causing hypercalcemia.[2,3] Other laboratory abnormalities include a leukemoid reaction, possibly related to the production of granulocyte colony-stimulating factor by the tumour cells. Diagnosis can be confirmed by liver biopsy, but a "sampling error" may occur, as happened in our case. There are no current therapies of benefit, and treatment remains palliative.

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HEALTH AND DRUG ALERTS

The Evra (ethinyl estradiol/norelgestromin) contraceptive patch: estrogen exposure concerns

DOI:10.1503/cmaj.051623

Reason for posting: The Evra contraceptive transdermal patch is appreciated by many women for its once-a-week convenience. Recently, however, the US Food and Drug Administration (FDA) warned that women using the US version of the patch, which contains 0.75 mg of ethinyl estradiol (the patch sold in Canada contains 0.60 mg), are exposed to 60% more estrogen in a monthly cycle than women taking a typical 35-µg oral contraceptive (www.fda.gov/cder/drug/infopage/orthoevra [accessed 2005 Dec 7]). The potential for excess estrogen exposure raises concerns about the risks of adverse effects, which include nausea, breast tenderness and venous thromboembolism.

Table 1: Mean systemic exposure to ethinyl estradiol with a typical 35-µg oral contraceptive v. the Evra 0.75-mg transdermal contraceptive patch

Parameter	Oral (cycle 2, day 21)	Patch (cycle 2, week 3)
C_{ss}, pg/mL	49.3	80
$AUC_{0\text{-}168}$, pg·h/mL	8281	12 971

Note: C_{ss} = steady-state concentration, $AUC_{0\text{-}168}$ = area under the curve.
Source: US Food and Drug Administration. *Proposed text of the labeling for Ortho Evra (norelgestromin/ethinyl estradiol transdermal system)* [product monograph]. Available: www.fda.gov/cder/drug/infopage/orthoevra (accessed 2005 Dec 7).

The drug: The Evra patch is applied a week at a time for 3 weeks, followed by a fourth week with no patch. This delivery system is intended to avoid gastrointestinal and hepatic first-pass metabolism of the contraceptive hormones. Patch users may experience more dysmenorrhea (13.3% v. 9.6%) and breast discomfort (18.7% v. 5.8%) than users of oral contraceptives. The patch may also be less effective for women weighing more than 90 kg.[1]

The patch was designed to administer 20 µg of ethinyl estradiol and 150 µg of norelgestromin (the primary active metabolite of norgestimate, the progestin component of the oral contraceptives Cyclen and Tricyclen) daily. When a patch is first applied, the rate of drug absorption plateaus by 48 hours; a steady state is reached within 2 weeks. Absorption rates through the buttock, upper outer arm, abdomen and upper torso are considered equivalent, and absorption appears unaffected by exercise or exposure to hot or cold water.

The FDA alert focused on recent unpublished studies comparing the mean pharmacokinetic profiles of the 0.75-mg transdermal patch with a "typical" oral contraceptive containing 250 µg of norgestimate and 35 µg of ethinyl estradiol. The systemic exposure to ethinyl estradiol is about 60% more for users of patches than of oral contraceptives, as measured by the area under the curve ($AUC_{0\text{–}168}$ 57%) and steady-state concentration (C_{ss} 62%; Table 1). The peak concentration of ethinyl estradiol is about 35% higher with the oral contraceptive than with the 0.75-mg patch.

Table 2: Mean systemic exposure to ethinyl estradiol with contraceptive patch use for up to 3 consecutive cycles*

Parameter	Cycle 1, week 1	Cycle 3, week 1	Cycle 3, week 2	Cycle 3, week 3
C_{ss}, pg/mL	46.4	47.6	59.0	49.6
$AUC_{0\text{-}168}$, pg·h/mL	6796	7160	10 054	8840

Note: C_{ss} = steady-state concentration, $AUC_{0\text{-}168}$ = area under the curve.
*This table is adapted from the product monograph for the Evra 0.60-mg norelgestromin–ethinyl estradiol hormonal contraceptive patch.[2]

The pharmacokinetics of the 0.60-mg patch are less clear (Health Canada promises a more thorough review of the matter), but in the Canadian product monograph[2] the week-to-week variability in the mean parameters presented appears to be considerable. For the third week of cycle 3, the exposure values (Table 2) look very similar to those for cycle 2 with the 35-µg oral contraceptive (Table 1).

What to do: Users of the 0.75-mg patch may be exposed to higher doses of estrogen than users of most oral contra-

Early release
All Health and Drug Alerts are posted online ahead of print and are available at www.cmaj.ca. This article was posted on Dec. 19, 2005.

ceptives. Theoretically, this increases the risk of venous thromboembolism and other estrogen-related adverse effects, although the degree of risk is unclear. Caution should be exercised in making direct comparisons of pharmacokinetic parameters of these different products. Studies involving larger numbers of women, specifically those using the 0.60-mg patch, may produce pharmacokinetic data that are more reliable.

Alternative contraceptives that feature minimal systemic exposure to estrogen include barrier methods and spermicides, the intravaginal ring (e.g., NuvaRing),[3] intrauterine devices, injectable progestogens and the progesterone-only "minipill" (e.g., Micronor).

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