Hormonal Contraceptives (HCs) in Drug Development:

Prohibited Drugs in Phase 3 Trials and Drug Interaction Considerations for "other" HCs

Myong-Jin (MJ) Kim, Pharm.D.
Team Leader
Office of Clinical Pharmacology
OTS/CDER/FDA

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Disclaimer

- I have no conflicts of interest

- The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the U.S. Food and Drug Administration (FDA)

Outline

- Background
- Phase 3 trials of hormonal contraceptives (HCs) and prohibited concomitant drugs
- Drug interactions with non-oral HCs
  - Injectables, transdermal system, vaginal ring, intrauterine system, and implants
  - Types of drug interaction studies conducted in drug development
  - What is included in their product labels
- Summary

Background

- The exclusion criteria of Phase 3 trials of HCs often include:
  - Any concomitant medication known or suspected to affect the systemic concentrations of HCs
  - Use of any medication that might interfere with the efficacy or safety of HCs

- HC product labels have similar standard language on drug interaction risks regardless of their administration routes
  - Oral, injectable, transdermal system, vaginal ring, intrauterine system, implants

Phase 3 Trials of HCs and Prohibited Concomitant Drugs

Study Entry Criteria and Phase 3 Trials

- Large trials have relatively broad entry criteria and the study populations may be diverse with regard to important covariates such as concomitant or prior therapy, disease stage, age, gender or race

- Analysis of the results of such trials for consistency across key patient subsets addresses concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria

Prohibited Concomitant Drugs in Phase 3 Trials of HCs

Use of additional steroid hormones
Anticoagulants (e.g., heparin, coumarin)
Antiepileptics, (hydantoin derivates, e.g., phenytoin or carboxamid derivatives; e.g., carbamazepine, oxcarbamazepine; other antiepileptics , e.g., felbamate, topiramate)
Hypnotics and sedatives (barbiturate derivatives, e.g., primidone)
Tuberculostatics (e.g., rifampicin)
Oral antimycotics (e.g., griseofulvin, ketoconazole, itraconazole, fluoconazole)
Virostatic agents (e.g., ritonavir)
Products containing St. John's wort
Continuous systemic use of antibiotics

Other Examples – Oral Contraceptives

St. John's wort
Undergoing treatment with anticoagulant(heparin or warfarin)

Barbiturates, antiepileptics, rifampin, griseofulvin or other hepatic enzyme-inducing drug
Etretinate, isotretinoin, tretinoin

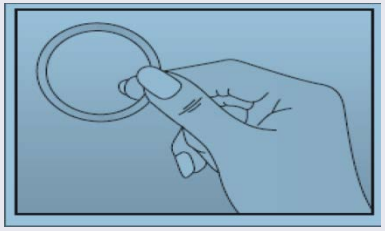
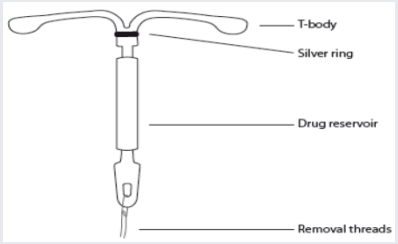
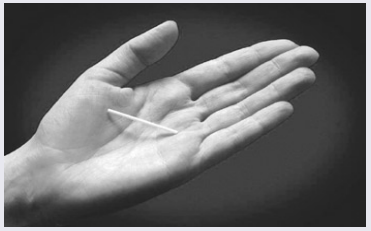
Chronic use of any medication that might interfere with the efficacy of OCs

Rifampin, barbiturates, phenylbutazone, phenytoin sodium, griseofulvin, ampicillin, tetracyclines

Antidepressants/anxiolytic drugs
Any hepatic enzyme-inducing drugs, including certain anticonvulsant medications (e.g. barbiturates including phenobarbital and primidone, phenytoin, carbamazepine, oxcarbazepine, felbamate, topiramate), rifampin, rifabutin, phenybutazone, dexamethasone, St. John's wort, modaflnil, or griseofulvin
Use of more than 14 days of anti-infectives that alter the intestinal flora (e.g., ampicillin, tetracycline)
Drugs requiring the simultaneous use of contraceptive in their labeling (e.g., isotretinoin)

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022573Orig1s000MedR.pdf, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/021241_S000_ORTHO-TRI-CYCLENE_MEDR.pdf, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021840s000_MedR.pdf, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021864s000_MedR_P2.pdf

Examples of Other HCs

Vaginal Ring	Intrauterine System	Implants
		
Barbiturates, primidone, carbamazepine, topiramate, rifampin, griseofulvin	Any concomitant medication known or suspected to have potential of altering serum concentrations of LNG (e.g., primidone, barbiturates, phenytoin, carbamazepine, rifampin, oxcarbamazepine and griseofulvin)	Strong CYP3A4 inducers • One subject with a 70% decrease in serum concentration of etonogestrel after starting rifampin (protocol violation) Use of antiepileptics, rifampin, rifabutin, troglitazone, griseofulvin, and sex steroids

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-187_NuvaRing_medr_P1.pdf http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203159Orig1s000MedR.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021529s000_MedR_P1.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021529s000_MedR_P2.pdf

Drug Interactions with non-oral HCs:

Injectable, transdermal system, vaginal ring, intrauterine system and implants

Standard Labeling Language on HC Drug Interactions

Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Products

- If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:
  - Barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's wort, topiramate

- HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of progestin have been noted in some cases of co-administration of HIV protease inhibitors. Significant changes (increase or decrease) in the plasma levels of the progestin have been noted in some cases of co-administration with non-nucleoside reverse transcriptase inhibitors.

- Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

- Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

Medroxyprogesterone Injectable

Every 3 months, intramuscular (IM) injection in the gluteal or deltoid muscle

Standard Language –

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of contraceptive drug products. Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with “Trade Name”

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020246s053lbl.pdf

Norelgestromine/EE Transdermal System

Apply a patch each week for 3 weeks. Week 4 is patch-free

Standard Language –

Drugs or herbal products that induce certain enzymes (for example CYP3A4) may decrease the effectiveness of CHC or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with CHCs

Oral administration of tetracycline for 3 days prior to and 7 days during wear of "Trade Name" did not significantly affect the PK of NGMN or EE

Etonogestrel/ Ethinyl Estradiol (EE) Vaginal Ring

Every 3 weeks followed by a 1-week ring-free interval

Standard Language -

DDI studies with the following:

- single dose (SD) vaginal miconazole nitrate capsule
- multiple doses (MD) of vaginal suppository or vaginal cream
- SD vaginal administration of water-based spermicide gel
- MD of amoxicillin or doxycycline
- use of tampons

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021187s024lbl.pdf

Two Levonorgestrel-Releasing Intrauterine Systems

Intrauterine system for up to 3 years	
Standard Language - Drugs or herbal products that induce certain enzymes, such as CYP3A4, may decrease the serum concentration of progestins.	Contraceptive effect of "Trade Name" is mediated via the direct release of LNG into the uterine cavity and is unlikely to be affected by drug interactions via enzyme induction or inhibition

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203159s002lbledt1.pdf;
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206229s000lbl.pdf

Etonogestrel Implants

Insert one implant subdermally. Must be removed no later than by the end of the 3rd year

Standard Language - Drugs or herbal products that induce certain enzymes, such as CYP3A4, may decrease the effectiveness of progestin HCs or increase breakthrough bleeding

"Trade Name" may become less effective in **overweight women over time**, especially in the presence of other factors that decrease etonogestrel concentrations, such as **concomitant use of hepatic enzyme inducers**

In women on **long-term treatment with hepatic enzyme inducing drugs**, it is recommended to **remove the implant** and to advise a contraceptive method that is unaffected by the interacting drug.

Levonorgestrel Implants – up to 5 years

Not recommended with phenytoin, phenobarbital, carbamazepine or oxcarbazepine

-Although clinical trials excluded women with epilepsy, published studies showed decreased LNG concentrations in women using these antiepileptic drugs along with LNG-containing contraceptives

Women using rifampin have become pregnant during clinical trials. Rifampin decreases serum levels of progestins

Long-term therapy with hepatic enzyme inducers: consider **a different method of contraception**

Short-term therapy with hepatic enzyme inducers: consider **a back-up method of contraception (such as condoms or spermicides)**

Herbal products containing St. John's wort may induce hepatic enzymes and may reduce the effectiveness of contraceptive steroids.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/20544se2-003_jadelle_lbl.pdf

Summary

- Phase 3 trials of HCs often excluded relevant concomitant drugs that might affect the efficacy/safety profiles of the investigational HCs

- HC product labels have standard labeling language on drug interaction regardless of their administration routes
  - Some have conducted DDI studies specific to their routes or formulations
  - A different method of contraception is recommended for implants (short vs. long-term use)
  - One implant mentions of lower efficacy concern in overweight women over time, especially in the presence of hepatic enzyme inducers