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Pharmacokinetics of weekly transdermal estradiol controlled delivery system in postmenopausal Chinese

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KEY WORDS estradiol; cutaneous administration; pharmacokinetics; biological availability; radioimmunoassay

AIM: To study Pharmacokinetical profile of weekly transdermal estradiol controlled delivery system (E_2-WTCDS) in 18 Chinese postmenopausal women. **METHODS**: Single and multiple daily doses of E_2-WTCDS were applied to an area of intact skin on the lower abdomen, using Estraderm TTS (E_2-TTS) from Ciba-Geigy Company as control. E_2 concentration in serum was measured by RIA. **RESULTS**: C_{max} 38±5 ng·L^{-1}, T_{max} 22±5 h, AUC 5651±386 ng·h·L^{-1}, C^{SS}_{max} 44±7 ng·L^{-1}, C^{SS}_{max} 35±4 ng·L^{-1}, FI 0.22 ± 0.10. The relative bioavailability of E_2-WTCDS was comparable to E_2-TTS during the same period of system application. **CONCLUSION**: E_2-WTCDS maintained relatively constant and effective serum estradiol concentrations and is suitable for once-weekly application.

Currently, exogenous estrogen therapy is mainly prescribed by the oral route of administration. However, administered orally, estradiol is metabolized almost completely by hepatic "first-pass" elimination. Furthermore, oral estrogens cause elevation of hepatic proteins, including the substrate of renin in particular, which in turn causes a rise in blood pressure[1,2].

Transdermal administration of estradiol can avoid such first-pass hepatic metabolism, prevent some of these undesired effects, as well as reduce the dose required[3,4]. In 1987, a transdermal therapeutic system of "Estraderm TTS" (Ciba-Geigy) which utilizes the membrane controlled drug delivery technologies was developed and commercialized. Transdermal therapy with Estraderm-TTS delivers the physiological estrogen estradiol directly into the blood stream both in unchanged forms and in physiological quantities. Estraderm-TTS raises circulating estradiol concentration to levels similar to those in the early follicular phase[5]. Estraderm-TTS thus provides for physiological estrogen replacement. Most recently, an advanced polymer matrix micro-reservoir controlled transdermal drug delivery system of "Weekly Transdermal Estradiol Controlled Delivery System" (E_2-WTCDS) was successfully developed in this institute. E_2-WTCDS is capable of producing a relatively constant serum level of estradiol with a duration longer than that achieved by Estraderm-TTS.

The purpose of this study was to characterize the estradiol concentration-time profiles and pharmacokinetics after single and multiple daily transdermal doses of E_2-WTCDS, in eighteen Chinese postmenopausal women.

MATERIALS AND METHODS

Drugs and Instruments Weekly Transdermal Estradiol Controlled Delivery System (E_2-WTCDS, 2.5 mg/10 cm^2, once a week), Institute of Materia Medica, Zhejiang Academy of Medical Sciences, (lot № 930818). Estraderm TTS (E_2-TTS, 4 mg/10 cm^2, twice a week), Ciba-Geigy Company (lot № B227000). The skin permeation rate of both E_2-WTCDS and E_2-TTS was 50 μg·d^{-1}. 1275 γ-counter, LKB company. Estradiol RIA Kits, Tianjin DuPont Company.

Subjects Eighteen postmenopausal women aged 60 ± *s* 3 a and weighing 54.4 ± *s* 7.2 kg, without endocrine disease and tumour history, entered the study. Each volunteer gave a written consent and underwent thorough physical examination. All the test results of their blood, urine, liver, kidney, and electrocardiogram were within normal ranges. At least 2 wk before the study, all were asked to be kept from medication.

Protocol In the single dose study, volunteers entered the study in an open, randomized crossover study design. A 10 cm^2 system either E_2-WTCDS or E_2-TTS was given to each volunteer. Immediately after removal the protective liner, system should be applied to an area of clean, dry, and

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intact skin on the lower abdomen. E_2-WTCDS was worn 7 d, and E_2-TTS worn 3.5 d. Blood samples (4 mL) were taken before application and at the following time periods after wearing: E_2-WTCDS 12, 24, 72, 120, 168 (↓), 172, 180, 192, 216 h; E_2-TTS 8, 24, 48, 84 (↓), 88, 96, 108, 132 h. The blood samples were collected in tubes and separated by centrifugation (3000 × *g* for 5 min). Serum fractions were frozen at −20 ℃ until being assayed. Each study was followed by a washout period of 2 wk.

In the multiple daily dose study, the transdermal systems were applied for 3 wk, E_2-WTCDS once a week (3 systems), E_2-TTS twice a week (6 systems). At the end of 168 h or 84 h, the systems were removed and replaced by a new system at a new site. Skin sites were rotated using a predetermined pattern, using each site only once. Blood samples were drawn immediately before each system wearing *and at the following time periods after application*: E_2-WTCDS 1st and 2nd wk at 24, 72, 168 h (↓ ↑), 3rd wk at 12, 24, 72, 120, 168 (↓), 172, 180, 192, 216 h; E_2-TTS 1st and 2nd wk at 8, 24, 84 h (↓ ↑), 3rd wk at 8, 24, 48, 84 (↓), 88, 96, 108, 132 h.

Drug analysis Estradiol concentration in serum was measured by radioimmunoassay method. Calibration curve was linear over the range of 5 − 100 ng·L^{-1}. The mean recovery from serum was 96 ± 2 %. The coefficients of variation of day-to-day and within-day were less than 4.8 % and 6.8 %, respectively.

Pharmacokinetics analysis The pharmacokinetic analysis was performed by analysis of individual data with a CRFA program on an IBM-FX 486 computer. C_{max}(C_{min}): the highest (lowest) observed serum concentration during the wearing interval; T_{max}(T_{min}): the time at which C_{max}(C_{min}) occurred; C_p(84), C_p(168): concentration at the time of system removal (84 h or 168 h); AUC (0 − 84), AUC (0 − 168): the area under the serum concentration-time curve during a wearing interval (0 − 84 h or 0 − 168 h) calculated by the linear trapezoidal rule. The fluctuation index (FI) was calculated from

$$FI = (C^{SS}_{max} - C^{SS}_{min}) \cdot \tau / AUC$$

All concentration values below the quantification limit were treated as zero in the calculation of mean data and pharmacokinetic parameters.

RESULTS

The serum concentration-time profiles of estradiol in 18 healthy postmenopausal women wearing a single transdermal dose showed mean estradiol concentration before system application was 2.2 − 2.5 ng·L^{-1}, both E_2-WTCDS and E_2-TTS raised serum levels of estradiol to maximum values of 38.3 ng·L^{-1} and 43.1 ng·L^{-1}, respectively, within 10 − 22 h of application of the systems, and then maintained relatively constant concentrations of 33 − 35 ng·L^{-1} and 30 − 34 ng·L^{-1}, respectively (Fig 1). However, the estradiol concentration after wearing E_2-WTCDS remained constant level for 7 d, while E_2-TTS only 3.5 d. In all cases, serum estradiol concentrations returned to baseline within 24 h of removing the systems. The pharmacokinetic parameters of E_2-WTCDS and E_2-TTS were given in Tab 1. The relative bioavailability of E_2-WTCDS was 105 ± 3 % *vs* E_2-TTS ($P > 0.05$).

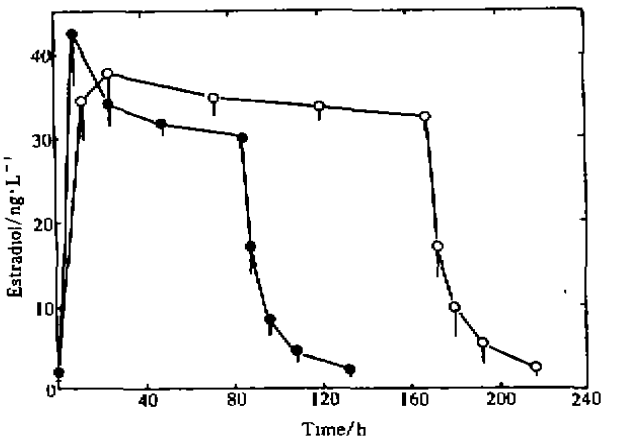

Fig 1. Estradiol concentration in serum after a single transdermal dose of E_2-WTCDS (○) and E_2-TTS (●) ($n = 18$).

Tab 1. Pharmacokinetic parameters of estradiol in 18 postmenopausal Chinese after single and multiple daily transdermal doses of E_2-WTCDS and E_2-TTS in random crossover. $\bar{x} \pm s$.

Parameters	E_2-WTCDS	E_2-TTS
Single dose		
T_{max}/h	22.0 ± 4.6	9.8 ± 5.1
C_{max}/ng·L^{-1}	38.3 ± 4.8	43.1 ± 5.4
AUC/ng·h·L^{-1}	5651 ± 386 (168 h)	2694 ± 158 (84 h)
Multiple dose		
T^{SS}_{max}/h	22.0 ± 4.6	9.8 ± 5.1
C^{SS}_{max}/ng·L^{-1}	43.8 ± 6.6	48.7 ± 6.8
C^{SS}_{min}/ng·L^{-1}	35.0 ± 3.8	30.5 ± 1.0
FI	0.22 ± 0.10	0.49 ± 0.16

The serum concentration-time profiles of multiple daily transdermal doses of E_2-WTCDS and

E_2-TTS remained constant within the range of 35.0 $-$ 43.8 ng·L^{-1} and 30.5 $-$ 48.7 ng·L^{-1}, respectively, during 3 wk wearing period (Fig 2). The Fluctuation Index of E_2-WTCDS and E_2-TTS were 0.43 and 0.22 respectively.

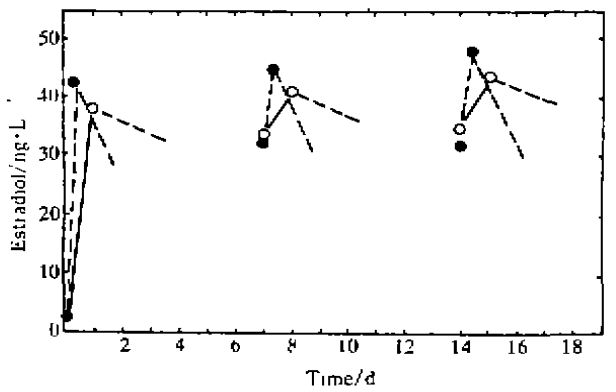

Fig 2. Multiple daily transdermal doses pharmacokinetic study, peak, and trough levels of E_2-WTCDS (○) and E_2-TTS (●) (n = 18).

DISCUSSION

The present study demonstrated that skin permeation rate of estradiol in postmenopausal women wearing transdermal systems were effectively controlled, and estradiol concentrations were restored to the level of premenopausal early follicular phase by E_2-WTCDS as well as E_2-TTS. In single transdermal dose study, $C_{max}^{E_2\text{-WTCDS}} < C_{max}^{E_2\text{-TTS}}$, $T_{max}^{E_2\text{-WTCDS}} > T_{max}^{E_2\text{-TTS}}$ ($P < 0.05$), the statistically significant differences were mainly caused by their different controlled delivery characteristics. E_2-TTS is a membrane permeation controlled delivery system with "burst release effect", level of estradiol concentration rises rapidly during the initial period after wearing, and then falls to a mean level. E_2-WTCDS is a matrix-microreservoir controlled delivery system, estradiol concentration increases a little slowly but is fairly smooth and steady. Due to the different maintaining times of E_2-WTCDS (168 h) and E_2-TTS (84 h), the relative bioavailability should be evaluated by their AUC of same periods of system application. The result indicated the relative bioavailablity of E_2-WTCDS was comparable to that of E_2-TTS ($P<0.05$).

In multiple daily doses study, T_{max} and T_{min} values of both systems on wk 3 corresponded well with the values on wk 1 and wk 2, E_2-WTCDS was 22, 168 h, and E_2-TTS was 9.8, 84 h, respectively. The result suggests the consistent absorption characteristics during 3 wk of application. The fluctuation of E_2-TTS in estradiol concentration was higher than that of E_2-WTCDS ($P<0.05$), it is mainly responsible for the "burst release effect" corresponding to single transdermal dose application. However, serum concentration of estradiol obtained with E_2-WTCDS were overlapping in the range similar to that of those obtained with E_2-TTS, suggesting that both systems should yield similar clinical therapeutic effects.

The AUC values of E_2-WTCDS and E_2-TTS for wk 3 were both slightly larger than that for wk 1 ($P<0.05$), with a wk 3-to-wk 1 ratios of 1.15 and 1.14, respectively. The values of C_{max} and C_p on wk 3 were slightly higher than that on wk 1 as well (Tab 2). This phenomenon indicates that slight accumulation occurred during multiple application of both E_2-WTCDS and E_2-TTS. Due to the short elimination half-life of estradiol ($\sim$1 h), the accumulation may be related to the "reservoir effect" of drug in epidermis stratum corneum[6].

Tab 2. Ratios of AUC, C_{max}, C_p for week 3 to week 1. n = 18, $\bar{x} \pm s$.

	E_2-WTCDS	E_2-TTS
AUC	1.15±0.09	1.14±0.08
C_{max}	1.14±0.14	1.13±0.13
C_p	1.08±0.09	1.05±0.08

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雌二醇周效控释贴片在中国经绝后妇女的药物动力学

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关键词 雌二醇；经皮给药；药物动力学；生物利用度；放射免疫测定

目的：研究雌二醇周效控释贴片（E_2-WTCDS）在中国经绝后妇女的药物动力学特性. **方法**：单剂量和多剂量 E_2-WTCDS 于下腹部皮肤给药，用放射免疫法测定不同给药时间血清中的雌二醇浓度，并以 E_2-TTS 作对照 **结果**：C_{max} 38 ± 5 ng·L^{-1}，T_{max} 22 ± 5 h，AUC 5651 ± 386 ng·h·L^{-1}，C^{SS}_{max} 44 ± 7 ng·L^{-1}，C^{SS}_{min} 35 ± 4 ng·L^{-1}，FI 0.22 ± 0 10. 在相同给药条件下 E_2-WTCDS 的生物利用度与 E_2-TTS 基本相同 **结论**：E_2-WTCDS 在一周中能维持一个相对平稳而有效的雌二醇血清浓度，宜每周给药一次.