

Oral Contraceptives and VTE across the Sentinel data network –An IMEDS Evaluation pilot assessment

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Abstract

Introduction

The risk of venous thromboembolism (VTE) with oral contraceptives (OCs) is well documented. Recently, questions have been raised about an increased risk of VTE of 4th generation OCs (containing drospirenone) compared to 2nd generation (containing levonorgestrel).

Objective

This IMEDS Evaluation pilot used a distributed network of FDA Sentinel data partners to examine the rate of VTE in new users of 2nd and 4th generation OCs using the standardised data analytics capabilities of the IMEDS Evaluation pilot

Methods

The analytic cohort consisted of women aged 15-44 who were new OC users (2nd or 4th generation). Patients with VTE risk factors were excluded.

Dispensings were defined by National Drug Code in outpatient pharmacy claims. VTE was defined by ICD9 codes 415.1 or 453.xx, occurring in the inpatient or emergency department setting.

Nine Sentinel data partners participated. Publicly available Sentinel modular programs were used. Feasibility data were reviewed to inform use of the more complex modular analyses. Consistent with typical FDA use of these programs, the analysis did not include a direct comparison or statistical testing; rather, the results include rates of VTE stratified by age, sex, and year.

Results

Between January 1, 2008 and April 30, 2015 there were 350572 new users of 4th generation OCs and 317363 new users of 2nd generation OCs. There were 158 new VTE events for 4th generation OCs, and 121 for 2nd generation OCs. The rate of VTE events per 10000 person-years was 8.56 for 4th generation and 6.58 for 2nd generation OCs (interquartile range from 5.86 to 9.23 for 4th generation OCs, and from 0 to 7.07 for 2nd generation OCs across the data partners).

Conclusions

In line with the literature, rates of VTE were greater for 4th generation than 2nd generation OCs. Limited variation was seen across data partners, although some partners had few events. Limitations include lack of confounding control, no direct comparisons or matching, and VTE defined only by diagnosis code. The pilot shows the value of the large distributed data network in exploring safety issues by a pharmaceutical sponsor.

Background

The risk of venous thromboembolism (VTE) with oral contraceptives (OCs) is well documented and extensively studied, see for example (1). While several studies evaluating the incidence of VTE and related adverse events among patients exposed to oral contraceptives that have also used large, electronic databases(1,2), none of these have taken advantage of a large distributed network of observational databases such as those available in the FDA's Sentinel network(3).

Objectives

The aim of this pilot assessment was to examine new users of second generation and fourth generation oral contraceptives (OCs) with respect to the occurrence of venous thromboembolism (VTE) in the Sentinel data network using the standardised data analytics capabilities of the IMEDS-Evaluation pilot (figure 2)(4).

Methods

The cohort for this analysis consisted of women aged 15-44 who are new users of 2nd generation OCs (levonorgestrel-containing products) and 4th generation (drospirenone-containing) OCs. Patients with evidence of VTE risk factors were excluded: cancer, renal failure, chronic cardiovascular diseases, inflammatory or autoimmune conditions, epilepsy, anticoagulant use, NuvaRing use major surgery, trauma, or pregnancy.

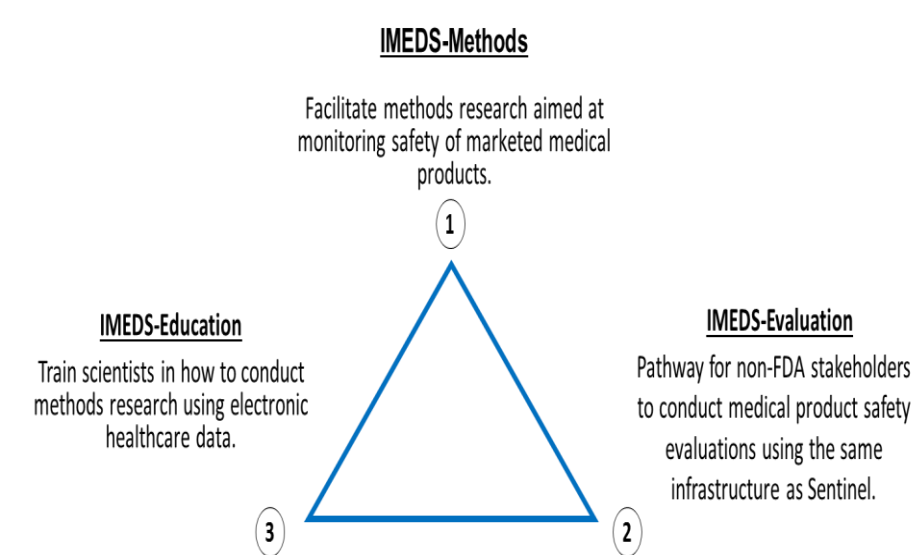
Dispensings were defined by National Drug Code in outpatient pharmacy claims records. VTE was defined as ICD9 codes 415.1 or 453.xx, occurring in the inpatient or emergency department setting.

Age stratification was conducted into three age groups (15-29, 30-39, 40-44).

Analyses were conducted across nine Sentinel data partners participating in the pilot. Publicly available Sentinel modular programs and summary table query tools (Modular Program QRP version 2.09, Summary Table version 5.0) were used. Summary table data were reviewed to inform use of the more complex modular analyses. Consistent with typical FDA use of these programs, the analysis did not include a direct comparison or statistical testing, rather, the results include rates of VTE stratified by age, sex, and year.

Figure 1. IMEDS Program Overview

A public-private partnership within the Reagan-Udall Foundation designed to build upon the significant progress made on research methodology by FDA's Sentinel Initiative, including its Mini-Sentinel pilot, and the Observational Medical Outcomes Partnership (OMOP).



Results

As shown in table 1, between 1st January 2008 and April 30th 2015 across the 9 data partners there were 350572 new users of 4th generation OCs and 317363 new users of 2nd generation OCs, leading to 1899922 and 1460766 dispensings respectively. There were a total of 158 new treatment episodes with VTE events for 4th generation OCs, and 121 for 2nd generation OCs. The rates of new episodes with VTE events per 10000 person-years were 8.56 for 4th generation and 6.58 for 2nd generation (details of variation across the data partners see figure 1 and table 2). Rates were slightly higher for both when exclusions were limited to 90 days (9.36 and 7.94 respectively).

Table 1. Oral Contraceptives (OCs) and VTE across participating data partners of the MSDD between January 1, 2008 and April 30, 2015, by Oral Contraceptive Exposure and Exclusion Criteria

| | 4 th Generation OCs | 2 nd Generation OCs |
|---|--------------------------------|--------------------------------|
| New Users | 350,572 | 317,363 |
| Dispensings | 1,899,922 | 1,460,766 |
| Days Supplied | 62,180,487 | 63,102,751 |
| Years at Risk | 184,485.20 | 183,852.50 |
| New Episodes w/ Events | 158 | 121 |
| Eligible Members | 26,697,378 | 26,697,378 |
| Member- Years | 417,687,515 | 418,529,339 |
| New Users /Eligible Members (Per 1000 members) | 13.13 | 11.89 |
| Days Supplied/ New User | 177.37 | 198.83 |
| Dispensings/ New User | 5.42 | 4.6 |
| Days Supplied/ Dispensing | 32.73 | 43.2 |
| New Episodes w/ Events /Years at Risk (Per 10000 Years) | 8.56 | 6.58 |

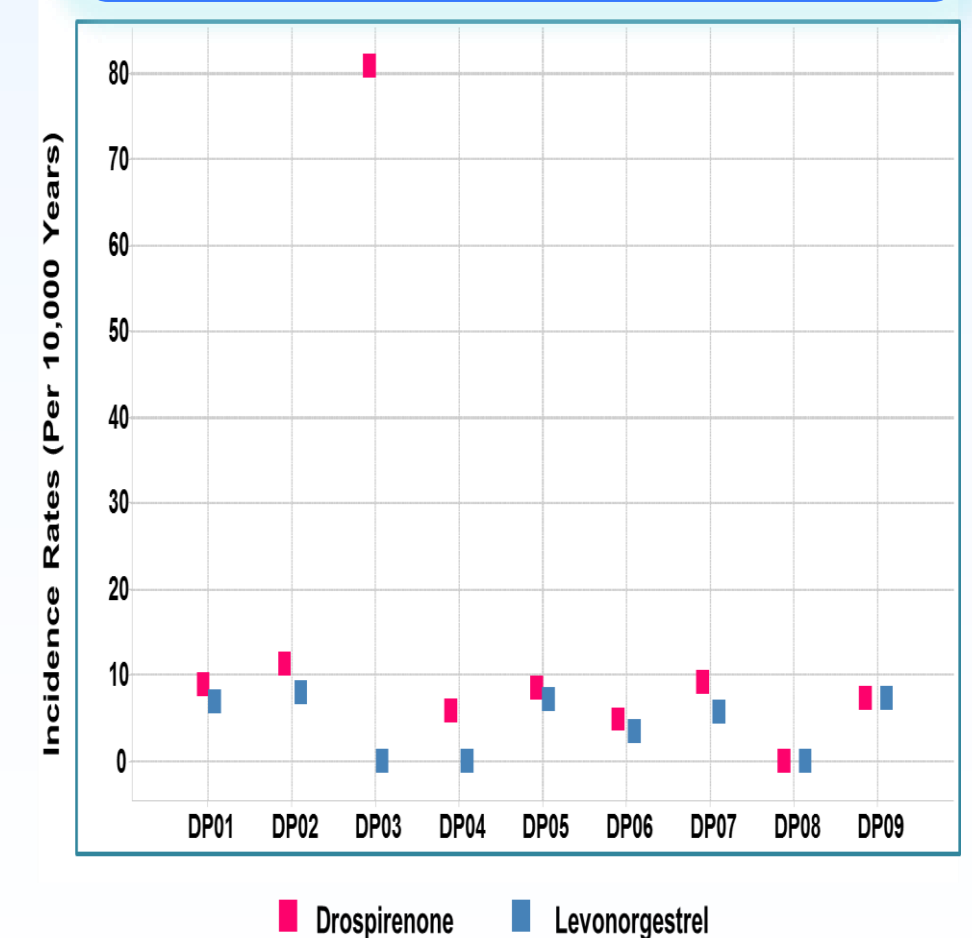
Results (Cont.)

Table 2. Summary Statistics Across participating Data Partners of MSDD

| | 4 th Generation OCs | | | 2 nd Generation OCs | | |
|-----------------------------|--------------------------------|------------------|--------------------------|--------------------------------|------------------|--------------------------|
| | New Users | Eligible Members | Days Supplied/Dispensing | New Users | Eligible Members | Days Supplied/Dispensing |
| Minimum | 159.00 | 23817.00 | 27.80 | 314.00 | 23817.00 | 33.30 |
| 25 th Percentile | 4040.00 | 428348.00 | 30.20 | 12867.00 | 428348.00 | 38.00 |
| Mean | 38952.40 | 2966375.30 | 39.00 | 35262.60 | 2966375.30 | 47.50 |
| Median | 8514.00 | 653439.00 | 33.40 | 13362.00 | 653439.00 | 45.30 |
| 75 th Percentile | 21188.00 | 1840769.00 | 46.20 | 15662.00 | 1840769.00 | 59.40 |
| Maximum | 167329.00 | 11841843.00 | 61.00 | 127269.00 | 11841843.00 | 67.50 |

Note: Minimum and maximum statistics for the three metrics are across all 9 data partners, and do not necessarily refer to the same data partner throughout a row

Figure 2. VTE Incidence Rates Among 4th and 2nd generation OC Users by DP



Conclusion

This rapid analysis approach shows rates of VTE were greater for 4th generation than 2nd generation OCs in line with the literature. Limited variation was seen across data partners, although some partners had few events. Limitations include lack of confounding control, no direct comparisons or matching, and VTE defined solely by diagnosis code. The pilot shows the potential of the large distributed data network in exploring safety issues and the value in leveraging Sentinel data and analytic tools.

Acknowledgement

We thank the participating data partners Group Health, Harvard Pilgrim, Healthcore, HealthPartners, Humana, Marshfield, Meyers Primary Care, Optum and Vanderbilt for their contributions, expertise and data provision for this pilot, but wish to emphasise that the conclusions are not necessarily those of the data partners themselves.

References

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