ELSEVIER

Contraception 73 (2006) 223–228

Contraception

Original research article

Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol

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Received 18 November 2005; revised 9 January 2006; accepted 10 January 2006

Abstract

Context: There is concern that a new transdermal contraceptive patch containing ethinyl estradiol (EE) and the progestin norelgestromin increases the risk for venous thromboembolism (VTE) compared to previously marketed oral contraceptives (OCs).

Objective: Quantitative information was obtained on the risk of nonfatal VTE in women using the contraceptive patch in comparison to women using OCs, norgestimate (either monophasic or triphasic) and 35 μg EE (norgestimate-35), an OC that has been marketed for over a decade.

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, 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). 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 and incidence rates of nonfatal VTE for new users of each of the study contraceptives.

Results: We identified 68 newly diagnosed, idiopathic cases of VTE in the study population. In the case-control analysis, the OR comparing the contraceptive patch to norgestimate-35 was 0.9 (95% CI 0.5–1.6). The overall incidence rate for VTE was 52.8 per 100,000 women-years (95% CI 35.8–74.9) among users of the contraceptive patch and 41.8 per 100,000 women-years among users of norgestimate-35 (95% CI 29.4–57.6), and the age-adjusted VTE incidence rate ratio (IRR) for current use of the contraceptive patch vs. norgestimate-35 was 1.1 (95% CI 0.7–1.8).

Conclusions: The risk of nonfatal VTE for the contraceptive patch is similar to the risk for OCs containing 35 μg ethinylestradiol and norgestimate.

Keywords: Contraceptive patch; Oral contraceptives; Venous thromboembolism

1. Introduction

The combination transdermal contraceptive patch has been marketed since 2002. This transdermal patch contains 0.75 mg ethinyl estradiol (EE) and 6 mg of the progestin norelgestromin (the active metabolite of norgestimate) and releases on average 20 μg of EE and 150 μg of norelgestromin into the systemic circulation per 24 h. According to a recent statement by the US Food and Drug Administration (FDA) in a press release dated November 10, 2005, "Women who use the transdermal patch are exposed to about 60 percent more total estrogen in their blood than if they were taking a typical birth control pill containing 35 μg of estrogen" [1]. A pharmacodynamic study found that the maximal blood level (peak blood level) of EE is about 60% lower with the patch than with a birth control pill containing 30 μg EE [2]. The new bold warning in the approved product labeling for the contraceptive patch states, "However, it is not known whether there are changes in the risk of serious adverse events based on the differences in pharmacokinetic profiles of EE in women using the transdermal patch compared with women using oral contraceptives (OCs) containing 35 μg of EE" [1].

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doi:10.1016/j.contraception.2006.01.001

Oral contraceptives containing estrogen–progestin combinations have been associated with an increased risk of deep vein thrombosis and subsequent pulmonary embolism, collectively referred to as venous thromboembolism (VTE) [3–8]. The absolute risk of venous thrombosis has been reported to increase from a baseline risk of less than 1 per 10,000 women-years to 3 to 4 per 10,000 women-years during use of OCs. [7].

In the premarketing clinical trials of the transdermal patch, one case of idiopathic VTE and one case of VTE after surgery were diagnosed in 3330 users with a cumulative treatment duration of about 1800 years (22,176 cycles) [9]. However, the low number of users in the clinical trials limited a precise risk estimate of this uncommon adverse event and a reliable quantitative comparison with other OCs.

We conducted a study that compared the risk of nonfatal VTE in women using the transdermal patch to that of women using monophasic or triphasic norgestimate-containing OCs with 35 μg of EE (norgestimate-35), which have been marketed for over a decade.

2. Methods

2.1. Data resource

Data for this study were derived from the PharMetrics database. PharMetrics is a US-based, ongoing longitudinal database with information on about 55 million people going back as far as 1995. The database is made up of data contributed by managed care health plans throughout the United States and contains information on paid claims for pharmaceuticals, medical diagnoses and procedures as well as demographic information such as patient's year of birth, gender and enrollment details for each subject in the database. Drug prescriptions are coded using the National Drug Code provided by the US FDA. Each drug claim is entered as a separate entry and includes information on the specific entity dispensed, the date of dispensing, the quantity dispensed and the length of the supply. All diagnoses are coded using the ICD-9 coding system. Procedure codes are also included in the database coded using the CPT-4 system. All events described above are noted with the date on which the initial service was delivered. Additional codes describe other aspects of the patient's condition at the time of the hospitalization.

The methods applied in this study were similar to those previously described for the study of contraceptive safety [5,6]. The present study was designed to take into account the evaluation of a recently marketed drug and the use of a comparison drug, which has been marketed for over a decade, since no other more recently marketed OC was available. We required that all cases and controls be new users of either study drug after April 1, 2002, when the transdermal patch was first marketed. Important variables that were controlled in the design were (1) age, since users of the new drug may have a different age distribution than users of the older comparison drug; and (2) calendar time (i.e., the date of diagnosis), since the two contraceptives will have highly different usage characteristics in relation to calendar time. We also explored duration of use, which may be correlated with both drug use and the risk of VTE.

2.2. Base population

We conducted a case-control study nested in the population of users of the transdermal patch and norgestimate-35 OCs, aged 15 to 44 in the PharMetrics database. All subjects were required to have filled at least one new prescription for a study drug after April 1, 2002, the date that the transdermal patch was first marketed in the United States. Follow-up medical information was available as far forward as March 31, 2005.

As a first step, we organized the PharMetrics data files sent to us 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 and control, the authors conducted a review of each individual patient computer record with the particular study contraceptive identity masked. Agreement on inclusion of women as cases or controls was achieved by consensus without knowledge of contraceptive exposure.

2.3. Cases

Cases were women aged 15 to 44 years old who were current users of the transdermal patch or norgestimate-35 and who had a first-time recorded claim for a clinically diagnosed deep vein thrombosis or pulmonary embolism with hospitalization, a visit to the emergency room or positive indication of VTE from diagnostic test results, and who subsequently received prolonged anticoagulation therapy. Cases were included if the diagnosis of VTE was recorded for the first time after April 1, 2002. A requirement for inclusion was that there were at least 6 months of medical history prior to the diagnosis (index date). In addition, in order to determine when subjects started using the study contraceptive, we required that there be at least 4 months of history in their claims record before the first recorded study contraceptive. The 4-month period is based on the finding that contraceptive prescriptions in the PharMetrics database are written for no longer than 3 months at a time. Thus, a window of at least 4 months provided assurance that the first identified prescription is a new prescription and not a refill of an existing prescription. The case had to be currently exposed to one of the study drugs. Exposure was determined from the prescription claims data prior to the date of diagnosis of VTE (index date). Current exposure 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. Long-term anticoagulation must have been started promptly, and no estrogen-containing contraceptive could

Table 1
Characteristics of cases and controls

Characteristic	Cases ($n=68$)		Controls ($n=266$)	
	n	%	*n*	%
Age				
15–29	27	40	104	39
30–39	26	38	103	39
40–44	15	22	59	22
Index year[a]				
2002	8	12	31	11
2003	33	49	130	50
2004	22	32	85	31
2005	5	7	20	7

[a] Year of diagnosis of the VTE event.

be initiated after the date of diagnosis, strengthening the clinical diagnosis of VTE.

Potential cases were excluded from the case group if important clinical risk factors for VTE were present in the 3 months prior to the index date [10]. These included significant lower limb injury, major surgery, severe trauma or pregnancy. Subjects with any history of cancer (other than nonmelanoma skin cancer), renal failure, chronic cardiovascular disease, or inflammatory or autoimmune conditions were also excluded.

2.4. 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.

2.5. 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 were considered as potential confounders, as well as number of physician and emergency room visits in the 6 months prior to the index date.

We analyzed the cohort data to estimate incidence rates and 95% confidence intervals. Current person-time was accumulated from the first study drug prescription to the last prescription plus 45 days. If there was a gap in the prescription fill dates of greater than 100 days, the person-time accumulation stopped at the last prescription before the gap, plus 45 days; person-time accumulation then resumed at the next record of a prescription for a study drug. We estimated incidence rate ratios (IRRs) using Poisson regression. We examined possible effect modification by including multiplicative interaction terms in the model, and we compared the fit of nested models using likelihood ratio testing [11].

Duration of contraceptive use was defined as the time interval (in months) from the first use of the study contraceptive to the index date. A subject was defined as a switcher if there was a recording for a different hormonal contraceptive product at any time in the patient's record that preceded the use of the study contraceptive.

Calculations were performed using SAS release 8.02 (SAS Institute, Cary, NC) and Stata release 8.2 (StataCorp LP, College Station, TX).

This study was exempt from review by the Boston University Medical Center Institutional Review Board.

3. Results

We identified 68 cases of VTE and 266 controls (women without VTE), matched by year of birth and index date. Among the 68 cases of idiopathic VTE, there were 31 among women currently exposed to the transdermal patch and 37 currently exposed to norgestimate-35. Fifty-seven cases were hospitalized, 38 (67%) with a diagnosis of pulmonary embolism and 11 were diagnosed as outpatients, only 4 (36%) with a diagnosis of pulmonary embolism. All 11 cases in the outpatient setting were prescribed warfarin and 9 cases also received low-molecular-weight heparin.

Characteristics of the cases and controls are listed in Table 1 and their exposure to the transdermal patch or norgestimate-35 is summarized in Table 2. The unadjusted matched odds ratio (OR) for VTE for the transdermal patch vs. norgestimate was 0.9 (95% CI 0.5–1.6) (Table 2). After adjusting for duration of exposure, the OR remained 0.9. A history of switching from another hormonal contraceptive had no effect on the OR, nor did restricting the analysis to women who were hospitalized for VTE, or adjusting for the frequency of physician's office or emergency room visits during the 6-month period before the index date.

In the study population, there were 215,769 women who satisfied all the conditions for inclusion in this study. These women contributed an estimated 147,323 women-years of current exposure to the study contraceptives (58,752 women-years for the transdermal patch and

Table 2
Odds ratio for VTE comparing users of contraceptive patch to users of norgestimate-35

Exposure	Cases		Controls		Odds ratio[a]	95% CI
	n	%	*n*	%		
Norgestimate-35	37	54	139	52	1.0	Reference
Contraceptive patch	31	46	127	48	0.9	0.5–1.6

[a] Conditional on age, index date.

88,571 women-years for the comparison contraceptive). The overall incidence rate for VTE in the study population was 52.8 per 100,000 women-years (95% CI 35.8–74.9) among users of the contraceptive patch and 41.8 per 100,000 women-years among users of norgestimate-35 (95% CI 29.4–57.6). Adjusted for age, the VTE IRR for current use of the transdermal patch vs. norgestimate-35 was 1.1 (95% CI 0.7–1.8). The data did not provide evidence for effect modification by age ($p=.10$). Regardless of which contraceptive was used, the incidence of VTE increased with increasing age. The incidence per 100,000 women-years was 26.7 (95% CI 17.6–38.9) among women aged 15–29 years, 67.2 (95% CI 43.9–98.5) among women aged 30–39 years and 197 (95% CI 110–326 per 100,000 women-years) among women aged 40–44 years ($p<.001$ for test of trend).

4. Discussion

Spontaneous reports of thrombosis in users of the transdermal patch have raised major public concern about its safety. In contrast to OCs, no gastrointestinal or hepatic first-pass metabolism occurs after transdermal application, and for postmenopausal estrogen therapy it has been suggested that this difference may result in a lower clinical risk of VTE with transdermal estradiol than oral estrogen [12,13]. So far, no formal studies have been available to investigate whether these spontaneous reports reflect a higher risk of VTE or indeed whether the transdermal contraceptive patch may have a lower risk of VTE than comparable OCs.

The findings of this study provide evidence that the risk of nonfatal VTE with subsequent long-term anticoagulation is not higher in current transdermal contraceptive patch users compared to current users of the norgestimate-35 OC (OR 0.9, 95% CI 0.5–1.6; IRR 1.1, 95% CI 0.7–1.8). In the current study, the risk of VTE in users of the transdermal patch was compared to the risk in users of norgestimate-35 because norelgestromin is the active metabolite of norgestimate, the progestin released by the transdermal patch. This methodology is the most efficient design to study risk differences in relation to the route of administration and also allows for the important comparison to a drug that has been marketed for more than a decade.

The current epidemiologic study used a case-control design, which has often been used in the past to study the safety of hormonal contraceptives [3,5,6,14,15]. A nested case-control study design is standard for drug safety studies for evaluating contraceptive safety since it insures comparability between cases and the comparison group at the time of the case event [16]. As in prior studies, age and calendar time were closely controlled, i.e., the controls were matched to cases on year of birth, and the date from which exposure was determined (the index date) was identical in cases and controls. This procedure equalizes the potential influence of age and calendar time on the relative effect of the two contraceptives. There is, however, one feature of this study that differs from prior studies. Whereas prior studies compared contraceptives that had been marketed for many years, the current study involves the comparison of an estrogen-containing contraceptive (the transdermal patch) that has been marketed for only 3 years with norgestimate-containing OCs that have been available for more than a decade. In the PharMetrics database, new use of the transdermal patch increased markedly over the first few years after April 2002, whereas that of norgestimate-35 decreased over the same time period. Among women included in this study, the proportion who started using the transdermal patch rose progressively from 23% in 2002 to 55% in 2004, whereas the proportion of norgestimate-35 users fell correspondingly. We have controlled for this difference by including only women with new use of one or the other study contraceptives after April 1, 2002, the date that the transdermal patch became available. Although it is possible that norgestimate-35 may have been used by cases or controls in the distant past, previous studies have convincingly demonstrated that only current use is relevant to the risk of VTE, and thus this possible difference in the past use of the two study drugs is unlikely to have had a material effect on the results obtained [3].

We limited the study to nonfatal outcomes because the PharMetrics database does not capture deaths that occur outside a health care facility. However, fatal cases of VTE during use of hormonal contraceptives have been reported to represent only a small proportion of all VTE cases, and failure to identify them in this study is unlikely to have materially distorted the findings [5]. We also excluded patients with chronic medical conditions such as cancer, coronary artery disease and autoimmune disease. Although these were not commonly observed in this generally healthy young population of contraceptive users, the exclusion of such patients from the study population limits concerns about selective prescribing of the study drug based on the presence of clinical risk factors.

As in any epidemiology study, there may be some misclassification of cases. Any such misclassification would be nondifferential since we identified cases and controls without knowledge of the contraceptive to which they had been exposed. Nondifferential misclassification of a dichotomous variable tends to bias results toward the null. However, since we used the same operational definition of VTE in this study as in many other studies that we have carried out where differences in risk of VTE have been found, we consider this to be a minor issue [5,6,10,14].

We could not evaluate the effect of smoking in the current study since it is not regularly recorded in the PharMetrics database. However, smoking is believed to increase primarily the risk of *arterial* cardiovascular events in users of OCs, but not the risk of VTE, and smoking has not been a material confounder in previous studies comparing the association between OCs and VTE [5,6,15,17,18]. Also, neither height nor weight was recorded

in the current study. Although body mass index (BMI) is independently associated with a modestly increased risk for VTE, BMI has not confounded the association between use of hormonal contraceptives and VTE in prior studies [3,5,6,14]. Furthermore, when we evaluated the ICD-9 diagnosis for obesity we did find that obesity was associated with an increased risk ratio for VTE (OR=2.3), but inclusion of obesity in the model with exposure did not materially change the effect of exposure, providing additional reassurance that obesity is not an important confounder in this study. Although the ICD code is not an ideal proxy for obesity, we believed that the diagnosis would most often be used in the most obese women. Obesity was associated with VTE as it has been in past studies [3,5,6,14], yet it did not confound the effect of the contraceptives we compared. This indicates that the ICD code was probably a reasonable proxy given that the information was limited. If there were a strong tendency for the patch to be preferentially prescribed to thinner women, it is possible that the OR for VTE with the patch calculated in this study is an underestimate of the true risk.

The effect of duration of use of contraceptives could not be fully explored since the study period encompassed only 3 years and a substantial proportion of contraceptive users had used them for less than 1 year. Further studies over time will allow for a more comprehensive evaluation of the effect of longer duration of use.

Samples of the transdermal patch were distributed in the first years that the drug was marketed. This would not have been true of norgestimate-35 during the study period. We cannot rule out some influence of this difference that applied to both cases and controls, but the nature of the results was such that any effect is likely to have been modest.

Over 215,000 women exposed to one of the study drugs in our study population provided information on the clinically important question of the risk of VTE in relation to the transdermal patch. Because of the prospective nature of data collection, the information on exposure was collected before the outcome had occurred, all eligible patients with the outcome were included, and the likelihood of correct diagnoses of VTE was increased by the documentation of long-term use of anticoagulants. We were able to tightly control potential confounding due to age and calendar time. The rate of VTE associated with combination contraception use in this study was higher than that found in previous studies [5,6], but this study encompassed women up to age 44, whereas the earlier studies included only women up to age 39. This difference would at least partially account for the somewhat higher rate of VTE in this study.

In summary, although higher mean circulatory levels of EE have been reported among users of the contraceptive patch compared to users of combined OCs, our results indicate that the risk of nonfatal idiopathic VTE among new users of the transdermal patch is similar to that of new users of norgestimate-35.

Acknowledgments

The current study was supported by a grant from Johnson & Johnson Pharmaceutical Research and Development. The contraceptive patch was developed by the R.W. Johnson Pharmaceutical Research Institute and is marketed by Ortho-McNeil Pharmaceuticals. S. Russmann is supported by a Merck Sharp & Dohme International Fellowship in Clinical Pharmacology.

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