

Original research article

Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 µg of ethinyl estradiol

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Abstract

Context: In 2006, we published a study that indicated that the new transdermal contraceptive patch containing ethinyl estradiol (EE) and the progestin norelgestromin did not increase the risk for venous thromboembolism (VTE) compared to oral contraceptive containing norgestimate and 35 µg of EE.

Objective: This report updates information on the risk of nonfatal VTE in women using the contraceptive patch in comparison to women using oral contraceptives containing norgestimate (either monophasic or triphasic) and 35 µg of EE (norgestimate-35) using an additional 17 months of data.

Design, Setting and Participants: Nested case-control design based on information from PharMetrics, a US-based company that collects and organizes information on claims paid by managed care plans. The study was nested among all women, aged 15 to 44 years, who started either the contraceptive patch or norgestimate-35 after April 1, 2002. Cases were women with current use of one of these two study drugs and a documented diagnosis of VTE in the absence of identifiable clinical risk factors (idiopathic VTE) who were not in the earlier study. Up to four controls were matched to each case by age and calendar time.

Main Outcome Measures: Odds ratios (ORs) comparing the risk of nonfatal VTE in new users of the two contraceptives.

Results: We identified 56 new cases of newly diagnosed, idiopathic VTE in the updated study population. The OR comparing the contraceptive patch to norgestimate-35 was 1.1 (95% CI 0.6–2.1).

Conclusions: After evaluating an additional 17 months of data, the results indicate that the risk of nonfatal VTE for the contraceptive patch is closely similar to the risk for oral contraceptives containing 35 µg of EE and norgestimate.

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Keywords: Contraceptive patch; Oral contraceptives; Venous thromboembolism

1. Introduction

ORTHO EVRA® is a transdermal contraceptive patch marketed in 2002, which delivers ethinyl estradiol (EE) and 17-deacetylnorgestimate, the primary active metabolite of norgestimate. This contraceptive is designed to deliver effective steady-state levels of the two hormones during the 7-day period of wear.

In 2006, we published the results of an observational case-control study on the risk of nonfatal idiopathic venous thromboembolism (VTE) comparing current users of the

ORTHO EVRA® patch (transdermal patch) with current users of an oral contraceptive containing norgestimate and 35 µg of EE [1]. The study encompassed 68 VTE cases and 266 matched controls and yielded an odds ratio (OR) for the patch compared to the oral contraceptive of 0.9 (95% CI 0.5–1.6). Since concern about the comparative risk for VTE of the patch and traditional oral contraceptives remains, we have repeated our study on this issue using data which have accrued since the earlier publication in 2006 [1].

2. Methods

Data for the current study were again derived from the PharMetrics database. PharMetrics is a US-based, ongoing

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Table 1
Characteristics of cases and controls

| Exposure | Cases (%), n=56 | Controls (%), n=212 | Univariate OR (95% CI) |
|----------------------------|--------------------|------------------------|---------------------------|
| Age | | | |
| <30 | 30 (53.5) | 116 (55) | ^a |
| 30–39 | 18 (32) | 64 (30) | ^a |
| 40–44 | 8 (14) | 32 (15) | ^a |
| Obesity | 4 (7) | 7 (3) | 2.3 (0.7–8.4) |
| Gyn disorder | 7 (12.5) | 24 (11) | 1.2 (0.5–3.3) |
| Back pain | 9 (16) | 16 (7.5) | 2.2 (0.9–5.1) |
| CVD | 1 (2) | 0 (0) | ^b |
| Hypertension | 3 (5) | 4 (2) | 2.8 (0.6–12.4) |
| Hyperlipidemia | 4 (7) | 7 (3) | 2.3 (0.7–8.4) |
| Diabetes | 3 (5) | 1 (<1) | ^b |
| Asthma | 3 (5) | 4 (2) | 2.4 (0.5–10.7) |
| Thyroid disease | 0 (0) | 2 (1) | ^b |
| Switch within 6 months | 5 (9) | 14 (7) | 1.3 (0.4–4.0) |
| Switch within 12 months | 7 (12.5) | 30 (14) | 0.7 (0.3–1.7) |
| ER Visits (1+) | 6 (11) | 6 (3) | 1.7 (0.9–3.4) |
| Physician visits (1+) | 8 (14) | 28 (13) | 0.9 (0.6–1.3) |

^a Matching variable.

^b Could not be calculated.

longitudinal database with information on around 55 million covered lives going back as far as 1995 [1]. It is made up of data contributed by managed care plans throughout the United States and it contains information on paid claims for pharmaceuticals, medical diagnoses and procedures as well as demographic information on all subjects. The current update of the original study encompasses all data that were collected by PharMetrics through September 2006. The study design was identical to that used in our prior study [1].

We organized the PharMetrics data files into individual patient records. This enabled us to create a comprehensive chronological record for each patient that contained information on all drugs prescribed, diagnoses and procedures, both inpatient and outpatient. To assess the eligibility of each potential case of VTE, we conducted a review of each individual patient computer record with the particular study contraceptive identity masked. Agreement on inclusion of women as cases of VTE or controls was achieved by consensus of all authors without knowledge of contraceptive exposure.

2.1. Cases

New cases of idiopathic VTE were women aged 15–44 years old, current users of the transdermal patch or norgestimate-containing oral contraceptives with 35 µg of EE and who had a first-time recorded claim for an ICD-9 diagnosis of deep vein thrombosis or pulmonary embolism at any time during the study period and had subsequent claims for anticoagulant treatment. We excluded cases of VTE that were included in our prior study [1]. The date of the VTE diagnosis was the index date for each case. As before, cases

were required to have been enrolled in their health plan for at least 6 months prior to the index date and to have started using the study contraceptive some time after April 1, 2002. In order to determine their current use of the study contraceptive, we required that there be at least 4 months of history in their claims record before the first recorded study drug dispensing. The 4-month period is based on the knowledge that prescriptions in the PharMetrics database are written for no longer than 3 months at a time. Finally, the case must have stopped using the study contraceptive after the VTE event.

Potential cases who had important risk factors were excluded, e.g., prior use of an anticoagulant medication, recent major surgery, lower limb disorders, epilepsy or recent pregnancy, defined as within the 90 days prior to the VTE.

2.2. Controls

Up to four women who did not have a diagnosis of VTE were matched to each case by year of birth and the index date of the case (calendar time). When more than four matched controls were available for a case, we used random selection to select four controls. As with cases, all controls were required to be current users of one of the study contraceptives, to have at least 6 months of enrollment in their health plan prior to the index date (the event date of their matched case), to have started their study contraceptive use after April 1, 2002, and to have at least 4 months of history in their claims record before the first recorded study drug prescription to confirm that they were new users. The exclusion criteria applied to cases were also applied to controls.

2.3. Exposure

Potential cases were classified at their index date as currently exposed to either the transdermal patch or a norgestimate-containing oral contraceptive with 35 µg of EE. Current use of hormonal contraceptives was defined as having a recorded claim for a study contraceptive prescription whose filled use extended to within 30 days before the index date or beyond the index date.

2.4. Statistical methods

We analyzed the matched case-control data using conditional logistic regression. Duration of contraceptive use prior to the index date and switching from a different hormonal contraceptive, number of physician and emergency room visits in the 6 months prior to the index date and other variables noted in Table 1 were considered as potential confounders.

3. Results

We identified 56 cases of newly diagnosed, idiopathic VTE in current users of study contraceptives who were not included in our earlier study. We matched these cases to 212 controls matched according to birth year, and the index

Table 2
Odds Ratios for VTE among users of the transdermal patch compared to users of OCs containing norgestimate/EE 35 µg in the present study

| Exposure | Cases, n=56 | Controls, n=212 | Unadjusted OR (95% CI) |
|-----------------------|-------------|-----------------|------------------------|
| Norgestimate/EE 35 µg | 36 | 140 | 1.0 (–) ^a |
| Transdermal patch 20 | | 72 | 1.1 (0.6–2.1) |

^a Reference.

date of the case. About 54% of cases and controls were aged less than 30 years, 32% were 30 to 39 and 14% were aged 40 to 44.

The distribution of cases and controls according to age, calendar time and other variables considered in the analysis is provided in Table 1. There were some covariates that were independently associated with VTE but in no case did they materially change the main effect measure. The OR for diagnosed VTE in users of the transdermal patch compared to users of a norgestimate-containing hormonal contraceptive with 35 µg of EE was 1.1 (95% CI 0.6–2.1) (see Table 2). No covariate was found to produce more than a 10% change in the relative risk estimate.

When we combined the data from the original report [1] with those of this update, there were 124 cases and 478 controls in all. The OR for VTE in these women comparing the transdermal patch use to use of a norgestimate-containing hormonal contraceptive with 35 µg of EE was 1.0 (95% CI 0.7–1.5) (see Table 3).

4. Comment

This report contains information on newly identified cases of contraceptive-associated nonfatal VTE identified in the updated PharMetrics database, which contains medical information on patients through August 2006. Controlling for age, calendar time and other variables, this report found no evidence in these new data of a significantly increased risk of VTE in users of the transdermal patch compared to users of norgestimate-containing OCs with 35 µg of EE (OR 1.1, 95% CI 0.6–2.1). When data from the earlier report are combined with the updated data, the OR is 1.0 (95% CI 0.7–1.5).

Another paper that evaluated the association of VTE with use of the patch and of norgestimate-containing OCs was recently published by Cole et al. [2] In this study, the authors found that the patch was associated with an increased risk for VTE (relative risk >2) compared to norgestimate-containing OCs. There were several differences between the Cole et al. study and our study, including differences in case selection and definition. In the Cole et al. study, most cases were validated through medical record abstraction which we were not able to do in our study. However, all cases in our study had outpatient claims for systemic anticoagulants, the use of which is one of our criteria for verification of the occurrence

of VTE. In the absence of medical record review, this requirement serves to include only confirmed cases in the study since it is unlikely that the treating physician would prescribe anticoagulation to a healthy young woman if the diagnosis of VTE had not been established. Another key difference between the studies is that, to ensure comparability between exposure groups, we restricted our study to women who had new use of a study contraceptive (either the transdermal contraceptive or other norgestimate-containing contraceptive) recorded after April 1, 2002, when the transdermal contraceptive product was first marketed. Women who subsequently switched to the other product were eligible for our study. By contrast, the study of Cole et al. had an asymmetric criterion for eligibility. Women could have been long-term users of norgestimate-containing contraceptives before April 1, 2002, and still be eligible for their study. However, no long-term users of the transdermal contraceptive system before that date were eligible for their study because the product was not available before that date. On the assumption that women who have done well for some time on a particular treatment are more likely to stay on that treatment than to switch to a new therapy, the norgestimate-containing contraceptive users in the study of Cole et al. are likely to be more experienced users of hormonal contraceptives than the transdermal contraceptive users. If there is a “survivor cohort effect” that results in a lower incidence of VTE among more experienced contraceptive users, as they suggested, this is more likely to have resulted in a lower risk of VTE among the norgestimate-containing contraceptive users than the transdermal contraceptive users in their study. This difference between the design of our study and that of Cole et al. may help to explain why the incidence of VTE among norgestimate users reported by Cole et al. (18.3/100,000 woman-years) was substantially lower than the incidence we found among norgestimate users (41.8/100,000 woman-years), while, by contrast, the incidence they reported among transdermal contraceptive users (40.8/100,000 woman-years) was more similar to the incidence we reported for transdermal contraceptive users (52.8/100,000 woman-years).

In summary, as in our previously reported study, we found that the risk of idiopathic VTE among women using the transdermal patch is similar to the risk among those using a norgestimate-containing hormonal contraceptive with 35 µg of EE.

Table 3
Odds ratios for VTE among users of the transdermal patch compared to users of OCs containing norgestimate/EE 35 µg

| Exposure | Cases, n=124 | Controls, n=478 | Unadjusted OR (95% CI) |
|-----------------------|--------------|-----------------|------------------------|
| Norgestimate/EE 35 µg | 73 | 279 | 1.0 (–) ^a |
| Transdermal patch 51 | | 199 | 1.0 (0.7–1.5) |

Data from the original and present study combined.

^a Reference.

Acknowledgment

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References

[1] Jick SS, Kaye JA, Russmann S, Jick H. Risk of non-fatal venous thromboembolism in women using a contraceptive transdermal patch

and oral contraceptives containing norgestimate and 35 µg of ethinyl estradiol. *Contraception* 2006;73:223–8.

[2] Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol* 2007;109:339–46.