How best is to discontinue postmenopausal hormone therapy: Immediate or tapered?

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Received 27 December 2005; received in revised form 3 June 2006; accepted 9 June 2006

Abstract

Background: To evaluate the differences between the immediate and tapered cessation protocols of hormone therapy in terms of recurrence of menopausal symptoms.

Materials and methods: In this prospective, randomized clinical study 70 consecutive patients in whom hormone therapy was no longer preferred were recruited from the menopause clinic of a university hospital and rank randomized into two groups. In group 1 (n = 35) hormone therapy was immediately discontinued and in group 2 (n = 35) the medication was tapered. Every patient was questioned about vasomotor symptoms before the initiation of hormone therapy at the first visit, and then revisited at the end of 2 and 4 weeks.

Results: We did not find any statistically significant difference between two protocols in terms of symptom severity and frequency at the end of 2 and 4 weeks of discontinuation. Although statistically insignificant, the symptoms tended to recur in fewer patients and in a less severe form in both groups when compared with their pretreatment status.

Conclusions: Tapering or immediate discontinuing of hormone therapy did not affect the recurrence rate and severity of menopausal symptoms at the end of 4 weeks.

Keywords: Hormone therapy; Discontinuing; Immediate; Tapering; Hot flushes

1. Introduction

Hormone therapy (HT) has found wide application area for more than three decades for purposes to alleviate vasomotor and urogenital symptoms, to prevent osteoporosis, and to protect cardiovascular system. Albeit, there was accumulation of massive data concerning pros and cons of HT, vast majority of them was derived from observational studies. On July
9 2002, the National Heart, Lung, and Blood Institute of National Institutes of Health announced that it was halting the arm of the Women’s Health Initiative (WHI) study evaluating combined estrogen and progestin use in postmenopausal women [1]. This arm of the WHI study, a randomized placebo-controlled trial, assessed the effects of combined HT use in healthy postmenopausal women with an intact uterus. After review of the reported data, the data and safety monitoring board of the study concluded that the risk of combined HT use in this study population outweighed the benefits. This announcement and also the data derived from Heart and Estrogen/Progestin Replacement Study (HERS) [2,3], another large, randomized, double blinded, and placebo-controlled study, clearly pointed that there is an urgent need to review our knowledge about the use of HT. This issue is also addressed in the European Menopause and Andropause Society (EMAS) 2004/2005 position statements on peri- and postmenopausal hormone replacement therapy. According to the EMAS clinical recommendations, estrogen progestin therapy (EPT) should not be used as prevention against coronary heart disease (CHD). It also has comments on the results from both the secondary prevention HERS and EPT of WHI study which highlights that EPT does not confer cardiac protection and may increase the early risk of CHD [4].

Under the light of recent developments, reviewing the indications in patients who were receiving HT for a long time, and even more discontinuing their medications became an urgent issue for many practitioners. Nevertheless, the scientists and clinicians who were seeking the ways to increase the compliance to the medication until now, noticed that there is not any scientific data about how to discontinue the medication being used.

In our randomized prospective clinical study, we aimed to determine whether there is a difference between the immediate and tapered cessation protocols of HT in terms of recurrence of menopausal symptoms (hot flushes, sweating) on patients in whom HT discontinuation was preferred.

2. Materials and methods

Seventy-two consecutive patients from the menopause clinic of Baskent University Hospital were informed about recent developments on HT. After potential risks and benefits of HT clearly outlined, they were invited to enroll our study if they have chosen not to continue their medication. Seventy of 72 patients preferred to discontinue the HT, and rank randomized into two groups. In group 1 \((n = 35)\), HT was immediately discontinued and in group 2 \((n = 35)\) the medication was used once every other day for 2 weeks and then discontinued. Two of the patients refused to discontinue the medication. When they have chosen to enroll our study, a written consent was obtained. The study was approved by Ethical Committee of Baskent University.

Every patient was questioned about the presence and severity of vasomotor symptoms (VMSs) before the initiation of HT at the first visit, and then revisited at the end of 2 and 4 weeks. During these visits VMSs were noted on a symptom scale (Fig. 1). The severity of hot flushes was maintained as they have been perceived by patient and as suggested in the US Food and Drug Administration’s Guidelines [5], in so that:

- Mild: a temporary warmth sensation, no sweating, does not interfere with the daily activity.
- Moderate: a temporary warmth sensation, sweating, interferes with the daily activity to a lesser degree.
- Severe: a temporary warmth sensation, sweating, interferes with the daily activity severely, night sweating included in this group.

The frequency was noted as average daily episodes of hot flushes in each severity group.

Symptom scores were obtained by using the severity and frequency of symptoms. Basically, one point was given for every mild hot flush, two for a moderate hot flush, and three for a severe hot flush. These were all added together to make the hot flush score. Scores were also grouped as none (0 point), mild (1–8 points), moderate (9–16 points) and severe (17 and higher points) for purposes of description.

The level of significance was taken as \(\alpha = 0.05\). The power was assumed to be as 0.80 \((\beta = 0.20)\). The clinically important difference (effect size) was determined as 2 scores in hot flush symptom scoring. Standard deviation of symptom scores was estimated as \(\sigma = 4\). Given above assumptions a sample size of 64 patients was calculated. A total of 70 patients were recruited in order to compensate missing values.
Statistical analyses were done by SPSS 11.0.0 Standard Version (SPSS Inc., Chicago, IL, USA). Data were compared by using $\chi^2$ and Student’s t-test. Homogeneity of variances was evaluated by Levene’s test and Mann–Whitney $U$-test when appropriate. Data were expressed as mean ± standard error of mean (S.E.M.) and used throughout the text without further annotation.
3. Results

Demographic characteristics of patients are demonstrated in Table 1. The mean age, duration of menopause, duration of HT was similar in both groups 1 and 2. The groups were homogeneous for the type of medication that has been used (Table 2).

The patients were also asked for the presence and severity of VMSs before the institution of HT. The pretreatment severity scores did not show any statistical difference between the groups.

At the end of 2 weeks, in group 1, 17 patients (48%) had no symptoms, while there were mild, moderate and severe symptoms in 15 (42.9%), 1 (2.9%), and 2 (5.7%) patients, respectively. In group 2, 19 patients (54.3%) had no symptoms and there were mild, and severe symptoms in 15 (42.9%), and 2 (5.7%) patients, respectively (Table 3). A mild vaginal bleeding is observed in 3 (8.6%) and 2 (5.7%) patients in group 1 and group 2, respectively.

We did not find and statistically significant difference between immediate or tapered cessation of HT in terms of symptom severity and frequency at the end of 2 and 4 weeks of discontinuation (Fig. 2).

Table 1
Demographic characteristics and summary of hot flash scores

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 35)</th>
<th>Group 2 (n = 35)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>53 ± 3.8</td>
<td>53.3 ± 4.6</td>
<td>0.798</td>
</tr>
<tr>
<td>Duration of menopause (years)</td>
<td>6.3 ± 0.68</td>
<td>5 ± 0.52</td>
<td>0.149</td>
</tr>
<tr>
<td>Duration of HT (years)</td>
<td>3.03 ± 0.31</td>
<td>3.31 ± 0.37</td>
<td>0.555</td>
</tr>
<tr>
<td>Presence of VMSs before treatment (%)</td>
<td>77.1</td>
<td>80</td>
<td>0.327</td>
</tr>
<tr>
<td>Hot flash score at 2nd week</td>
<td>3.06 ± 0.87</td>
<td>1.97 ± 0.65</td>
<td>0.323</td>
</tr>
<tr>
<td>Hot flash score at 4th week</td>
<td>3.23 ± 1.10</td>
<td>2.83 ± 1.04</td>
<td>0.792</td>
</tr>
</tbody>
</table>

HT: hormone therapy; VMS: vasomotor symptom.

Table 2
Dispersion of the type of medication used over the groups 1 and 2

<table>
<thead>
<tr>
<th>Type of medication</th>
<th>E2 (1 mg) + NETA (0.5 mg)</th>
<th>E2 (2 mg)</th>
<th>E2 (2 mg) + NETA (0.5 mg)</th>
<th>Tibolone (2.5 mg)</th>
<th>CEE (0.625 mg) + MPA (2.5 mg)</th>
<th>Trisequens™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>1 (2.9%)</td>
<td>3 (8.6%)</td>
<td>12 (34.3%)</td>
<td>7 (20%)</td>
<td>8 (22.9%)</td>
<td>4 (11.4%)</td>
</tr>
<tr>
<td>Group 2</td>
<td>1 (2.9%)</td>
<td>8 (22.9%)</td>
<td>6 (17.1%)</td>
<td>13 (37.1%)</td>
<td>5 (14.3%)</td>
<td>2 (5.7%)</td>
</tr>
</tbody>
</table>

E2: estradiol; NETA: norethindron acetate; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate; Trisequens™: E2 (2 mg) – (E2 (2 mg) + NETA (1 mg)) – E2 (1 mg) (Novo Nordisk, Denmark).

Table 3
VMS severity at the end of 2 and 4 weeks in each group

<table>
<thead>
<tr>
<th></th>
<th>At the end of 2 weeks</th>
<th>At the end of 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n)</td>
<td>Group 2 (n)</td>
</tr>
<tr>
<td>None</td>
<td>17 (48%)</td>
<td>19 (54.3%)</td>
</tr>
<tr>
<td>Mild</td>
<td>15 (42.9%)</td>
<td>13 (37.1%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (2.9%)</td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (5.7%)</td>
<td>1 (2.9%)</td>
</tr>
</tbody>
</table>

Group 1: immediate cessation; group 2: tapered cessation.
4. Discussion

Menopausal hot flushes are defined as “episodes of flushing, increased heart rate, skin blood flow and skin temperature, and a sensation of heat” [6]. The prevalence of hot flushes is reported to be ranging between 67% and 88% [7,8]. In the present study similar prevalence rates were observed (Table 1). Those high rates of prevalence make this phenomenon as one of the major morbidities during menopause. Although various non-hormonal treatment modalities, which were derived mainly from breast cancer survivors [9–13], have been suggested to alleviate this “bothersome” complaint, HT is recognized to be first line treatment option in postmenopausal patients without malignancy. After WHI study and its echoes in many professional communities dealing with women’s health, it is almost universally accepted to utilize HT more cautiously and definitely less widely. Restriction of its use to the lowest dosage and shortest duration brought the difficulty of treating hot flushes and the necessity to discontinue when inappropriate. Discontinuation or limited usage of HT causes the reappearance of VMSs, mainly hot flushes. The Study of Women’s Health Across the Nation (SWAN) may clarify how long symptoms persist beyond the menopause transition or HT cessation and severity of these symptoms [14]. When we first decided to design this study, the first problem was how to taper off the medication being used. Because the dosage of estrogen was 1–2 mg of estradiol or 0.625 mg of conjugated estrogen and, formulations did not allow decreasing the hormones gradually, we found it practical to use the drug once in every 2 days. In our study we evaluated the VMSs up to 4 weeks after the cessation of HT. The data derived from the study of Grady et al. also supported that 4 weeks of follow-up would suffice [15]. They observed that troublesome symptoms have begun a median of 1 week (interquartile range, 0–4 weeks) after stopping hormone therapy. Lack of follow-up beyond this period can be regarded as a limitation of the study. But it should be remembered that the aim of the study was not to evaluate how long it takes for VMSs to fade out, but to compare the severity of symptom scores on the basis of cessation methods.

The measurement of intangible, subjective phenomena, such as hot flushes, can present unique methodological challenges [16]. The use of self report diaries for data collection has long been established as a valid approach to obtaining data on subjective phenomena such as patient reported symptoms and perceptions. Although objective techniques for measuring hot flush frequency, such as sternal skin conductance monitoring, are available there is currently no gold standard for measuring subjective impact of hot flushes on various daily activities or on overall quality of life (QOL) [17]. However, there are several instruments developed in order to meet this demand. Hot Flush Daily Interference Scale developed by Carpenter [18] is one of the proposed tools for the assessment of hot flushes and its impact on QOL. Another tool is proposed by Sloan et al. which was utilized in the clinical trials of North Central Cancer Treatment Group [16]. We adopted to use a physician-based questionnaire and modified hot flush scoring system which follows the same basic principles of aforementioned tools for purposes of simplicity and accuracy.

While 78.55% of patients were experiencing hot flushes before the institution of HT, only 48.57% of patients were facing hot flushes at the end of 4 weeks of cessation. Moreover, while 28 (40%) and 9 (12.9%) patients before the initiation of HT were describing their symptoms as severe and moderate, respectively, only 4 (5.7%) and 2 (2.9%) of the patients were having severe and moderate symptoms after 4 weeks of cessation, respectively. Although we did not find any statistically significant difference between immediate and tapered cessation protocols in the aspect of symptom recurrence, there seems to be an inclination of symptoms to recur in fewer patients and in a less severe form in both groups when compared with their pretreatment status. A point of note that we asked the women to recall their VMSs prior to beginning HT. Since an average of 3 years has passed after the institution of HT, women might tend to recall their past symptoms.
more than they actually happened. As the data are also subject to bias, and the study design did not focus on the pretreatment hot flush scores, it would be inappropriate to draw a valid conclusion for this inclination.

5. Conclusions

Tapering or immediate discontinuing of HT did not affect the recurrence rate and severity of menopausal symptoms at the end of 4 weeks. How best to stop HT is still a controversial issue. Although our study is small, it does provide some evidence for physicians on the best approach to the cessation of HT. Larger clinical trials may be difficult but would further clarify the situation.

After the discontinuation of the HT, symptoms tended to recur in fewer patients and in a less severe form. But, again, large studies focusing on the frequency and severity of pretreatment VMS are needed to support this finding.

With the advent of ‘tailor made therapy’ concept, the physicians dealing with the women’s health are more sensitized about the fact that every woman needs different dosages of hormone to achieve the same level of clinical effect. In accordance with this, pharmaceutical industry simultaneously marketed ‘low’ and ‘ultra low’ dosage preparations together with yesterday’s so-called ‘optimal’ dosage regiments. Those new regiments, in our view can also allow to taper off the medications more gradually, the clinical implementation of which should be assessed by future studies.

References