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Statin Roundup: Label Changes and Safety Issues

The past year has seen numerous changes in labeling and concerns for safety issues with the cholesterol-lowering statin drugs, particularly lovastatin (*Mevacor*) and simvastatin (*Zocor*). A review of recent issues:

1. Some statin users report cognitive impairment.
2. Increases in blood glucose and Type 2 diabetes are associated with statin use.
3. New drug interactions leading to risk of myopathy and myalgia
4. Contraindicated drugs: itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, cyclosporine, gemfibrozil
5. Lovastatin dosing changes: no more than 40 mg daily of lovastatin when given with amiodarone and no more than 20 mg daily with verapamil, diltiazem.
6. Danazol contraindicated with simvastatin and lovastatin doses more than 20 mg daily.
7. Simvastatin dosing changes: no more than 20 mg daily of simvastatin when given with amiodarone, amlodipine or ranolazine and no more than 10 mg daily when given with verapamil or diltiazem.
8. Use caution when combining with fibrates or > 1 g/day of niacin.
9. Limit use of simvastatin 80 mg daily to those patients currently stable on that dose for more than one year.
10. Limit grapefruit juice to < 1 quart daily.

The good news is a lifting of liver enzyme monitoring requirements. The FDA notes that routine monitoring has not shown to be a good predictor of liver damage with statins. Baseline LFTs are recommended then monitoring according to clinical concerns.

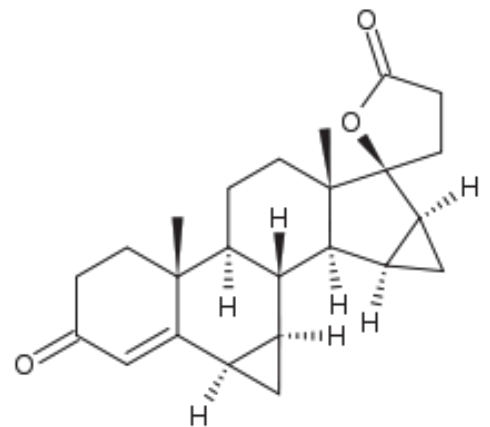
References

Increased risk of blood clots forces changes in oral contraceptive labeling

The Food and Drug Administration (FDA) is now requiring updated labeling regarding clot risk for oral contraceptives containing the progesterone, drospirenone. Drospirenone is a synthetic progestin which is chemically similar to spironolactone. Birth control brands *Yasmin*, *Yaz*, *Beyaz*, *Safyral* and their various generics contain drospirenone and are indicated for pregnancy prevention, acne treatment and treatment of premenstrual dysphoric disorder (PMDD). These hormonal contraceptives are also used off-label to treat polycystic ovarian syndrome (PCOS).

FDA began its review of these products in 2011 after studies showed an increased risk of blood clots in wom-

en using oral contraceptives with drospirenone over oral contraceptives with other forms of progesterone. The label change comes on the heels of an FDA-sponsored study which showed a three-fold increase in thromboembolism in women on these birth control pills.



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This observational study was conducted in four sites around the U.S. and reviewed data for over 835,000 women enrolled in three different health plans. Women ranged in age from 10 to 55 and had record of at least one contraceptive prescription over a 6 ½-year period from 2000 to 2007. Patients with diagnosis of serious illness such as sickle cell anemia, HIV, cancer and organ transplant were excluded.

Drospirenone-containing contraceptives were compared to norelgestromin contraceptive patches, etonogestrol/ethinyl-estradiol contraceptive ring as well as four oral hormonal contraceptives with low dose (up to 35 mcg) ethinyl estradiol. Outcomes included patient record of diagnostic codes for hospitalization for acute myocardial infarction, ischemic stroke, and thromboembolic disease such as pulmonary embolism (PE) and deep venous thrombolism (DVT). Overall and cardiovascular deaths were also measured.

Average length of contraceptive use was 155 days with a total of nearly 900,000 person-years. Incidence rates were calculated according to how long the patient had used contraceptives, 0 to 3 months, 4 to 6 months, 7 to 12 months or more than 12 months. The incidence rate ratio for venous thromboembolism (VTE) for drospirenone contraceptives was nearly double other contraceptives after 3 months of use (IRR = 1.9, 95% CI 1.26 – 2.95) and nearly triple at 7 to 12 months of use (IRR = 2.9, 95% CI 1.59 – 5.28). Risk of VTE was also increased for the patch (IRR = 1.55, 95% CI 1.17 – 2.07) and the ring (IRR = 1.74, 95% CI 1.42 – 2.14), particularly after 12 months of use when the VTE risk nearly triples for the patch². When analyzed by age, patients from 10 – 34 were found to have an increased VTE risk over those 35 – 55. Few cardiovascular outcomes were identified in this study, thus no specific association with contraceptive use was noted.

The risk of blood clot with hormonal contraceptives is well-established and as high as five times the risk of

clot in women not using hormones. A 2009 study published in BMJ suggested drospirenone itself could put patients at a six-fold increase of thromboembolism. Ultimately, this new FDA study confirms an increased risk of venous blood clot with drospirenone contraceptives as well as the contraceptive patch, particularly in users under age 35.

The FDA requires all contraceptives include label warnings for patients who smoke and are over 35. For those containing drospirenone, there are now stronger concerns for vascular incidents. In addition to the warning for smokers over 35, recommendations for patients who are having major surgery are to stop these birth control pills four weeks prior to the procedure and for two weeks after surgery. Women who are not breastfeeding and wish to use oral contraceptives after birth should wait until four weeks post-partum before starting a drospirenone contraceptive.

Though the risk of blood clot is increased in patients taking hormonal contraceptives over those who do not, this risk is still overall less than the hypercoagulability that occurs during pregnancy or immediately post-partum. To put things into perspective, the FDA estimates the risk of blood clot in women not using hormonal contraceptives to be up to 5 in 10,000 women per year¹. This risk increases up to 9 in 10,000 women using oral contraceptives, while during pregnancy blood clot can occur in as many as 20 women in 10,000. The post-partum period carries the greatest risk of thromboembolism with as many as 65 women in 10,000 affected.

Providers should counsel patients on risks of contraceptives that contain drospirenone and advise them of signs of blood clots. Any adverse events that occur can also be reported to the MedWatch program to assist in post-marketing surveillance.

References

Drug Info Question: Levetiracetam for Post-traumatic Seizures

Drug Info Question:

Should levetiracetam be used first line for posttraumatic seizure prophylaxis?

Yoadys Fernandez, PharmD Candidate 2012

Response

Seizures are a recognized complication in patients with acute traumatic brain injury. Within the first week or two after injury, post traumatic seizure incidence is about 6-10 % but may be as high as 30 % in severe patients.

Seizure prophylaxis during the first seven days post-trauma has been shown to reduce the incidence of early seizures; however it does not necessarily prevent the

later development of epilepsy. Phenytoin (Dilantin) has been the agent of choice for many years, but due to its potential for drug interaction, numerous side effects and need for close serum drug monitoring, many clinicians substitute it with levetiracetam (*Keppra*).

A retrospective cohort study -conducted by Carter and colleagues evaluated the use of phenytoin and levetiracetam in patients with traumatic brain injury who received early post-traumatic seizure prophylaxis between January 2007 and August 2008.

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A total of 101 patients met the inclusion criteria: 36 patients were in the levetiracetam group and 65 patients in the phenytoin group. The study concluded that the incidence of seizure and adverse effects were not significantly different between the groups (seizures-10.9% in the phenytoin group versus 16.2% in the levetiracetam; adverse effects-6.3% in the phenytoin group versus 8.1% in the levetiracetam group).

A cost minimization analysis comparing both agents indicated equal effectiveness between them in the prevention of seizures; however, the mean institutional cost per patient was approximately \$151 for phenytoin versus \$ 411 for levetiracetam. They also analyzed the mean charge per patient and it was approximately \$ 2,300 vs. \$3,500 in favor of phenytoin.

Levetiracetam became the dominant strategy only in the presence of marked mental status deterioration associated with phenytoin therapy.

A cost utility analysis conducted by Cotton and colleagues also favored phenytoin for posttraumatic seizure prophylaxis unless levetiracetam prevented 100 % of seizures and cost less than \$ 400 for a 7 day course. The cost/effectiveness ratio were \$1.58/QALY for phenytoin versus \$ 20.72/QALY for levetiracetam. This led to the conclusion that phenytoin was more cost effective than levetiracetam at all reasonable prices.

Further analysis would be required to reassess this recommendation once levetiracetam becomes more affordable and more robust clinical trials are available demonstrating a significant clinical advantage over phenytoin for the prevention of seizures in patients with posttraumatic brain injury.

References

April Drug Shortages

Check with your hospital for specific quantities

- Acetylcysteine Inj
- Diazepam Inj
- Etomidate Inj
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