Pharmacokinetics Of Andromen Forte 5% Cream: A Dose Finding Study

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Summary

Objective:

To determine the pharmacokinetics of a single dermal dose application of Andromen Forte 5% cream in androgen deficient men.

Methods:

Androgen deficient men (n=14) were recruited to participate in a 12 hour pharmacokinetic blood sampling study at the Department of Andrology, Concord Hospital. Three doses (50mg, 100mg, 200mg) of Andromen Forte 5% cream were applied in a single application to the skin of the lower abdomen. Plasma testosterone was measured by validated immunoassay at 0, 1, 2, 4, 6, 8, 10,and 12 hours after dermal application of cream. Urine testosterone output was estimated over the 12 hour period by urine collection. Safety variables included monitoring of application site, and routine biochemical and haematological screens before and after the 12 hour study.

Results:

Three doses (50mg, 100mg, 200mg) of Andromen Forte 5% cream all demonstrated increases in plasma testosterone which were sustained for at least 12 hours after the single dose application of cream to the lower truncal skin. The two higher doses (100mg, 200 mg) produced a greater increase in plasma testosterone than the lowest dose (50mg) but there was no significant difference between 100mg and 200mg doses.

Summary:

Andromen Forte 5% cream can increase plasma testosterone concentrations into the physiological range sufficient for therapeutic replacement purposes. Physiological plasma testosterone concentrations can be maintained by doses of 100mg and 200mg for at least 12 hours after application.

STUDY DESIGN

Testosterone has been marketed for many decades in many different formulations for androgen replacement therapy of men with hypogonadism.
A transdermal testosterone cream, Andromen® Forte 5% w/w, offers a novel new non-invasive means of effectively administering testosterone to hypogonadal males. Andromen® Forte has not been evaluated by the TGA, but has been available for general prescribing in the state of Western Australia since 1998.

The study was an open-label, clinical trial with sequential dose escalation design. The primary end-point is the time-course of the plasma testosterone concentrations for 12 hours following dermal application of a single dose of Andromen Forte 5% cream. Secondary end-points include safety (haematological and biochemical variables, skin irritation) and urinary testosterone output.
The planned sample size was five per dose for each dose level with three planned doses.
Planned dose increments

- Initial dosage 50 mg (2cm cream)
- 2nd dose 75 mg (3cm cream)
- 3rd dose 100 mg (4 cm cream)

Doses were to be titrated if sufficient rises in serum testosterone levels were not observed with allocated dose. The protocol allowed for further dose escalation including 150 mg (6 cm cream) or 200 mg (8 cm cream). The 200 mg dose was the highest dosage included for trial as per the protocol.
The study protocol was approved by the CSAHS Ethics Review Committee (Concord Hospital) in 2001. All subjects accepted into the trial had signed an informed consent.

SUBJECTS AND METHODOLOGY

Participants were recruited from men under the age of 50 years attending the Department of Andrology for routine androgen replacement therapy. These men have classical androgen deficiency due to testicular or hypothalamo-pituitary disorders.

Inclusion criteria

- Established androgen deficiency
- Requiring androgen replacement therapy
- Willing to comply with the study design
- Sufficient time since elapsed last testosterone dose (4 months after last T implants, 3 weeks after last testosterone ester injection, 4 days after last dose of oral testosterone undecanoate)

Exclusion criteria

- Contra-indications to testosterone
- Allergy to the cream base or ingredients used in Andromen Forte 5% cream

Androgen deficient men (five recruited for each of 3 doses, 14 completed the study and one did not attend due to illness) were studied before and for 12 hours after a single administration one dose of Andromen Forte 5% cream. All participants had venous access for blood sampling maintained by a sterile disposable intravenous

cannula. Blood was sampled for plasma testosterone measurements before application of cream and at 1, 2, 4, 6, 8, 10 and 12 hours after cream administration. Blood was also obtained for biochemical and haematological values before and at the end of the 12 hours study. Urine samples were obtained at the start and end of the 12 hour blood sampling period. The time since last bladder emptying was recorded for both samples.Measured doses of cream was applied on the right side of the torso between the level of the nipple and underwear line. Immediately following dispensation of the cream, the participant applied the cream with a rubbing motion to his torso until the cream was absorbed into the skin.
Plasma testosterone was measured within a single immunoassay for each dose using Delfia immunoassay reagents (Perkin Elmer) as described previously [1, 2] with a between-assay coefficient of variability of 7.5% at a mean concentrations of 30 nM/L. Unconjugated (free) testosterone was measured using the same testosterone assay in extracts of urine samples. Urinary free testosterone excretion rate was calculated before and during study with correction for urine creatinine excretion rate. Biochemical and hematological variables were measured by standard autoanalyser methods. Mean and standard error of the mean of plasma testosterone was plotted for each dose as absolute plasma concentrations and as increments above the participants own pre-treatment baseline against time. Due to the limited sampling timeframe, no formal pharmacokinetic parameters (C_{max}, T_{max}, AUC) could be estimated.

RESULTS

All volunteers agreed to participate in the study except for one volunteer in the 200 mg dose who was sick and unable to attend on the scheduled day.
The CSAHS Ethics Committee approved two protocol amendments accelerating the dose escalation. After the results of the plasma testosterone levels of the first dosage of 50 mg Andromen Forte 5% cream were reviewed, it was decided to accelerate the dose escalation so that the second dose would be 100 mg instead of 75 mg. After the results of the 100 mg dosage were reviewed, it was decided to proceed to the 200 mg dosage of cream for the third phase of the trial.

Plasma testosterone concentrations were measured within a single assay for each dose. Plasma testosterone concentrations were increased for each dose (see Figure and Table 1) The increases for 100mg and 200mg were greater than for 50mg. For all doses, the plasma testosterone concentrations remained elevated for 12 hours after application.
There were no clinically significant changes in biochemistry or hematological safety variables due to participation in the study.
No subject demonstrated any evidence of visible skin changes nor did any participant report pain or discomfort at the application site.

CONCLUSIONS

Andromen Forte 5% cream can increase plasma testosterone concentrations into the physiological range sufficient for therapeutic replacement purposes. Physiological plasma testosterone concentrations can be maintained by doses of 100mg and 200mg for at least 12 hours after application.
Detailed clinical and pharmacokinetic trials with this product are underway.

References

1. **Ly LP, Jimenez M, Zhuang TN, Celermajer DS, Conway AJ, Handelsman DJ** 2001 A double-blind, placebo-controlled, randomized clinical trial of transdermal dihydrotestosterone gel on muscular strength, mobility, and quality of life in older men with partial androgen deficiency. J Clin Endocrinol Metab 86:4078-88.

2. **Jin B, Conway AJ, Handelsman DJ** 2001 Effects of androgen deficiency and replacement on prostate zonal volumes. Clin Endocrinol (Oxf) 54:437-45.

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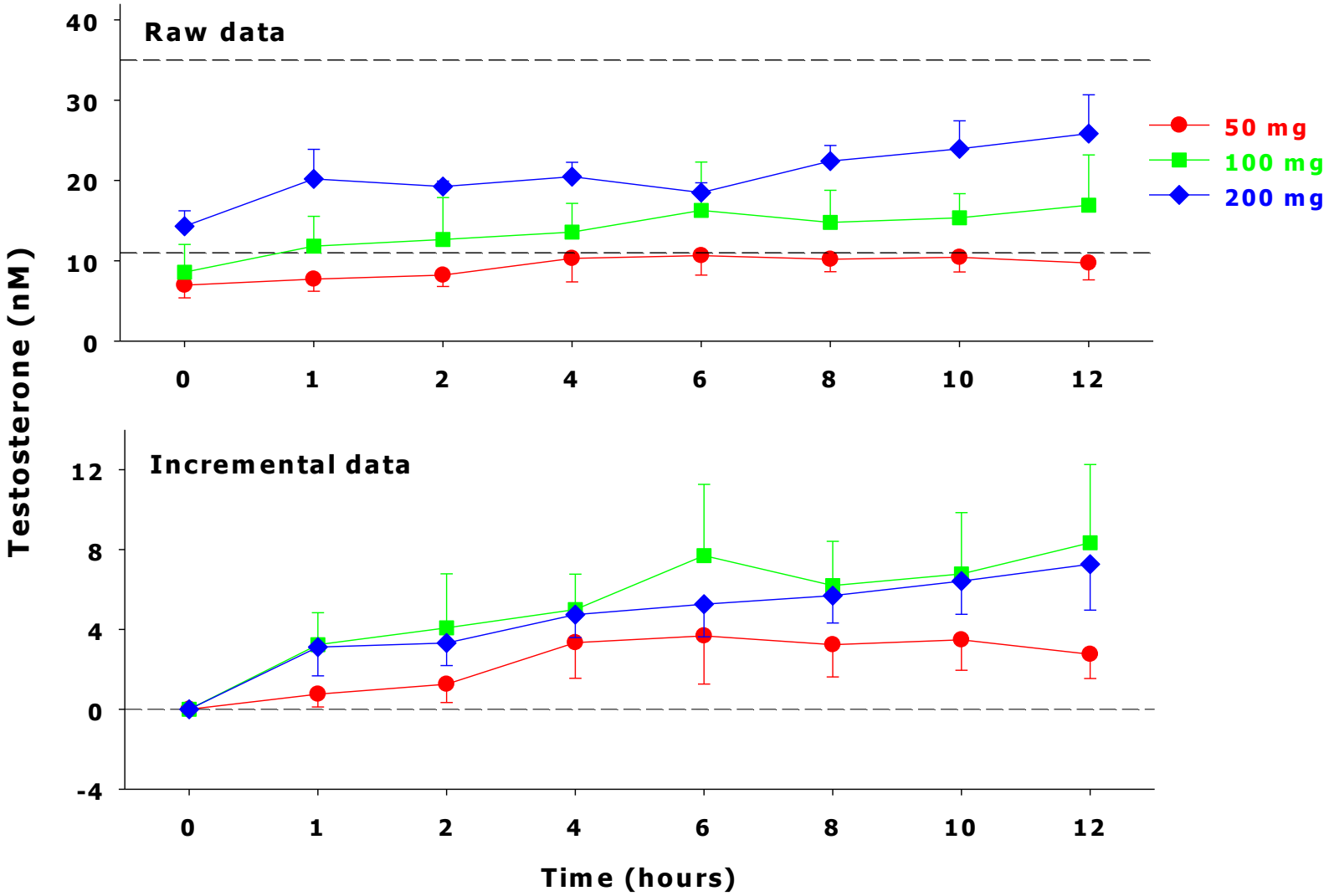
Raw data
Incremental data
Testosterone (nM)
Time (hours)
50 mg
100 mg
200 mg
40
30
20
10
0
12
8
4
0
-4
0
1
2
4
6
8
10
12

Plasma Testosterone Concentrations After Single Application of Andromen Forte 5% Cream

Subjects (ID)	Diagnosis	0	1	2	4	6	8	10	12
50 mg dose									
KP (1)	Secondary hypogonadism	1.4	2.8	3.2	3.1	8.7	9.3	8.5	4.2
JX (2)	Primary hypogonadism	9.2	8.2	9.7	10.9	8.6	10.3	11.7	9.4
SD (3)	Castrate	9.1	11.8	11.7	12.8	20.3	15.5	16	16.4
CB (4)	Prolactinoma	9.6	9.4	7.7	19.6	8.2	10.1	11.1	11.8
RE (5)	Primary hypogonadism	5.5	6.4	8.8	5.1	7.4	5.8	4.9	6.8
100 mg dose									
DD (6)	Klinefelter syndrome	3.8	12.4	11.5	14.4	17	15.7	19.5	14.2
PP (7)	Primary hypogonadism	19.5	23.7	31.9	25.6	38.4	29.3	22.6	40.8
PB (8)	Castrate	2.1	1.6	0.9	4.1	3.9	5.8	5	3.6
AC (9)	Kallmann's syndrome	14	14.5	12.1	14.5	14.7	13.4	13.8	13
BC (10)	Castrate	3.5	6.9	6.9	9.3	7.4	9.7	15.9	13
200 mg dose									
SM (11)	Hemochromatosis	19.7	20.9	20.7	21.3	19.5	20.8	26	23.1
JG (12)	Castrate	10.6	30.3	19.9	24.9	21.5	25.4	23.9	37.6
RG (13	Castrate	DNA*							
GB (14)	Klinefelter's syndrome	12.9	15.8	17.6	16.4	16.5	25.8	31.3	28.2
BJ (15)	Primary hypogonadism	14	13.8	18.8	19.3	16.5	17.7	14.6	14.5

* Did not attend due to illness on scheduled day.