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Thromboembolism as the adverse event of combined oral contraceptives in Japan

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ABSTRACT

Background: The risk of thromboembolism associated with combined oral contraceptives (COCs) in Japanese women is not clear yet. The aim of this study is to estimate the current risk of thromboembolism among COC users in Japan.
Methods: We used the Pharmaceuticals and Medical Devices Agency (PMDA) database disclosed by PMDA from April 2004 to December 2013, and extracted thromboembolic events among adverse events from the adverse event information of COC products.
Results: Of the 581 thromboembolic events, venous thromboembolism (VTE) accounted for 394 events, arterial embolism and thrombosis (ATE) were 154, and thrombosis of unspecified sites was 33. In VTE, deep vein thrombosis and pulmonary embolism were the most frequent (78.4%), followed by cerebral vein thrombosis (11.4%). In ATE, cerebral infarction was the most frequent (76.0%) and approximately 6.9-fold higher than coronary heart diseases. The annual estimated incidence per 10,000 person-years of VTE, ATE and all thromboembolisms in current users of all COCs were 1.11 (95% confidence interval: 1.00–1.24), 0.37 (0.30–0.44), and 1.56 (1.42–1.71), respectively. The frequency of all thromboembolic events that developed within 90 days from the start of COCs was 45.5%, and that within 360 days was 81.2%. Sixteen deceased cases were suspected to be associated with thromboembolism, and the estimated mortality rate between 2009 and 2013 was 0.50 (0.30–0.84) per 100,000 person-years.
Conclusions: Incidence rates of thromboembolism, particularly VTE, in Japanese current COC users became clear for the first time, being slightly lower than people in Western countries.

1. Introduction

Venous thromboembolism (VTE) associated with combined oral contraceptives (COCs; estrogen combined with progestin) was reported for the first time by Jordan in 1961 [1]. Since then, the increased risk of VTE associated with current COC use has been confirmed [2–11]. The risk of VTE in women using COCs is attributed to changes in hemostasis [12]. When attention was paid to VTE as an adverse event of COCs, the role of estrogen was pointed out. Nowadays, we know that estrogen increases gene expression as well as plasma levels of coagulation factors [13] and decreases anticoagulant factors such as protein S [14] and a tissue factor pathway inhibitor (TFPI) [15]. On the other hand, progestin stimulates the gene expression of protein S [16].

Thromboembolism is an unavoidable adverse event of COCs. However, the risk of thromboembolism associated with COCs in Japanese women is not clear yet, although Adachi et al. reported 29 cases of thromboembolism associated with COC use in Japanese women between 1992 and 2001 throughout Japan [17]. The deceased cases of VTE caused by therapeutic use of estrogen and progestin (low dose estrogen progestin; LEP) for dysmenorrhea were only reported by mass media in 2013 in Japan. The constituents of these remedies are the same as COCs. Such hormone therapies for dysmenorrhea have been approved for health insurance coverage since 2008 in Japan, and the associated thromboembolism is thought to increase with the recent increase in the quantity of those prescriptions.

Although large databases with safety information are available in Western countries, Japan does not have them, but is beginning to construct them for adverse events. In the past, the Ministry of Health, Labor and Welfare (MHLW) made it obligatory for pharmaceutical companies, hospitals, physicians, pharmacists, and others to report the adverse events with medicines. The Pharmaceuticals and Medical

Abbreviations: VTE, (venous thromboembolism); ATE, (arterial embolism and thrombosis); COCs, (combined oral contraceptives); PMDA, (Pharmaceuticals and Medical Devices Agency); TFPI, (tissue factor pathway inhibitor); LEP, (low dose estrogen progestin); MHLW, (Ministry of Health Labor and Welfare); EE, (ethinylestradiol); DVT, (deep vein thrombosis); PE, (pulmonary embolism).

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Devices Agency (PMDA) accepted the notification from companies, hospitals, physicians and others after April 2004, and established the Japanese Adverse Drug Event Report Database (PMDA database). For encouraging the utilization of adverse event information, it became available as CSV format after April 2012. Then, we could extract adverse events including thromboembolism from this database disclosed by PMDA from April 2004 to December 2013. The aim of this study is to estimate the current risk of thromboembolism among COC users in Japan.

2. Methods

2.1. Subjects

In this study, we used the PMDA database from 1 April 2004 to 31 December 2013 (see homepage, i.e., http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp; http://www.info.pmda.go.jp/fsearchnew/jsp/menu_fukusayou_base.jsp), and extracted thromboembolic events among adverse events from the adverse event information of COC products. Contraceptives were categorized according to estrogen content and progestin content [18]: mestranol or ethinylestradiol (EE) combined with norethisterone (the first-generation COCs), EE combined with levonorgestrel or norgestrel (the second-generation COCs), EE combined with desogestrel (the third-generation COCs), EE combined with drospirenone (the fourth-generation COCs) and progestin only (norethisterone, levonorgestrel, levonorgestrel releasing intrauterine device and dienogest). In cases with the prescription of several drugs, a suspected drug for an adverse event is defined as one given until just prior to the expression of an adverse event. Because a patient sometimes takes several medicines including the same components in a short period, there is a possibility that several physicians or companies report an adverse event independently. We then tried to eliminate the overlap cases based on patient registration information such as age, body weight, height, the duration of administration, the date of adverse event occurrence, and the kinds of adverse events.

2.2. Inclusion criteria and definition of thromboembolic event

The cases of thromboembolism were all COC users who experienced adverse events reported in this database during this period. The adverse events included VTE and arterial embolism and thrombosis (ATE). We defined both VTE and ATE based on the following ICD-10 codes: I26 (pulmonary embolism), I80 (venous thrombosis of the lower extremities [except I80.0, i.e. superficial thrombophlebitis]), I81 (portal vein thrombosis), I82 (other venous embolism or thrombosis), I63 (cerebral infarction), I67.6 (cerebral vein thrombosis), and I20-I25 (coronary heart diseases), I74 (arterial embolism and thrombosis). We defined it as one thromboembolic event of deep vein thrombosis (DVT) when the thrombosis of the pelvic vein, inferior vena cava or the right atrium was complicated by the venous thrombosis of the lower extremities as a series of venous thromboses. In addition, we defined a case of pulmonary embolism (PE) complicated with DVT as one thromboembolic event for the same reason. Moreover, we counted it as one case when VTE was complicated with another thromboembolic event of ATE, or ATE was complicated with another part of ATE at the same time.

2.3. Calculation of annual estimated number of COC prescribed patients

Data of the annual number of each kind of COC prescription from January 2009 to December 2013 throughout the country were obtained from IMS Health, JPM, a commercial agency that collects the reliable data nationally and internationally on drug use and sales.

The annual estimated number of prescribed patients (person-years) was estimated as follows: when each patient was supposed to take one COC tablet every day for one year, she took 13 sheets for one year. Then, the annual number of prescribed patients was estimated as the number of annually prescribed sheets nationwide divided by 13. On the other hand, in the case of dienogest, when each patient was supposed to take two tablets every day for 365 days, the annual number of prescribed patients was estimated as the number of annually prescribed tablets nationwide divided by 730 (2 times 365).

2.4. Duration of use

The duration of COC use was estimated as the period from the starting date until the end date of use or the date of the onset of the thromboembolic event.

2.5. Details of ethics approval

The study was approved by the Ethics Committee of Hamamatsu University, School of Medicine (approval number E 14-266/2014). It was performed in compliance with the Declaration of Helsinki. Consent was not obtained, but the presented data are anonymized and there is no risk of identification.

2.6. Statistical analysis

The estimated incidence rates of thromboembolism with 95% confidence interval (95% CI) in current users of different COCs were calculated by supposing Poisson distribution. Statistical analysis was done using SPSS version 20.

3. Results

3.1. Reported number of thromboembolic events

A total of 1199 adverse events, which include nausea, vomiting, irregular bleeding, anemia, and so on, associated with COC use were reported in the PMDA database between 1 April 2004 and 31 December 2013. We extracted 581 thromboembolic events from among these adverse events. Of the 581 thromboembolic events, VTE accounted for 394, ATE for 154, and thrombosis of unspecified sites was 33. Three cases of VTE (PE with DVT) were complicated with cerebral infarction and one case of ATE was complicated with another part of ATE. Therefore, overall cases of thromboembolism were 577. In 394 events of VTE, 153 (38.8%) were DVT only, 66 (16.8%) were PE only, 90 (22.8%) were PE with DVT, 45 (11.4%) were cerebral vein thromboses, and 40 (10.2%) were other venous embolisms or thromboses (7 portal veins, 6 retinal veins, 2 jugular veins, 2 subclavian veins, 2 splenic veins, 1 hepatic vein, 1 renal vein and 19 unknown parts). Thus, in VTE, the most common was DVT, PE and their combination (78.4%). It should be specially noted that cerebral vein thrombosis was as much as 11.4%. In 154 arterial thrombotic events, 117 (76.0%) were cerebral infarctions, 17 (11.0%) were coronary heart diseases, and 20 (13.0%) were other arterial embolisms and thromboses (7 mesenteric arteries, 4 renal arteries, 4 central retinal arteries, 2 peripheral arteries, 1 carotid artery, 1 spinal artery and 1 unspecified arterial thrombosis). Thus, in ATE, the most common was cerebral infarction (76.0%) which was approximately 6.9-fold higher than coronary heart diseases. Events with thrombosis of unspecified sites were 33. No case of thromboembolic events was reported in users of norethisterone, levonorgestrel and levonorgestrel releasing intrauterine device, though 9 cases of thromboembolic events (5 cases of VTE and 4 cases of ATE) were reported in the users of dienogest (Table 1).

3.2. Estimated incidence rates of thromboembolic events

The estimated incidence rates of thromboembolic events in current users of COCs with different types of progestin and progestin only were calculated by using the annual estimated number of prescribed patients from January 2009 to December 2013 (Table 2). The annual