#392 Pharmacokinetics of oestriol cream using quantitative liquid chromatography tandem mass spectrometry

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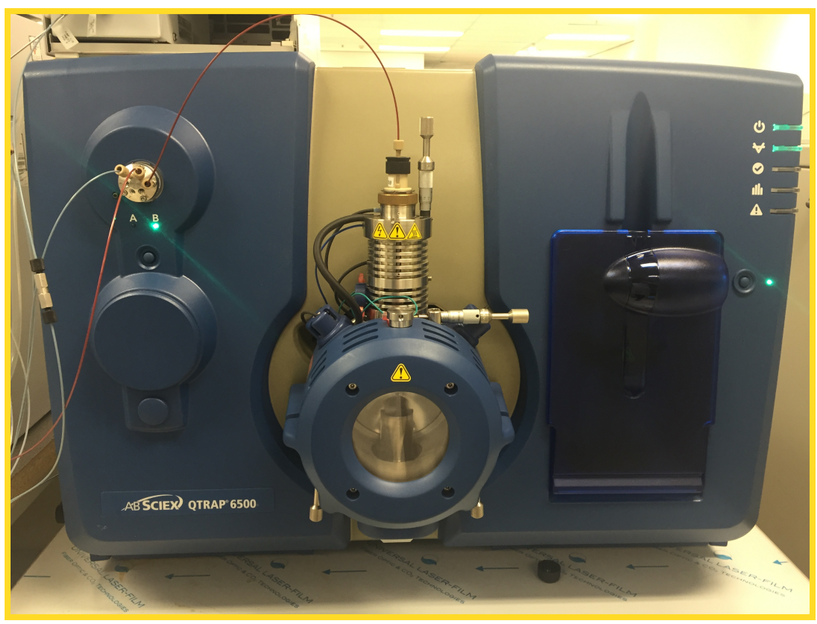
Introduction

- Vaginal oestrogen is often prescribed by Urologists and Urogynaecologists to treat women with urinary incontinence, prolapse, and/ or recurrent cystitis
- After the publication of the association between oral oestrogen and breast cancer (1), patients often query its safety
- Previous studies demonstrating that oestriol (E_3) cream is safe, relied on demonstrating serum E_3 levels below the nominal postmenopausal threshold of 100 pmol/L in current cream users (2)
- These measurements were performed using radioimmunoassay (RIA), originally developed for infertility investigations and known to have low specificity and sensitivity
- With the modern development of quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) assays, changes in serum E_3 levels in vaginal E_3 cream users can be measured much more accurately than with the previously used RIA

- **Aim:** to measure the pharmacokinetic (PK) profile of E_3 cream by assessing the interindividual and intraindividual differences before, and for a 24-hour period after, E_3 cream application.
- **Hypothesis:** serum levels could transiently increase to >100pmol/L, but should not remain elevated for more than 8 hours and return to pre-E_3 cream levels within 24 hours.



Methods and Materials

- 10 post-menopausal women who had been applying oestriol cream 2-3 times a week for at least 12 weeks were recruited
- They omitted the cream for at least 36 hours prior to the study
- These women attended our unit at 8am. A cannula was sited and a first sample of serum taken at baseline for E_3 measurement (0 hours)
- They were then asked to measure E_3 cream with the applicator to achieve a dose of 0.5mg and apply this to the lower 1/3 of vagina digitally, rather than inserting the cream high in the vagina, which has been shown to increase absorption in the uterus (first pass uterine effect (3)).
- Serum was taken at 1, 2, 3, 5, 8, 10 and 12 hours post cream application
- The patients went home for the night and returned to the unit at 8am for the last serum E_3 sample (24 hours)
- The lower limit of quantification of the LC-MS/MS assay is 5 pmol/L (CV 5%)
- Intraindividual differences in E_3 were also evaluated in 5 of the 10 women, they had the same procedure repeated within a median of 9 months (IQR 2-13).

Results

- Women had been using E_3 cream for a median of 26 months (IQR 12-46)
- Median vaginal pH levels measured 4.7 (IQR4.4-5)
- E_3 was absorbed rapidly in most patients (Fig. 1):
  - Median peak serum E_3 concentration 416 pmol/L at 2 hours (range 1-5 hours, Table 1).
  - E_3 levels fell to <100 pmol/L in the majority of women (6/10) within 8 hours
  - At 24 hours 9/10 women demonstrated oestriol levels <10pmol/L
- Interindividual variability for peak levels was high: range 245.1-1066.4 pmol/L
- Intraindividual variations were less marked in 5 women that repeated the PK study, with similar peaks during the two 24-hour periods
- No association was found between levels of E_3 and BMI.

Patients/ hours	1	2	3	4	5	6a,b	7a,b	8a,b	9a,b	10a,b
0	8.8	8.8	<5	10.3	5.7	<5	<5	<5	17.5	<5
						<5	<5	<5	7.6	<5
1	127.8	56.3	917.9	124.9	138.2	45	442.8	209.4	632.7	288.4
						177.3	580.0	307.2	627.3	84.4
2	332.3	323.9	1066.4	297.4	342.7	79.7	725.4	275.8	920.0	530.4
						245.1	923.5	229.5	1006.5	272.0
3	NS	642.7	667.0	245.2	266.0	107.2	460.6	197.1	987.5	503.8
						117.1	866.6	124.1	875.6	310.4
5	215.1	474.4	356.2	125.1	114.1	135.7	100.1	71.2	646.7	323.5
						39.3	897.7	40.5	481.7	415.5
8	137.1	131.3	36.0	27.0	32.2	39.2	17.4	15.0	NS	48.0
						12.7	141.9	10.3	NS	252.7
10	96.1	77.6	12.2	9.6	19.0	29.3	5.3	7.2	NS	24.2
						8.6	25.1	<5	NS	127.3
12	60.4	60.4	15.9	NS	14.1	15.5	<5	1.7	NS	10.0
						3.4	7.8	<5	20.3	61.8
24	27.8	NS	6.6	9.2	5.8	<5	<5	0.9	29.2	<5
						2.5	5.1	<5	8.1	5.8

Table 1. E_3 levels in pmol/L. NS= no sample. a and b are the test-retest samples of same patient.

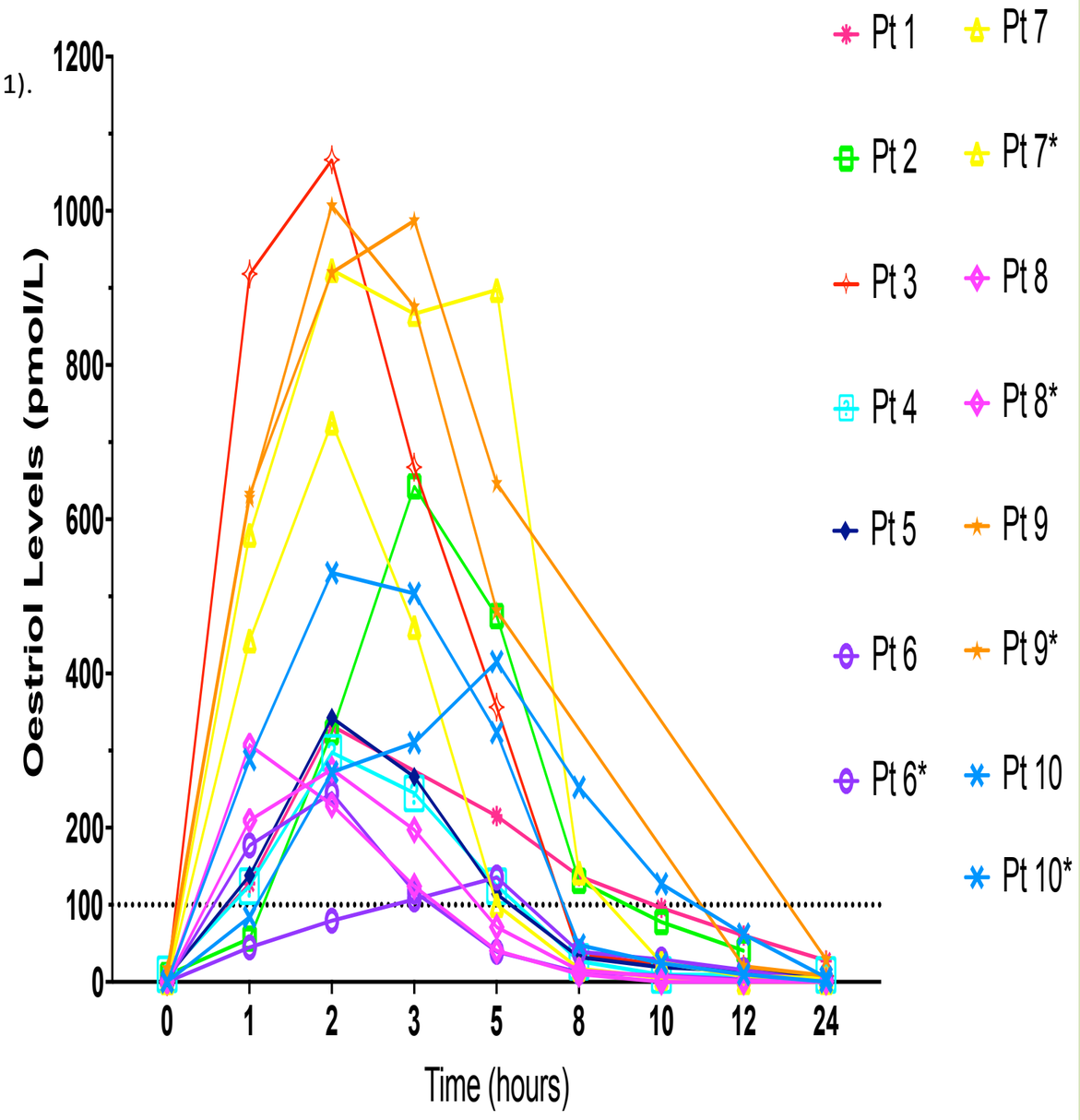


Fig 1. E_3 levels in pmol/L against hours. Same colour used for test-retest results..

Discussion

- We have developed a highly precise analytical technique to assess E_3 serum PK levels
- Oestriol in postmenopausal women is almost absent or below the LLOQ of a sensitive and specific assay to detect (< 5pmol/L)
- There are wide variations in an individuals response to oestriol cream with median peak values reaching 416 pmol/L at 2 hours and rapidly returning to baseline levels (ie undetectable) within 24 hours in the majority of women
- There was much less intraindividual variation in the retested patients (n=5)
- A woman's capacity to replicate the absorption profile suggests that local factors influence absorption in chronic users of topical E_3 in a predictable way and that dosing of E_3 cream to local symptoms and serum levels could titrate the amount of E_3 administered topically
- Chronic users were thought to have less E_3 absorption following adaptation/ cornification of the epithelium from E_3 exposure
- However, 4 patients demonstrated pronounced differences in absorption profiles with peak levels confirming wide interindividual variations in E3 Pharmacokinetics in postmenopausal women..

Conclusion

- In this novel study we found serum E_3 levels of women using E_3 cream as a chronic treatment to vary greatly between users
- This was less so within single users who were measured twice
- The majority of women had E_3 levels below 100 pmol/L after 8 hours and undetectable levels within 24 hours

References

1. Chlebowski, R.T., et al., Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. Jama, 2003. 289(24): p. 3243-53.
2. Mattsson, L.A. and G. Cullberg, Vaginal absorption of two estriol preparations. A comparative study in postmenopausal women. Acta Obstet Gynecol Scand, 1983. 62(5): p. 393-6.
3. Cicinelli, E., et al., Placement of the vaginal 17beta-estradiol tablets in the inner or outer one third of the vagina affects the preferential delivery of 17beta-estradiol toward the uterus or periurethral areas, thereby modifying efficacy and endometrial safety. Am J Obstet Gynecol, 2003. 189(1): p. 55-8.