glycosylated hemoglobin (HbA1c) 3.5-7.0%.

the levels were within the normal female range. Glycosylated hemoglobin (HbAlc), a measure of glucose intolerance, was nearly significantly higher in the CT group. The means for both groups, however, were within the normal range. Cholesterol and triglyceride levels did not differ. Systolic blood pressure was higher in CT subjects, diastolic levels were similar.

Spironolactone and low-dose gonadal steroids were effective in decreasing body and facial hair and in increasing breast size. Softening of facial features and decrease in beard hair is seen in sequential photographs of one subject over 18 months (Fig. 2).

DISCUSSION

Combined therapy with spironolactone, cyclic conjugated estrogen and medroxyprogesterone appears to be effective therapy for male to female transsexualism. Although this is not a double-blind randomized trial, the comparison of results of a conventionally-treated group with an otherwise identical prospectively-studied group has at least descriptive value. Serum T is a measure of the degree of gonadal suppression. T levels are clearly lower on the combined treatment.

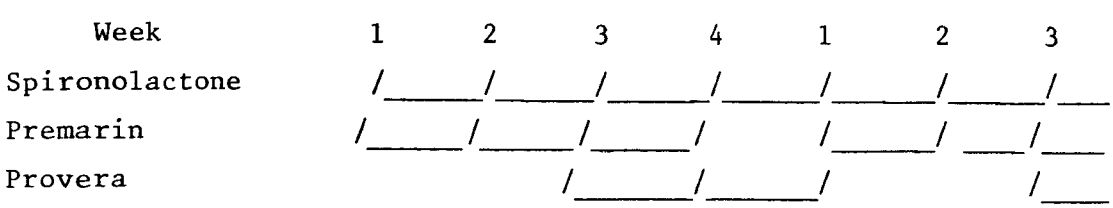
No quantitative assessment of the antiandrogen activity of these differing therapies is available. However, the beard hair was universally observed to decrease in diameter, pigment and extent of distribution. Body androgenic hair in the middle of the chest and abdomen as well as non-androgenic limb hair definitely decreased. Breast tissue increased and nipples developed, although areolae appeared to be less pigmented when lower doses of estrogen were prescribed. The average size of breast tissue was approximately 8 by 8 cm.

The benefit of adding cyclic or continuous medroxyprogesterone is difficult to quantify. It was given to: 1. decrease the theoretical risk of estrogen-related neoplasia; 2. help suppress gonadotrophins; 3. stimulate breast development; and 4. act as an antiandrogen (14). Medroxyprogesterone was the preferred progestogen because it is reported to not lower HDL cholesterol levels (16).

In the SPS group, 3 of 23 individuals had pre-existing hypertension which decreased to normal after a year of therapy. The SPS group had lower HDL levels. HDL cholesterol is estrogen-dependent and the CT group had been on larger doses of estrogen (Fig. 2). However, the levels were adequate enough

Figure 1: a) Diagramatic presentation of the timing of spironolactone, conjugated estrogen (Premarin R) and medroxyprogesterone (Provera R) in cyclic form. Premarin is taken for the first 3 of 4 weeks and provera for the last 2 of 4 weeks; b) A modification of this schedule, in which both spironolactone and provera are taken continuously, is more common.

a) CYCLIC ANTIANDROGEN AND HORMONE THERAPY



b) MODIFIED CYCLIC ANTIANDROGEN AND HORMONE THERAPY

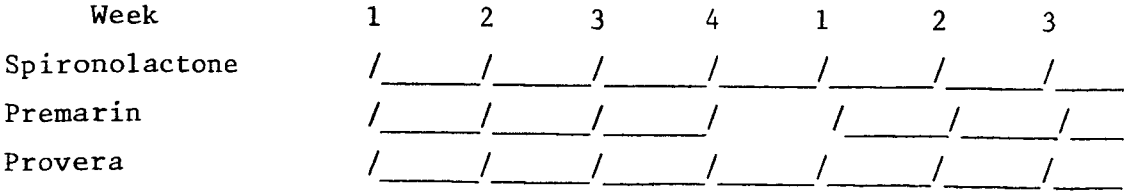


Figure 2. This biological male is seen in an employment photo on the left, after 6 months of experimental anitandrogen and cyclic female steroid use in the middle, and after 12 months of therapy on the right.

to provide protection from ischemic heart disease. The risk for development of diabetes mellitus, as indicated by HbA1c levels, was nearly significantly less in the experimental group.

In summary, spironolactone is a very effective addition to estrogen for the therapy of the male to female transsexual. The addition of medroxyprogesterone may well improve breast development, but the effect, as differentiated from spironolactone, is difficult to quantify. Results of the experimental therapy suggest it not only improves feminization at a lower estrogen dose, but also decreases the risk for estrogen-related complications such as hypertension and weight gain.

REFERENCES

1. Meyer, G.D. 1983. Therapy of male gender dysphoria. Current Psychiatric Therapies, 22: 61-66.
2. Armstrong, C.N. 1980. Transsexualism: a medical perspective. J. Medical Ethics, 6(2): 90-91.
3. Roberta, L.G. 1983. Issues in diagnosis and treatment of transsexualism. Arch. Sex. Behav., 12(5): 445-473.
4. Benjamin, H. 1964. Clinical aspects of transsexualism in the male and female. Amer. J. Psychotherapy, 18: 458-469.
5. Hamberger, C. 1969. Endocrine treatment of male and female transsexualism. In Transsexualism and Sex Reassignment. Richard Green, John Money (Eds.). pp. 291-304. John Hopkins Press: Baltimore.
6. Steiner, B.W. 1985. The management of patients with gender disorders. In Gender Dysphoria. Betty W. Steiner (Ed.). Plenum Press: New York.
7. The Coronary Drug Project Research Group. 1973. The coronary Drug project. Findings leading to discontinuation of the 2.5 mg/day estrogen group. JAMA, 225: 652-657.
8. The Veterans Administration Co-operative Urological Research Group. 1967. Treatment and survival of patients with cancer of the prostate. Surg. Gyne. Obstet., 124: 1011-1017.
9. deMarinis, M., Arnett, E.N. 1978. Cerebrovascular occlusion in a transsexual man taking mestranol. Arch. Intern. Med., 138: 1732-1733.
10. Fortin, C.J. et. al. 1984. Myocardial infarction and severe thromboembolic complications: as seen in estrogen-dependent transsexual. Arch. Intern. Med., 14: 1082-1083.
11. Lehrman, K.L. 1976. Pulmonary embolism in a transsexual man taking diethylstilbestrol. J. Am. Med. Assoc., 235: 532-533.
12. Goodwin, W.E. and Commings, R.H. 1984. Squamous metaplasia of the verumontaniem with obstruction due to hypertrophy: longterm effects of estrogen on the prostate in an ageing male to female transsexual. J. Urol., 131: 553-554.
13. Messina, M., Manieri, C., Biffignandi, P., Massucchetti, C., Novi, R.F. and Molinathi, G.M. 1983. Antiandrogenic properties of spironolactone. Clinical trial in the management of female hirsutism. J. Endocrinol. Invest., 6: 23-27.
14. Gordon, G.G., Southren, A.L. and Tochimoto, S. 1970. Effect of medroxyprogesterone acetate (Provera) on the metabolism and biological activity of testosterone. J. Clin. Endocrinol., 30: 449-456.
15. Whitaker, M.D., Prior, J.C., Scheithauer, B., Dolman, L., Durity, F. and Pudek, R. 1985. Gonadrophin-secreting pituitary tumour; report and review. Clinical Endocrinol., 22: 43-48.
16. Hirvonen, E. et. al. 1981. Effects of different progestogens during post menopausal replacement therapy. New Engl. J. Med., 304: 560-563.