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Effectiveness and Adverse Drug Reactions of Hormonal Replacement Therapy in Menopausal Women, Health Promotion Center, Region 4 Ratchaburi

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ABSTRACT

Objective To study and report the effect and adverse drug reactions (ADR) of 4 Hormonal replacement therapy (HRT) that prescribed to Health Promotion Center's patients. There are EV+NT (estradiol valerate 2.0 mg/tablet for 21 days plus norgestrel 0.5 mg/tablet for the last 10 days),CE (conjugated estrogens 0.625 mg/tablet), Tibolone 2.5 mg/tablet 28 days and CE+MT (conjugated estrogens 0.625 mg/tablet for 21days and medrogestone 5.0 mg/tablet for the last 10 days).

Design Retrospective descriptive study.

Setting Health Promotion Center, Region 4, Ratchaburi , Thailand.

Subjects Menopausal women who recieved HRT from Health Promotion Center, Ratchaburi were included in this study. The subjects divided into 2 groups, group 1 continuous group, personal interview one hundred menopausal women who took HRT more than 3 months and group 2 missing group, mailed questionnaires to one-hundred and fourty three menopausal women who did not contact with Health Promotion Center more than 1 month.

Result After taking EV+NT(n=63) and CE(n=48) more than 4 weeks, the vasomotor symptoms, psychological symptoms, urogenital symptoms and musculo-skeletal symptoms decreased significantly ($p<0.05$), but after taking tibolone (n=19) more than 4 weeks, only vasomotor symptoms, psychological symptoms and urogenital symptoms decreased significantly ($p<0.05$), and CE+MT(n=7) had a few users, so it could not show significant. Breast tenderness was common adverse drug reaction of 4 HRT, EV+NT(41.3%), CE(50%), tibolone(31.6%) and CE+MT (57.1%). Return of monthly bleeding found in EV+NT (38.1%), CE+MT(14.3%) and tibolone (10.5%). Spotting found in EV+NT (9.5%) tibolone (21.0%) and CE+MT (14.3%). Weight gain found in EV+NT(28.6%), CE(22.9%), tibolone(10.5%), CE+MT (14.3%)and leg edema only found in tibolone (5.3%). Stop HRT 74.4% was a main cause of the missing group, and the reasons for stop HRT were on busy 28.7%, menopausal symptoms recovering 21.8%, ADR18.4%, fear of cancer 13.8%, lack of advice for continuous used 12.6% and financial problem for HRT 2.3%.

Conclusion EV+NT and CE showed significantly more effective and more ADR than tibolone.

Key words : menopausal women, hormonal replacement therapy (HRT), effectiveness, adverse drug reaction (ADR)

At present, Hormonal Replacement Therapy (HRT) is generally acknowledged to be the most effective for amelioration in short-term and long-term sequelae of estrogen deficiency symptoms occuring in menopausal women.[1,2] HRT composed of estrogen or estrogen plus progestogen given continously or sequentially combined HRT. Unopposed estrogen recommended for hysterectomized women, estrogen plus progestogen recommended for women with an intact uterus, progestogen are given in addition to estrogen to prevent estrogen induced proliferation of the endometrium.[1,3] Each HRT consisted of different estrogen and/or progestogen and presented in different routes, such as oral, injection, transdermal (patch), percutaneous (cream), vaginal (cream, tablet).

Health Promotion Center, Region 4, Ratchaburi, Department of Health, Ministry of Public Health, Thailand, provides 4 kinds of oral HRT for menopausal women. They are EV+NT(estradiol valerate 2.0 mg/day for 21 days plus norgestrel 0.5 mg/day for the last 10 days), CE (conjugated estrogens 0.625 mg/tablet), tibolone 2.5 mg/day, 28 days and CE+MT(conjugated estrogen 0.625 mg for 21 days and medrogestone 5.0 mg/day for the last 10 days). All these 4 HRT composed of different active ingredients and different strengths so that its provided different effectiveness and different adverse drug reactions (ADR).

Therefore, it is logical to study the effect of HRT for alleviate the menopausal symptoms by compared mean menopausal scores before and after taking HRT and to report adverse drug reactions. (ADR) of these 4 HRT for a basic data in rational drug use of HRT (cost-effectiveness - ADR) on Thai menopausal women at Health Promotion Center, Region 4, Ratchaburi.

Materials and Methods

This retrospective descriptive study was performed at Health Promotion Center, Region 4 Ratchaburi, Thailand. The subjects were menopausal women who received HRT from Health Promotion Center, Ratchaburi were included in this study. The subjects divided into 2 groups. Group 1 Continuous Group, one-hundred menopausal women who took HRT more than 3 months, chosen by purposive sampling. Group 2 Missing Group, one-hundred and fourty three menopausal women who took HRT for any duration but did not contact with Health Promotion Center, Ratchaburi, more than 1 month after appointment schedule, until 1 June, 1997, chosen by simple random sampling .

Collected data by personal interview in continuous group during July 1,1997 - March 6,1998 by the authors when subjects visit phyician after took HRT more than 3 months , and mailed questionnaires to missing group on September 2-5, 1997 and followed up by second mailed on October 10,1997. We could collect 121 returned questionnaires, one subject dead, and three subject said that they did not take it all. There were 117 complete questionnaires (81.8%).

Questionnaires consisted of baseline characteristics, menopausal symptoms, kind of drug, duration, effectiveness on short-term sequelae of menopausal symptoms, ADR and reasons for leaving out (the last for missing group). Menopausal symptoms (short-term sequelae) were recorded by the patient who filled in the menopausal clinic's self assessment form of menopausal clinic, Ministry of Public Health, before HRT was started, then after 1,3 months and everytime they visited physician. Questionnaires was advised and approved by assistant professor of Faculty of Pharmacy, Silapahorn University and 3 physicians of Obstetrics and Gynaecology Department, Heath Promotion Center, Ratchaburi.

Menopausal Clinic's self assessment form consisted of 19 symptoms which could be grouping into 4 categories as

1. Vasomotor symptoms (hot flushes, sweating)
2. Psychological symptoms (headache, irritability, depression, unlove feelings, anxious feelings, insomnia, unusual tiredness)
3. Urogenital symptoms (dry vagina, dyspareunia, no sexual enjoyment, loss of libido, incontinence, frequency of micturition)
4. Musculo - skeletal symptoms or climacteric arthralgia (back pain, joint pain, muscle pain)

For each symptoms a score was given from 0,1,2, and 3 for absent, mild, moderate and severe complaints respectively.

Data are presented in number, percentage and mode. Statistical comparisons of menopausal scored were performed with paired t - test. Signification was defined as P value < 0.05.

Results

Most of the subject in both groups were surgical menopause, continuous group 47%, missing group 32.5%(table 1), and EV+NT users, continuous group 46%, missing group 62.4%(table 2). Main complaints of menopausal symptoms were hot flushes and irritability in continuous group, backpain and irritability in missing group (table 3). Continuous group took HRT 4 - 144 months (Mode 6 months 10%), they stopped HRT sometimes 38.0%. After stop using 1 - 3 months, menopausal symptoms recurred, so they restarted HRT again. 33% switched to another HRT, and switched for 3 HRT 2.0% according to physician order. 24.2% of 2 HRT users switched back to the first HRT because they felt that the latter one was not as good as the first one.

Table 1. Type of menopause, percentage and age of study subjects

Subjects	Continuous Group			Missing Group		
	Age	N	%	Age	N	%
Premenopause	43-56	23	23.0	38-52	29	24.8
Perimenopause	41-55	14	14.0	41-57	31	26.5
Natural menopause	38-62	16	16.0	46-58	19	16.2
Surgical menopause	36-59	47	47.0	34-63	38	32.5
Total		100	100.0		117	100.0

Table 2 . Number and percentage of 4 HRT on continuous group and missing group

	Continuous group		Missing group	
	N	%	N	%
EV+NT	63	46.0	73	62.4
CE	48	35.0	33	28.2
Tibolone	19	3.9	4	3.4
CE+MT	7	5.1	7	6.0
Total	137*	100.0	117	100.0

* Some subject used more than 1 HRT.

Table 3. Main complaints of menopausal symptoms of continuous group and missing group

Menopausal symptoms	Continuous Group %	Missing Group %
1. Hot flushes	65.0	68.4
2. Irritability	60.0	80.3
3. Dry skin	59.0	69.2
4. Unusual tiredness	57.0	79.5
5. Back pain	56.0	81.2
6. Joint pain	56.0	70.9
7. Increased sweating	51.0	-*
8. Dry vagina	49.0	70.1
9. Loss of libido	49.0	65.0
10. Insomnia	47.0	65.0
11. Headache	-*	75.2

*lower than rank 10

Missing group took HRT 1/2 - 18 months (Mode 1 month 19.7%). Main cause of missing was stop HRT 74.4%. While they still continued HRT only 18.8% from nearby hospital or drugstore, which they took the same HRT 66.7% and switched to another HRT 33.3%. The reasons for stop HRT were busy 28.7%, menopausal symptoms recovering 21.8%, ADR 18.4%, fear of cancer 13.8%, lack of advice for continuous use, and the last reason was financial problem. (table 4)

Table 4. Reasons for stop HRT on missing group

Reasons for stop medication	%
Busy	28.7
Menopausal symptoms recovering	21.8
ADR	18.4
Fear of cancer	13.8
Lack of advice for continuous use	12.6
Take other medications	9.2
Physician ordered to stop HRT	4.6
Financial problem	2.3

Note. Some subjects comment more than 1 reason

Effectiveness

In continuous group, after taking EV+NT(N=63), CE(N=48) , and tibolone (N=19) 2-4 weeks, mean vasomotor symptoms scores decreased statistically significant ($p < 0.05$), but mean scores of psychological symptoms, urogenital symptoms, and musculo - skeletal symptoms decreased statistically significant ($p< 0.05$) when took more than 4 weeks, except tibolone mean scores of musculo - skeletal symtoms did not reach statistically significant. CE+MT had a few users, so it could not show statistically significant. (table 5,6)

Table 5. Mean menopausal scores before and after taking 4 HRT in term of vasomotor and psychological symptoms

Drugs	Mean menopausal scores									
	Vasomotor symptoms					Psychological symptoms				
	Before treatment		After treatment		P value	Before treatment		After treatment		P value
	X	SD	X	SD		X	SD	X	SD	
EV+NT	2.49	2.29	0.88	1.57	0.000*	6.44	4.69	3.98	4.07	0.000*
CE	3.00	2.35	0.55	1.36	0.000*	5.45	5.22	2.68	4.02	0.007*
Tibolone	2.12	2.42	0.62	0.92	0.056*	3.62	3.78	2.00	3.16	0.024*
CE+MT	3.33	2.52	2.00	3.46	0.270	10.33	5.69	8.00	6.56	0.250

* P< 0.05 is considered as statistically significant

Table 6. Mean menopausal scores before and after taking 4 HRT in term of urogenital and musculo - skeletal symptoms

Drugs	Mean menopausal scores									
	Urogenital symptoms					Musculo-skeletal symptoms				
	Before treatment		After treatment		P value	Before treatment		After treatment		P value
	X	SD	X	SD		X	SD	X	SD	
EV+NT	5.28	4.86	3.98	4.43	0.002*	3.33	2.72	2.81	2.72	0.027*
CE	4.35	4.62	2.81	3.79	0.034*	2.94	2.48	2.00	2.19	0.020*
Tibolone	3.38	3.34	2.00	2.27	0.020*	2.00	2.20	1.62	2.39	0.402
CE+MT	7.00	1.00	7.00	1.00	NS	3.00	3.61	3.00	3.61	NS

*p< 0.05 is considered as statistically significant. NS = no statistically significant

Adverse drug reactions (table 7)

Return of monthly bleeding of EV+NT was highest among 4 HRT(38.1%). Duration of return monthly bleeding of EV+NT 4 - 36 months, (36 months = 1 case occured 2 years post menopause and Mode equally 4 and 6 months = 4 cases) Duration of return monthly bleeding of tibolone was 1 - 2 months(10.5%) (1 month = 1 case, 2 months = 1 case). CE+MT has a few users but it also showed some return of monthly bleeding(14.3%).

Another common ADR of HRT was breast tenderness found in CE(50%), EV+NT (41.3%), Tibolone (31.6%), CE+MT (57.1%). Weight gain, dizziness, and fatigue also found in 4 HRT, but in different proportion. Leg edema only found in tibolone (1 case).

Table 7 Adverse drug reactions (ADR) of 4 HRT in continuous group and missing group

ADR	Continuous Group				Missing Group			
	EV+NT N=63 %	CE N=48 %	Tibolone N=19 %	CE+MT N=7 %	EV+NT N=73 %	CE N=33 %	Tibolone N=4 %	CE+MT N=7 %
Return of monthly bleeding	38.1	2.1	10.5	14.3	16.4	3.0	0.0	28.6
Breakthrough bleeding	0.0	0.0	0.0	14.3	0.0	0.0	0.0	14.3
Spotting	9.5	0.0	21.0	14.3	8.2	0.0	0.0	0.0
Breast tenderness	41.3	50.0	31.6	57.1	6.8	9.1	0.0	0.0
Dizziness	15.9	8.3	15.8	14.3	5.5	21.2	50.0	0.0
Fatigue	6.3	6.3	10.5	0.0	6.8	6.1	0.0	14.3
Weight gain	28.6	22.9	10.5	14.3	2.7	9.1	0.0	0.0
Leg edema	0.0	0.0	5.3	0.0	0.0	0.0	0.0	0.0
Others	23.8	12.5	31.6	0.0	13.7	12.1	25.0	14.3

Discussion

The results demonstrated that EV+NT and CE could alleviate vasomotor symptoms in a short time, meanwhile psychological symptoms, urogential symptoms and musculo - skeletal symptoms alleviated longer.

In this study EV+NT showed good effectiveness on Thai menopausal women that compatible with WHO report[1] and a study of Krasean et al[4] which showed that estradiol valerate 2.0mg daily (same estrogen, and same dose of EV+NT) administered orally was sufficient to relief menopausal symptoms. However, it also showed high incidence of ADR, especially a long duration of return monthly bleeding, which compatible with Kenemans P. et al[3] and Krasean et al.[4]

CE+MT had a few user, so it could not show statistically significant on both effective and ADR.

CE 0.625 mg daily also showed good effects on Thai menopausal women which compatible with WHO[1] that CE. 0.625 mg daily usually sufficient for symptomatic menopausal relief. Physicians of Health Promotion Center prescribed CE for hysterectomy or surgical menopause which agreed on WHO[1] and Kenemans P.et al.[3] So it no return of monthly bleeding, or irregular bleeding. Nevertheless it occured high rate of breast tenderness, and some weight gain, dizziness and fatigue. These ADR were common found on estrogen.[1,5]

Tibolone showed good effects on Thai menopausal women on vasomotor, psychological and urogenital symptoms, but less effects on musculo - skeletal symptoms. These results were discordant with Kobchitt et al[6] who found that tibolone decrease climateric symptoms and also were discordant with Ross LA et al[7] that tibolone was effective in reducing vasomotor symptoms and vaginal dryness, but effect on a range of other symptoms such as headache and insomnia is unclear. Return of monthly bleeding also found on tibolone which compatible with Kobchitt et al,[6] Rymer J.et al[8] and Ginburg J. et al.[9]

Subjects who took HRT discontinuously (38%) said that, after stop HRT about 1-2 months the menopausal symptons recurred, it showed that effect of HRT still persisted about 1-2 months which similar to Krasean et al[4] and Hass S. et al[10] who found that hormonal effects still persisted 2-8 wks.

The reasons for stop HRT in this study were fear of cancer, bleeding, and weight gain which were the same reasons worldwide.[1] High price of HRT was another reason to stop HRT occasionally or

permanently on Thai menopausal women. (EV+NT=176.00 baht/cycle, CE=70.00baht/cycle, tibolone=731.50 baht/cycle, CE+MT=195.80 baht/cycle)

Moreover, one reason to stop HRT was the lack of advice for continuous using, and 3 subjects told that they did not take HRT all of it, so HRT drug counselling and Menopause clinic services should be reviewed such as exchanging any ideas between patients and counsellors, presenting complete information both positive and negative effects in order to obtain good compliance.

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