Lab: Nested Case-Control Study Design

Safety of the Transdermal Contraceptive Patch

Background

Combination oral contraceptives (COCs) have been available since the 1960s. Currently, more than 100 million women world wide use this method of contraception. The evidence linking COCs to adverse arterial and venous thrombotic events was recognized soon after they entered the market in the early 1960s. To minimize these risks, the composition of COCs has changed over the years: the hormonal content has decreased, most notably with respect to the estrogen component. In addition, different progestin components are used in combination hormonal contraceptive produces. Finally, women using COCs are more carefully screened for risk factors that contribute to thrombotic events, *and* are more carefully monitored for blood clots once they begin treatment.

In November of 2001, the norelgestromin/ethinyl estradiol transdermal contraceptive patch system (Ortho Evra, Ortho-McNeil Pharmaceuticals Inc, Raritan, NY) was approved for marketing by the U.S. Food and Drug Administration. The product was launched in April of 2002. At the time of its initial marketing, it was not known whether use of this hormonal contraception system was associated with the same, lesser, or greater risk of myocardial infarction (MI), ischemic stroke (IS), or venous thromboembolism (VTE) compared to currently marketed COCs.

Read

Cole, J. A., Norman, H., Doherty, M., & Walker, A. M. (2007). Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. Obstet Gynecol, 109(2 Pt 1), 339-346. Link

Questions

1. This study is both a cohort study and as a nested case-control study.

- **(a)** The cohort study used computerized linked medical records to identify COC and transdermal patch use. What are the advantages and disadvantages of using computerized linked medical records to do an epidemiologic study? (Make sure you brainstorm various pros and cons on the discussion board before trying to answer this question.)
- **(b)** What are the advantages of doing the cohort study before doing the case-control study? What are the advantages of doing the case-control study nested in a cohort?

2. A total of 98,790 women using the transdermal patch and 256,981 women using norgestimate-containing (NGM) COCs were studied. What is the reason for restricting the study to women using these hormonal contraceptive products as opposed to, say, comparing rates of adverse events in women using the patch and using no hormonal contraception, i.e., what is the reasoning behind have a "nonexposed" group that is exposed to COCs?

3. Rates within the groups.

(a) Table 1 (p. 343) lists incidence rates and age-adjusted incidence rate ratios for disease outcomes investigated by this study. The first paragraph on p. 343 states the number of person-years in each cohort. *Show* how the rates of VTE were calculated in each of the sub-cohorts.

(b) *Show* how the rate ratio (*RR*) for VTE was calculated.

(c) What was the average follow-up time per Ortho Evra exposed subject? What was the average follow-up time per COC-exposed subject? [Average time per user = (person-time is subcohort) ÷ (no. of people in the sub-cohort).]

4. For acute MI, the rate ratio associated with patch exposure was 1.8 (95% CI 0.6 − 6.8). The author states "Although the incidence rate ratio for AMI associated with the transdermal contraceptive system use compared with norgestimate-containing OC use was elevated … the estimate is consistent with a wide range of both protective and causative levels of association" (p. 345, column 1, ¶3). Interpret this statement.[1]

5. The article states "To investigate the possibility of residual confounding, we conducted a case-control analysis nested within the study cohort" (p. 341, column 2, para 2).

(a) How many controls were selected per case?

(b) How were controls selected?

(c) What variables were evaluated as potential confounders? How were these potential confounders evaluated?

6. Ignore the matching done in the study. Take the data in Table 2 for the VTE outcome and display it in a 2-by-2 table. Calculate the OR associated with patch use.

7. The investigators performed various statistical adjustments, yet they state "none of the [adjustments based on the] covariates derived from the medical and pharmacy claims data resulted in a greater than 10% change in the exposure effect" (p. 343, c. 1, para. 4). Therefore, they reported the unadjusted rate ratio from the cohort analysis in their abstract (i.e., "incidence rate ratio 2.2"). Justify use of the crude statistical analysis.

8. Cohort studies are observational studies; clinical trials are experimental. Do you think a randomized intervention trial be ethically and practically conducted to test the hypothesis that Ortho Evra increased the risk of VTE, MI, and IS? Explain your reasoning.

9. Rarely, if ever, can a single study provide conclusive evidence strong enough for action. However, when combined with other sources of information, and when combined with a sound biological and other types of reasoning, a single study can provide crucial results. Do you think the current study provides sufficient evidence to pull Ortho Evra off the market?

[1] This question requires knowledge about statistical estimation and confidence intervals.