DOI:10.1111/j.1365-2125.2005.02373.x

Deep vein thrombosis and pulmonary embolism reported in the Prescription Event Monitoring Study of Yasmin®

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Keywords
oral contraceptives postmarketing, product surveillance, venous thrombosis

Received
4 June 2004
Accepted
15 October 2004

Aim
To evaluate cases of deep vein thrombosis (DVT) and pulmonary embolism (PE) reported in a prescription event monitoring study of Yasmin®, an oral contraceptive.

Methods
Reports of DVT/PE and events suggestive of DVT/PE were followed up by questionnaire.

Results
Thirteen cases (DVT five; PE eight), each with possible risk factor(s), were identified in 15 645 females using Yasmin®. Applying complete case analysis, the crude incidence rate was 13.7 cases per 10 000 woman-years (95% confidence interval 7.3, 23.4).

Conclusions
Yasmin is associated with venous thromboembolism. An incidence rate has been calculated, but this may be subject to bias and should be interpreted with caution.

Introduction

Yasmin®, a combined oral contraceptive (COC) containing ethinyloestradiol (30 μg) and a new progestogen, drospirenone (3 mg), was launched in the UK in May 2002. The association between oestrogen-containing oral contraceptives and venous thromboembolism (VTE) is well established [1]. Until 1995, it was generally thought that the progestogen component of COCs did not contribute to the risk of VTE [1]. However, a number of studies published in late 1995 and early 1996 reported an increased risk of VTE for users of the so-called third-generation COCs containing the progestogens, desogestrel or gestodene, compared with second-generation COCs, containing levonorgestrel [1]. These findings were unexpected and led to debate over possible bias and confounding. New studies, re-analyses of the original studies and a meta-analysis have since been published [1, 2]. The data have been reviewed by independent expert committees and it is now accepted that there is a higher risk of VTE with third-generation COCs than with second-generation COCs [1, 3]. Biochemical and clinical studies were conducted to investigate whether there was a biological mechanism which would provide support for the epidemiological findings [1, 4]. Some studies have shown that third-generation COCs have a more pronounced effect on procoagulant, anticoagulant and fibrinolytic pathways compared with second-generation COCs. These changes would be con-

sistent with a greater prothrombotic effect and the clinical significance of these findings is under investigation [1, 4].

VTE is a rare event in young women and the risk associated with a new COC cannot generally be determined from clinical trials [5]. The prescribing information for Yasmin® states that 'It is not yet known how Yasmin® influences the risk of VTE compared with other oral contraceptives' [6]. Prescription event monitoring is an observational method of postmarketing surveillance which was established to monitor the safety profile of newly marketed medicines under primary care conditions in England [7]. In this paper, we describe cases of deep vein thrombosis (DVT) and pulmonary embolism (PE) reported in the Prescription Event Monitoring study of Yasmin®.

Methods

Prescription Event Monitoring has been described elsewhere [7]. Patients were identified from dispensed NHS prescriptions issued in England between May 2002 and December 2002. Simple questionnaires (green forms) were posted to the prescribing general practitioners (GPs) 6–12 months after the first prescription for each individual patient. GPs were asked to report any health-related events which had occurred since Yasmin® was prescribed. GPs who reported that a patient had developed a DVT or PE were sent a follow-up questionnaire requesting additional information on presentation, investigations, risk factors for VTE and outcome of the event.

A cumulative listing of events reported on the green forms was reviewed by two Drug Safety Research Unit (DSRU) physicians to identify signs and symptoms suggestive of DVT or PE (e.g. chest pain, dyspnoea, swollen calf). Green forms, where a DVT or PE was not recorded but a sign or symptom suggestive of either event was described, were reviewed independently by the same physicians to determine whether follow-up for more information was required. When agreement on the need for follow-up could not be reached, a third physician reviewed the forms independently and made the final decision. A questionnaire similar to that for cases of DVT or PE was sent for green forms identified for follow-up.

Results

Green forms were sent for 30 797 patients prescribed Yasmin®; 17 877 (58.0%) were returned, of which 15 684 contained clinical information (50.9%; n = 30 797). The main reasons for missing clinical information were: the patient was no longer registered with the practice, the form was returned blank or the GP had no record of prescribing Yasmin®. Green forms received for patients taking Yasmin® as part of a gender reassignment programme (n = 22) or where the sex of the patient could not be identified (n = 17) were not included in this analysis, leaving 15 645 forms containing clinical information on female patients for review. Age was known for 13 369 female patients (85.5%; n = 15 645), the mean (SD) was 26.5 (± 6.9) years. Information on duration of use was available for 12 595 females (80.5%; n = 15 645). The median treatment period was 320 days [interquartile range (IQR) 159–349]; 9482 woman-years of use were recorded.

Follow-up questionnaires were sent for 16 individual cases of DVT or PE. One questionnaire for DVT was not returned. From information provided on the green form, the event occurred at an unspecified time after Yasmin® was stopped. Follow-up was received for 15 cases; diagnosis was not confirmed on investigation for two cases of DVT.

Seventy follow-up questionnaires were sent for green forms with signs or symptoms suggestive of DVT or PE. Fifty-eight questionnaires were returned (82.8%; n = 70); eight contained no clinical information. No further cases of DVT or PE were identified from the remaining 50 questionnaires (71.4%; n = 70).

Therefore, five cases of DVT and eight of PE in 13 females using Yasmin® were identified (Table 1). None of the cases had a previous history of DVT or PE. In each case, Yasmin® was taken during the month before the event and was discontinued as a result of the event. Diagnosis was confirmed by ultrasound or imaging procedures, with the exception of one case of PE where the event occurred outside the UK. The latter patient was being treated with an anticoagulant. None of the cases was confirmed to have both a DVT and PE during these episodes. No deaths were recorded. Thirteen cases of DVT or PE occurred during the 9482 woman-years of use, giving a crude incidence rate of 13.7 cases per 10 000 woman-years of use (95% confidence interval 7.3, 23.4), based on a complete case analysis of the 12 595 women with information on duration of use. The mean (SD) age of the cases was 33.9 years (± 8.2). The median time to onset of event from starting Yasmin® was 155 days (IQR 84.5–291.5). Each of the cases had one or more possible risk factors for DVT or PE (Table 1).

Discussion

To our knowledge, this is the first description of cases of DVT and PE in users of Yasmin® in the primary care setting in England. Five cases of DVT and eight cases of PE were identified in 15 645 females. Each of the cases had one or more possible risk factors for VTE.

Table 1
Cases of deep vein thrombosis (DVT)[a] and pulmonary embolism (PE)[a] during use of Yasmin®

Case	Age (years)	BMI (kg m^{-2})	OCP used during 12 months preceding Yasmin[b]	First time user of OCP	Time to onset (days)	Possible risk factors for DVT/PE[c]
DVT (*n* = 5)						
1	21	21	No	Yes	155	Homozygous for factor V Leiden.[d] Current smoker.[e]
2	22	Not known	Dianette[f]	No	161	Recent hospital admission with constipation. Immobility due to abdominal and back pain. Current smoker[e]
3	29	20	Dianette[f]	No	42	Current smoker.[e] (Negative screen for factor V Leiden after sibling had a DVT and was found to be heterozygous for factor V Leiden)
4	44	Not known[g]	Not known	No	320	Prothrombin mutation[d,h]
5	46	29	No	Not known	95	Fall resulting in calf muscle damage during month preceding event. Current smoker[e]
PE (n = 8)						
1	27	28	2nd generation COC[i]	No	149	Current smoker[e,j]
2	30	28	3rd generation COC[k]	No	361	Heterozygous for prothrombin gene mutation and moderate positive IgG anticardiolipin antibodies[d]
3	31	Not known	No	Yes	117	Current smoker[e]
4	34	29	No	No	71	Two long haul flights (>8 h) during month before event. Developed calf pain and pitting oedema before return flight to UK. Varicose veins.[l] Current smoker[e]
5	36	24	No	No	224	No risk factors reported other than age >35 years
6	37	26	2nd generation COC[i]	No	74	No risk factors reported other than age >35 years[m]
7	41	30	No	No	263	Obese
8[n]	43	25–29	2nd generation COC[i]	No	382	Atypical chest pain before flight (2–3 h), collapsed on leaving flight. Occasional low-dose chlorpromazine use

BMI, Body mass index; DVT, deep vein thrombosis; OCP, oral contraceptive pill; PE, pulmonary embolism. aHigher level terms in dictionary used by Drug Safety Research Unit. bInformation was requested on whether any other oral contraceptives were prescribed during the 12 months preceding use of Yasmin®. If yes, the brand name of the contraceptive was requested. cInformation was sought on personal and family history of DVT or PE and clotting abnormalities; any of the following conditions within 3 months of event—pregnancy, vaginal delivery, caesarian section, leg(s) in plaster cast, wheelchair bound, lower limb paralysis, medical condition resulting in immobility, surgery requiring general anaesthesia, cancer; flights within 1 month of event; use of antipsychotics, corticosteroids, oral antiplatelets, oral anticoagulants, heparin and other prescription or over-the-counter medicines within 1 month of event; other relevant medical history. dScreening conducted following DVT /PE. eCurrent smoker at time of prescribing. fContains cyproterone actetate and ethinyloestradiol. gDescribed by GP as 'thin'. hGP reported that no flights were taken within 1 month of event but a long haul flight (>8 h) was taken 14 weeks before event. Not known if there were any consequences as a result of this flight with relevance to event. iContains levonorgestrel and ethinyloestradiol. jGP reported that patient had none of the conditions listed above within 3 months of event. According to green form, histiocytoma removed 3.5 months before event—no further information on nature of condition. kContains desogestrel and ethinyloestradiol. lGP reported varicose veins as risk factor for this patient; no information on severity of condition provided. mThrombophilia screen to be conducted at a future date. nInformation on investigations not available as event occurred abroad; patient was treated with an anticoagulant.

One strength of this study is that it examines cases of DVT and PE in real-life clinical practice. Unlike clinical trials, prescription event monitoring studies have no exclusion criteria and provide information on the safety of drugs used by patients of all ages with a wide variety of comorbid conditions and concurrent drug use. Prescription event monitoring is complementary to the national spontaneous reporting scheme in the UK. Cases of DVT and PE reported as suspected adverse drug reactions to Yasmin® in spontaneous reporting schemes in two countries have been described in the literature [8, 9]. Neither of these publications provides comprehensive information on risk factors for VTE. In our study, GPs were asked to provide information for the cases on

a broad range of possible risk factors for VTE. Some of these risk factors are well established (e.g. immobility; thrombophilia; trauma), whereas there is no consensus in the literature over the magnitude of risk associated with some of the other reported risk factors (e.g. air travel, smoking) [1, 10–12]. Further work is required to examine the association between the possible risk factors identified in this analysis and the development of DVT or PE in users of Yasmin®.

It is unlikely that every possible risk factor has been accounted for in our study as we did not have access to the patients' medical records. However, we requested information on the patients' medical history, concurrent drug use and other factors which the GP considered may have contributed to the event. We were able to identify first-time users of COCs, which is important, as the risk of VTE is highest during the first year a women ever uses a COC [3]. However, accurate information on use of COCs before Yasmin®, in particular aspects such as duration of use, is difficult to obtain without access to medical records.

The incidence rate and accompanying confidence interval are based on a complete case analysis. Complete information on duration of use was available for 80.5% of the patients included in this study. This included all 13 cases of DVT/PE. It is possible that GPs may be more likely to provide complete information on patients who had experienced events of interest, and in this circumstance an analysis of complete case information would overestimate the incidence rate. We decided not to replace the missing values with substitute values as there are a number of additional factors described below which may also have influenced the incidence rate and it would be extremely difficult and possibly confusing to account for them all in any sensitivity analysis.

A weakness of our study is nonresponse bias; only 50.9% of green forms sent to GPs were returned with clinical information. It is conceivable that if all patients within the initial 30 797 patients prescribed Yasmin® who developed a DVT or PE were reported to us, then the incidence rate of 13.7 cases per 10 000 woman-years would be halved. Conversely, if the incidence rate was higher amongst the nonresponders, then the true incidence rate would be greater than 13.7 cases per 10 000 woman-years.

There are a number of other factors which may have influenced the incidence rate for this study. Selective prescribing to patients at risk of VTE is possible. For selective prescribing to have taken place, the GP must have been aware of a risk factor before prescribing. This would not have applied to cases where acute conditions, such as immobility or trauma, were reported or for patients found to have hereditary thrombophilia after the event. Yasmin® may have been selectively prescribed for first-time users of COCs and for patients with risk factors for VTE who were intolerant of other COCs. Only two of the 13 cases (15.4%) were first-time users of COCs. However, it is not possible to generalize to the entire cohort on the basis of such small numbers. Other patient characteristics of which the GP would have been aware include age and body mass index (BMI). It is noticeable that seven of the 10 cases with a specified BMI were reported to have a BMI of 25 kg m^{-2} or greater. For the purposes of this analysis, we considered a BMI of 30 kg m^{-2} or more to be a possible risk factor for VTE; however, some studies of COCs have reported that the risk of VTE is increased at a BMI of 25 kg m^{-2} or more [11]. The number of cases who are overweight may simply be representative of the general population in the UK. Alternatively, the initial claims that Yasmin® had a beneficial effect on skin and body weight may have resulted in selective prescribing [13]. It is well recognized that the risk of VTE increases with age; six of the 13 cases were over 35 years of age, with four cases aged ≥40 years [10].

Incidence rates may also be influenced by changes in clinical practice [14]. The investigation and diagnosis of VTE has become easier during recent years, although there is no reason to believe that patients taking Yasmin® would be more likely to be referred or investigated more thoroughly than users of other COCs. An unexpected finding in our study is the higher number of reports of PE ($n = 8$) compared with DVT ($n = 5$); it is not clear whether this is due to the difficulties in recognizing symptoms of DVT or reporting bias. In addition, the incidence rate may have been influenced by the relatively short duration of this study; the median treatment period was 320 days.

The information from our study adds to the present knowledge of the occurrence of DVT and PE in users of Yasmin® and related risk factors. Taking into account nonresponse bias and the potential effect of other bias, it should be borne in mind that the incidence rate for this cohort may well be an overestimate and should be interpreted with caution. Further research is required into the association between the use of Yasmin® and DVT or PE.

We thank the general practitioners who participated in this study. In addition, we thank Mr Scott Harris, medical statistician at DSRU, for statistical advice. Also, we thank the Prescription Pricing Authority for their important participation.

Competing interests

The Drug Safety Research Unit is a registered charity (No 327206). The DSRU receives unconditional grants from pharmaceutical companies but conducts its studies independently. The DSRU has received an educational grant from Schering Health Care, the manufacturer of Yasmin®. H. M. P, D. L and L. V. W have no competing interests to declare. Although S. A. W has no apparent competing interests, he has received lecturing and consultancy fees from pharmaceutical companies in the last five years. It is possible that some of these companies may benefit from the publication of this article.

Ethics requirement

The collection and analysis of data by Prescription Event Monitoring is exempted from review by NHS Research Ethics Committees according to NHS Research Ethics Committee Supplementary Operational Guidelines, November 2000.

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