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A PILOT STUDY OF ANDRO-FEME® CREAM (1% TESTOSTERONE)

Principal Investigator: Associate Professor John Eden
Reproductive Endocrinologist, School of Obstetrics and Gynaecology University of New South Wales

Director, Sydney Menopause Centre
Royal Hospital for Women
Locked Bag 2000
Randwick 2031

Telephone: (02) 9382 6777
Fax: (02) 9382 6444
Email : j.eden@unsw.edu.au

SUMMARY

Twenty one postmenopausal women complaining of poor libido who were considered suitable for testosterone treatment were treated with 2 cms of Andro-Feme® cream. Subjects had three blood levels over the first day of usage and then again two weeks later. On day one serum testosterone increased by an average of 1.4 nmol/l and on day fourteen testosterone levels had increased on average by 2.8 nmol/l compared with baseline levels. These serum levels are comparable to those achieved with injectible testosterone or testosterone implants. These data suggest that Andro-Feme® is likely to be a suitable alternative to implant therapy for women requiring testosterone replacement.

INTRODUCTION

For the last fifty years the treatment of menopausal symptoms is largely focused on the physiological replacement of the female sex hormones, oestrogen and progesterone. However, over the last decade in particular it has become evident that for some women female sex hormone replacement is not an adequate treatment for menopause problems.

Appendix 1 contains several articles reviewing testosterone therapy for women. These studies suggest that for some women testosterone replacement improves energy, cognition and libido when added to conventional oestrogen-progesterone therapy. During the reproductive years, testosterone is made in much larger amounts than oestradiol. Thus during the reproductive years serum levels of total testosterone generally fall between 1-3 nmol/l (1,000-3,000 pmol/l) compared with oestradiol which ranges between 100-1000 pmol/l. Testosterone is principally synthesized by the ovaries although there is also a significant contribution by the adrenals. In serum testosterone is bound to sex hormone binding globulin (SHBG) and it is believed that the small proportion of so-called 'free testosterone' is the biologically active fraction. Within the ovary testosterone is converted to oestradiol via the enzyme aromatase which is under the influence of pituitary derived follicle stimulating hormone (FSH). In some target organs such as skin and prostate testosterone is reduced by the enzyme 5 . reductase to the more potent dihydrotestosterone.

Research into testosterone replacement for women has been hampered by a lack of suitable products. Injectibles produce supra-physiological levels which rise rapidly over the first week after the injection, peak and then fall rapidly over the next 2-3 weeks. Testosterone implants are currently the most popular form of long term testosterone replacement and in the usual dose of a 100 mg implant every six months these too can produce levels that are supra-physiological. A suitable cream or gel is most desirable as dosage could be titrated against blood levels. Andro-Feme® has been available in Western Australia for some years now and used successfully by clinicians, however, formal pharmokinetic study have not yet been performed. This current study aims to overcome this lack of information.

SUBJECTS AND METHODOLOGY

The study was approved by the South Eastern Health Authority Ethic Committee. Twenty one postmenopausal women were recruited from the Private Practice of Associate Professor John Eden in the second half of 1999. All women were using hormone replacement therapy mostly Sandrena gel. All women were complaining of poor libido and wished to try testosterone replacement therapy in addition to their HRT. All subjects gave their informed consent and were provided with a patient information sheet and signed a consent form. All study participants had a clinical history recorded and physical examination carried out. Subjects had three samples of blood collected on day 1 and then 3 on day 14. On day 1 subjects were asked to have a sample of blood drawn between 8 and 9 am and then immediately apply 2 cms of Andro-Feme® cream to the inner aspect of their forearm. Another blood sample was collected 4 hours later and then 9 hours later (to measure total testosterone levels). Subjects then continued to use 2 cms of Andro-Feme® cream daily between 8 and 9 am. On day 14 subjects were asked to have a sample of blood drawn between 8 and 9 am (before using that day's dose of testosterone cream). Immediately after drawing the sample of blood their daily dose of Andro-Feme® cream was then applied to the forearm. Again a blood sample was drawn four hours later and then nine hours later. Subjects were asked to report any adverse events.

Total testosterone was measured by Sugerman's Pathology Services. Each patient's three samples were measured in one batch.

RESULTS

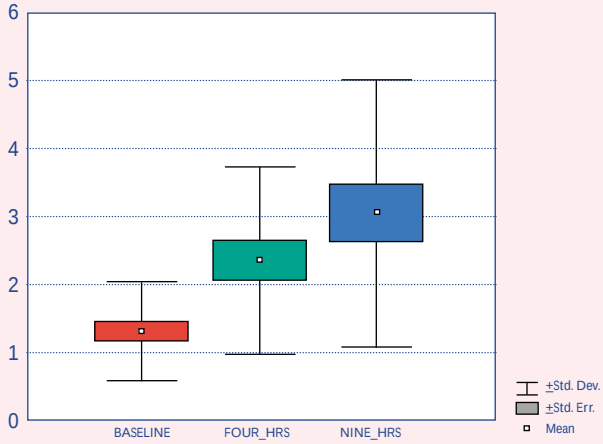
	1 BASELINE	2 FOUR_HRS	3 NINE_HRS	4 MEAN 3_4	5 D1INCRSE	6 IMPLANT?	7 CHR_0	8 CHR_4HRS	9 CHR_9HRS	10 MEAN	11 W2INCRSE	12 AGE
1	2.0	1.7	1.5	1.6	-.4	n	2.7	3.0	3.3	3.0	1.0	54
2	1.4	2.2	2.4	2.3	.9	n	4.1		6.5		5.1	56
3	.7	1.1	2.0	1.6	.9	n	3.1	3.5	5.7	4.1	3.4	51
4	1.3	4.0	4.3	4.2	2.9	n	6.7	5.2	3.5	5.1	3.8	50
5	.6	1.2	1.0	1.1	.5	n	1.2	1.5	2.0	1.6	1.0	39
6	1.0	3.1	2.0	2.6	1.6	n	6.3	7.8	7.2	7.1	6.1	50
7	.9	1.2	1.3	1.3	.4	n	2.2	3.2	4.9	3.4	2.5	52
8	.7	2.3	2.8	2.6	1.9	n	3.2	4.0	4.7	4.0	3.3	
9	1.3	3.1	7.9	5.5	4.2	n	5.1	2.9	6.6	4.9	3.6	49
10	2.2	2.2	5.2	3.7	1.5	y	6.3	3.9	3.3	4.5	2.3	53
11	2.7	2.7	3.1	2.9	.2	y	11.0	3.6	2.6	5.7	3.0	55
12	.9	.9	1.1	1.0	.1	n	1.9	3.8	1.5	2.4	1.5	63
13	.7	1.5	2.5	2.0	1.3	n	1.7	2.9	1.2	1.9	1.2	52
14	3.2	5.1	3.6	4.4	1.1	y	5.9	8.8	3.7	6.1	2.9	51
15	1.0	2.0	2.2	2.1	1.1	n	4.6	7.7	7.2	6.5	5.5	49
16	1.5	6.1	4.9	5.5	4.0	n	3.0	3.6	2.3	3.0	1.5	51
17	.5	1.7	1.3	1.5	1.0	n	4.1	3.1	2.8	3.3	2.8	55
18	.7	1.1	3.2	2.2	1.5	n						46
19	1.2	1.6	2.4	2.0	.8	n	1.2	1.2	2.4	1.6	.4	56
20	1.0	1.3	1.7	1.5	.5	n	1.4	7.4	2.1	3.6	2.6	50
21	2.0	3.4	7.7	5.6	3.6	n						

RESULTS

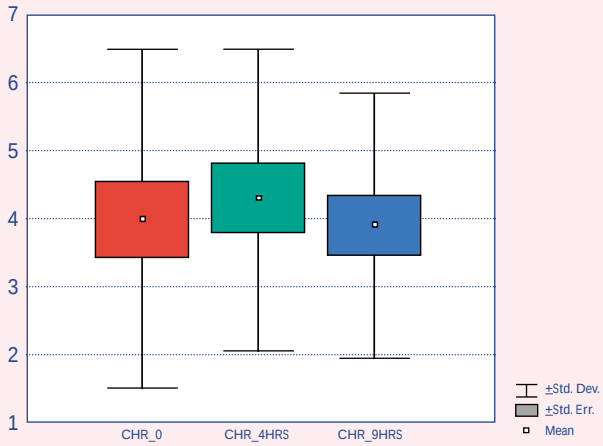
All twenty one women had three samples of blood drawn on day 1 and 19 women also had three samples drawn on day 14. Three of the women had been using testosterone implants prior to using the cream. The raw data is shown as a data file below. Column 1 represents the baseline testosterone levels, column 2 the testosterone level at 4 hours and column 3 the testosterone level at 9 hours on day one. Column 4 represents the mean of columns 2 and 3. Column 5 is the difference between column 4 and column 1 which represents the average increase in testosterone levels compared with baseline on day 1 of usage. Column 6 indicates whether the subject had prior usage of testosterone implants. Column 7 shows the baseline level on day 14 prior to the application of the cream. Column 8 shows the total testosterone level 4 hours after applying Andro-Feme® on day 14 and column 9 represents the testosterone level 9 hours after application of Andro-Feme® on day 14. Column 10 represents the mean of column 8 and 9. Column 11 shows the average increase compared with the baseline in column 1. Column 12 shows the age of the subject at entry into the study.

The table headed 'Descriptive Statistics' gives the mean with 95% confidence levels, median, minimum and maximum, standard deviations and standard errors. It can be seen that the average age of the subjects was 51.6 years, that their mean testosterone level at baseline was 1.3 nmol/l then 4 hours later 2.4 and 9 hours later 3.1 nmol/l on day one. The mean of the 4 and 9 hour results was 2.7 (95% CI 2.0 – 3.4). The mean increase on day 1 was 1.4 nmol/l (95% CI 0.8 – 2.0). On day 14 the mean testosterone level was 4.0 (95% CI 2.8 – 5.2). There was not a significant difference between the 3 testosterone levels on day 14 suggesting that a 'steady state' had been achieved. The average increase on day 14 compared with a baseline at day 1 was 2.8 nmol/l (95% CI 2.1 – 3.6), a statistically significant increase. These results have been summarized as a box and whisker plot for day 1 and day 14. Day 1 shows a significant rise at 9 and 4 hours compared with baseline whereas on day 14 there is no significant difference the three averages, again indicating steady state levels had been achieved.

Box & Whisker Plot for Day 1 testosterone results



Box & Whisker Plot for Day 14 testosterone results



CONCLUSIONS

This pharmacokinetic study shows that 2 cms of Andro-Feme® testosterone cream significantly increased total testosterone levels on day 1 of application. By 9 hours on day 1 the mean level was in the upper limit of normal for the female range. On day 14 levels collected at baseline, 4 hours and 9 hours after application gave results around 4 nmol/l which is just slightly above the upper limit of normal suggesting that some patients could in fact have their dose reduced. The results on day 14 also indicate that monitoring of testosterone levels after 2 weeks usage of the product are not time dependent. Thus in clinical practice it is suggested that a baseline testosterone level be collected prior to the usage of this product, that the usual dose of 2 cms of Andro-Feme® cream be used daily and then 2 weeks later a serum total testosterone level be estimated. It is recommended that if the total testosterone level is > 3.5 nmol/l that the amount of cream used be correspondingly reduced. It is clear from this pilot study that Andro-Feme® testosterone cream is a clinically useful product which produced stable levels of testosterone. Clinical trials with this product are underway.

Appendix 1
References on testosterone therapy

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9. Sherwin B, Gelfand M, Brender W 1985 Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in surgical menopause *Psychosomatic Med* 47:339-351
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STAT. BASIC STATS

DESCRIPTIVE STATISTICS

Variable	Valid N	Mean	Confid. -95.000%	Confid. +95.000%	Median	Minimum	Maximum	Std. Dev.	Standard Error
BASELINE	21	1.30952	.97848	1.64057	1.00000	.50000	3.20000	.727258	.158701
FOUR_HRS	21	2.35714	1.72994	2.98435	2.00000	.90000	6.10000	1.377887	.300680
NINE_HRS	21	3.05238	2.15591	3.94885	2.40000	1.00000	7.90000	1.969421	.429763
MEAN3_4	21	2.70476	2.02593	3.38359	2.15000	1.00000	5.55000	1.491300	.325428
D1INCRSE	21	1.39524	.82045	1.97002	1.10000	-.40000	4.20000	1.262726	.275549
CHR_0	19	3.98421	2.78416	5.18426	3.20000	1.20000	11.00000	2.489816	.571203
CHR_4HRS	18	4.28333	3.18913	5.37753	3.60000	1.20000	8.80000	2.200334	.518624
CHR_9HRS	19	3.86842	2.92324	4.81360	3.30000	1.20000	7.20000	1.961024	.449890
MEAN	18	3.99444	3.16590	4.82299	3.80000	1.56667	7.10000	1.666127	.392710
W2INCRSE	19	2.82105	2.06406	3.57804	2.83333	.40000	6.10000	1.570571	.360314
AGE	20	51.60000	49.41324	53.78676	51.00000	39.00000	63.00000	4.672428	1.044787

LAWLEY PHARMACEUTICALS 672 BEAUFORT STREET, MT LAWLEY 6050 TEL: 08 9371 9524 FREECALL 1800 627 506
FAX 08 9371 7853 EMAIL: lawleyph@iinet.net.au