Diane-35 (cyproterone acetate): safety concerns

Reason for posting: Diane-35, an oral contraceptive with anti-androgen properties, has been heavily marketed to young women[1] and has seen its Canadian sales jump by 45% between 2000 and 2001 alone.[2] However, many physicians may be unaware of concerns about the drug's safety profile[3] and the fact that it is not approved for use solely as an oral contraceptive.[4] The UK Committee on the Safety of Medicines recently issued a warning on the drug's risk of venous thromboembolism,[5] which was repeated verbatim by Health Canada in late December 2002.

The drug: Diane-35, which contains ethinylestradiol (35 μg) and cyproterone acetate (2 mg), provides effective birth control but is not indicated as such.[4] Cyproterone acetate has anti-androgen effects resulting in part from its blockade of androgen receptors, and Diane-35 is approved only as therapy for androgen-sensitive skin conditions, including hirsutism and severe acne unresponsive to oral antibiotic therapy.[4] Treatment with Diane-35 should be discontinued 3–4 menstrual cycles after a woman's skin condition has resolved.[4,5] Warnings to minimize a woman's exposure to the drug result in part from the association with venous thromboembolic disease.

Since cases of venous thromboembolism were first reported in the 1960s in women taking combination oral contraceptives, preparations have been developed with lower doses of estrogen (typically 30–40 μg of ethinylestradiol, as compared with > 50 μg originally) and different progestagen components.[6] The low-estrogen preparations are associated with lower rates of venous thrombosis, but they still carry risks of venous thromboembolism apparently related to their progestagen component. So-called "third-generation progestagens" (e.g., desogestrel) are associated with about double the risk of venous thrombosis of either the first- (norethindrone) or second-generation (levonorgestrel) progestagens,[7–9] although the association is controversial.[10] A Danish study showed no difference in risk of venous thromboembolism between levonorgestrel and cyproterone users;[11] however, a large case–control study involving nearly 100 000 women in the United Kingdom showed that women taking oral contraceptives containing cyproterone had quadruple the risk of venous thromboembolism as those taking levonorgestrel combinations.[3] Regarding fatal pulmonary embolism, a case–control study in New Zealand found that, compared with women taking no oral contraceptives, the adjusted odds ratio was 17.6 (95% confidence interval [CI] 2.7–113) among women taking cyproterone acetate, 5.1 (95% CI 1.2–21.4) among levonorgestrel users and 14.9 (95% CI 3.5–64.3) among desogestrel or gestodene users.[12]

Oral contraceptives users at increased risk of venous thromboembolism include those who are obese[7] and those who harbour prothrombotic mutations (factor V Leiden carriers have 35 times the risk as women without this mutation).[6] The degree to which other risk factors for venous thrombosis (injury, immobility, postoperative status or postpartum status) affect the risk associated with oral contraceptives is unknown. Table 1 lists various estimates of the risks of nonfatal venous thromboembolism. Unlike arterial thrombosis,[16] the risk of venous thrombosis among contraceptive users

Table 1: Estimates of risk of nonfatal venous thromboembolism

Group*	Estimated 1-year risk of nonfatal venous thromboembolism
Baseline (women not using OC)[6,13]	1 in 20 000 to 1 in 9090
Women using OC containing levonorgestrel[13,14]	1 in 6666 to 1 in 6211
Women using OC containing desogestrel†[13]	1 in 3333
Women using any low-dose OC[6,13]	1 in 3333
Women not using OC but who have factor V Leiden mutation[6]	1 in 1754
Women using OC containing cyproterone‡	1 in 1666
Pregnant women and those post partum[13,15]	1 in 1666 to 1 in 1500
Women using OC and who have factor V Leiden mutation[6]	1 in 350

Note OC = oral contraceptive.
*References listed are those used to calculate risk estimates.
†Based on relative risk of twice that among women using OC containing levonorgestrel.[7–9]
‡Based on relative risk of 4 times that among women using OC containing levonorgestrel.[3]

appears unaffected by the woman's age, history of hypertension or smoking status.[7] Venous thrombosis develops in women taking combination oral contraceptives usually within the first year after starting the drug.[17]

What to do: Diane-35 should be reserved for temporary use in women with serious acne and should not be used solely as an oral contraceptive. All women who use combination oral contraceptives are at risk of venous thromboembolism and should be informed of this rare but potentially serious adverse effect, particularly if they are taking Diane-35. Clearly caution, and not panic, is warranted. For example, switching 2220 women from Diane-35 to an oral levonorgestrel contraceptive for 1 year would prevent 1 case of nonfatal venous thromboembolism. Physicians should consider not prescribing Diane-35 for women at risk of venous thromboembolism (especially those who carry prothrombotic mutations), while recognizing that such an approach to preventing venous thrombosis is limited by the fact that most venous thrombotic events are truly idiopathic (i.e. the women have no clinically recognizable risk factors).[6]

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