The Use of Ella® (ulipristal acetate) and the Continued Controversy Surrounding Emergency Contraception

Stasha Razack, Pharm.D.
PGY1 Community Pharmacy Resident
H-E-B Pharmacy/The University of Texas at Austin College of Pharmacy
Resident Pharmacotherapy Rounds
October 26, 2012

OBJECTIVES

1. Summarize pertinent emergency contraception background information
2. Review the physiology of the menstrual cycle
3. Discuss the current orally available FDA-approved emergency contraceptive agents
4. Understand the current labeling and political controversy surrounding emergency contraception
5. Evaluate the literature on the safety and efficacy of ulipristal
BACKGROUND\textsuperscript{1,2}

- United States - highest rate of unintended pregnancies among developed countries
- 43 million women do not want to get pregnant, only 89% practicing contraception
- Timely use of emergency contraception (EC) can reduce risk of pregnancy by 89-99\% & prevent 1.5 million pregnancies each year

HORMONES AND THE MENSTRUAL CYCLE\textsuperscript{3}

FDA-APPROVED ORAL EMERGENCY CONTRACEPTIVE AGENTS\textsuperscript{1}

- Next Choice\textsuperscript{\textregistered} (Two 0.75 mg levonorgestrel tablets)
- Plan B One-Step\textsuperscript{\textregistered} (One 1.5 mg levonorgestrel tablet)
- Ella\textsuperscript{\textregistered} (One 30 mg ulipristal tablet)
<table>
<thead>
<tr>
<th></th>
<th><strong>Next Choice®</strong></th>
<th><strong>Plan B One-Step®</strong></th>
<th><strong>Ella®</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>0.75mg levonorgestrel</td>
<td>1.5mg levonorgestrel</td>
<td>30mg ulipristal</td>
</tr>
<tr>
<td>Directions</td>
<td>1 tab PO now and another tab 12 hours later OR both tabs PO now</td>
<td>1 tab PO now</td>
<td>1 tab PO now</td>
</tr>
<tr>
<td>Availability</td>
<td>OTC for age ≥17 Rx for age &lt;17</td>
<td>OTC for age ≥17 Rx for age &lt;17</td>
<td>Rx only</td>
</tr>
<tr>
<td>Approved timeframe to take after intercourse</td>
<td>Within 3 days</td>
<td>Within 3 days</td>
<td>Within 5 days</td>
</tr>
</tbody>
</table>

ULIPRISTAL- STRUCTURE AND MECHANISM OF ACTION

- **Selective progesterone receptor modulator (SPRM)** - antagonistic and partial agonistic effects
- Occupies the human progesterone receptor and prevents progesterone from binding
- Postpones follicular rupture when administered prior to ovulation (thus inhibiting or delaying ovulation)
- May alter normal endometrial cells, impairing implantation
MISOPROSTOL- STRUCTURE AND MECHANISM OF ACTION

- Binds to uterine cells to cause strong contractions leading to expulsion of tissue

LEVONORGESTREL- STRUCTURE AND MECHANISM OF ACTION

- Inhibits/delays ovulation, inhibits tubal transport of the egg or sperm, interferes with fertilization, or alters uterine lining

LABELING CONTROVERSY

- FDA definition of pregnancy
  - “fertilized egg implanted in uterine wall”
- FDA definition of abortion
  - “scientific and medical definition of abortion is after implantation [in the wall of the uterus]”
- Time interval between conception and implantation
  - Debate- timing of the start of pregnancy
- Labeling says emergency contraception works by blocking fertilized eggs from implanting in a woman’s uterus
  - Studies have not established this
- Emergency contraception delays ovulation, the release of eggs from the ovaries that occurs before the eggs are fertilized
- Emergency contraception may also thicken cervical mucus to prevent sperm from reaching the egg
POLITICAL CONTROVERSY

• Affordable Care Act
  o The health care law requires certain preventive health services and screenings to be covered in all new health insurance plans without cost sharing:
    ▪ Preventative health care services are included
    ▪ Patients will not be charged a co-payment for the services, and the costs of the services will not be applied to a patients’ deductible.
  o On August 1, 2011, the preventative health care list was expanded to include birth control alongside other women’s’ preventive services, such as an annual well-woman visit.

• Mitt Romney
  ▪ December 2005- Massachusetts governor established a state law for hospitals to provide emergency contraception to all rape victims

CONTRACEPTIVES IN NYC PUBLIC SCHOOLS

• CATCH = Connecting Adolescents to Comprehensive Health
• The New York City Department of Education
  o 13 city high schools
• School nurse supplies emergency contraception and birth control to girls ≥14 without telling parents
  o Parents may opt out of program after receiving school letter informing them of new policy
A LITERATURE REVIEW ON THE SAFETY AND EFFICACY OF ULIPRISTAL


<table>
<thead>
<tr>
<th>Study Purpose</th>
<th>Population</th>
<th>Trial Design</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Compare efficacy and adverse effects of CDB-2914 to levonorgestrel for EC</td>
<td>* N = 1672 women</td>
<td>* Randomized</td>
<td>* 832 received 50mg CDB-2914 and placebo 12h later</td>
</tr>
<tr>
<td></td>
<td>* Intention-to-treat</td>
<td>* Double-blind</td>
<td>* 840 received 0.75mg levonorgestrel and 0.75 levonorgestrel 12h later</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* Non-inferiority trial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>* Multi-center (1 consortium of family planning clinics in Los Angeles and 5 university based research centers)</td>
<td></td>
</tr>
</tbody>
</table>

---

![Flowchart](chart.png)

- **Women randomized N=1,672**
  - CDB-2914 n=832
    - Lost to pregnancy follow-up n=40
    - Efficacy evaluable n=775
    - Pretreatment pregnancy n=4
    - Additional emergency contraception after study treatment n=13
  - Modified intent to treat n=792
  - Efficacy evaluable n=774
  - Pretreatment pregnancy n=1
  - Additional emergency contraception after study treatment n=13

- Levonorgestrel n=840
  - Lost to pregnancy follow-up n=54
  - Modified intent to treat n=766
  - Efficacy evaluable n=774
  - Pretreatment pregnancy n=1
  - Additional emergency contraception after study treatment n=11
Methods

- Participants included healthy women seeking EC within 72h of unprotected intercourse
- Randomization of CDB-2914 or levonorgestrel
- Daily diaries used from time of EC use until next menses to record adverse effects and sexual activity
- Follow-up scheduled 5-7 days after expected onset of next menstrual period
- Post-treatment pregnancy established by positive urine analysis and confirmed by quantitative serum hCG test

Results

Effectiveness of Drug Based on the Interval from Exposure to Treatment

<table>
<thead>
<tr>
<th>Total</th>
<th>0-24 h</th>
<th>More Than 24-48 h</th>
<th>More Than 48-72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CDB</td>
<td>Levo</td>
<td>CDB</td>
</tr>
<tr>
<td>Exposed (n)</td>
<td>775</td>
<td>774</td>
<td>273</td>
</tr>
<tr>
<td>Expected pregnancies (n)*</td>
<td>47</td>
<td>42</td>
<td>19</td>
</tr>
<tr>
<td>Observed pregnancies (n)</td>
<td>7</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Effectiveness (% [95% CI])</td>
<td>85,68-83</td>
<td>69,46-82</td>
<td>100, N/E</td>
</tr>
</tbody>
</table>

*Calculated by using the estimated date of ovulation and the single-day pregnancy probabilities
N/E = not estimable by method use

Adverse Effects and Cycle Length After Treatment

<table>
<thead>
<tr>
<th></th>
<th>CDB-2914 Users (n=775)</th>
<th>Levonorgestrel Users (n=774)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle length (d)*</td>
<td>Before treatment</td>
<td>29.13</td>
<td>29.04</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>31.77</td>
<td>26.94</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>+2.64</td>
<td>-2.10</td>
</tr>
<tr>
<td>Symptoms experienced after treatment (%)</td>
<td>None</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Breast tenderness</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Lower abdominal pain</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Spotting†</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Bleeding†</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* One-way analysis of variance, treatment as factor
† Occurred in more than 25% of follow-up days

Conclusions

- CDB-2914 is at least as effective as levonorgestrel in preventing pregnancies after unprotected intercourse and has a similar side effect profile
- Pregnancy rates were < 2% in both arms of the study
Inclusion Criteria

- Women seeking EC within 120h of unprotected sexual intercourse
- Regular menstrual cycles (24-35 days)
- >16 years of age (UK), >18 years of age (US)

Exclusion Criteria

- Pregnant
- Breastfeeding
- Fitted with an intrauterine device
- Taking hormonal contraception
- Sterilized partner

Methods

- Participants presenting to a family planning clinic requesting EC within 5 days of unprotected sexual intercourse
- Block randomization of ulipristal or levonorgestrel
- Daily diary to record further acts of intercourse, contraceptive use, vaginal bleeding, concomitant medication use, and side effects

Follow-Up

- Follow-up done 5-7 days after expected onset of next menses
- If menses occurred and pregnancy test was negative, participation ended.
- If menses had not occurred, participants returned a week later.
- Urinary pregnancy test confirmed with serum hCG levels
Results

Pregnancy rates according to time from unprotected sexual intercourse to intake of emergency contraception

Most frequent adverse events

- 1696 women received EC within 72h of intercourse (ulipristal, n = 844; levonorgestrel, n = 852)
  - 15 pregnancies in ulipristal group
  - 22 pregnancies in levonorgestrel group
- 203 women received EC between 72h and 120h after intercourse (ulipristal, n = 97; levonorgestrel, n = 106)
  - 0 pregnancies in ulipristal group
• 3 pregnancies in levonorgestrel group

• 2 serious adverse events were possibly related to the use of EC
  • Ulipristal - case of dizziness
  • Levonorgestrel - molar pregnancy

• Meta-analysis (0-72h):
  • Ulipristal - 22/1617 (1.4%) pregnancies
  • Levonorgestrel - 35/1625 (2.2%) pregnancies
    ▪ OR 0.58, 0.33-0.99; p = 0.046

Conclusions

• Ulipristal is non-inferior to levonorgestrel for emergency contraception. Side effects- headache, dysmenorrhea, and nausea, are similar between both drugs

• Ulipristal provides women and health-care providers with an effective alternative for EC that can be used up to 5 days after unprotected sexual intercourse

<table>
<thead>
<tr>
<th>Study Purpose</th>
<th>Population</th>
<th>Trial Design</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1° endpoint: MRI-determined total fibroid volume (TFV) change</td>
<td>• N = 42 women</td>
<td>• Randomized</td>
<td>• 14 received 10mg CDB-2914 once daily x 12 weeks</td>
</tr>
<tr>
<td>• 2° endpoints: amenorrhea, quality of life (QOL)</td>
<td>• Pre-menopausal women aged 25-50 years</td>
<td>• Double-blind</td>
<td>• 14 received 20mg CDB-2914 once daily x 12 weeks</td>
</tr>
<tr>
<td></td>
<td>• Symptomatic with uterine fibroids &gt; 2cm. in diameter</td>
<td>• Placebo-controlled trial</td>
<td>• 14 received placebo (PLC) once daily x 12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 2nd 3-month treatment with CDB-2914 (treatment #2) offered</td>
</tr>
</tbody>
</table>

**Methods**

- **Treatment 1 (TX1)**
  - Following negative pregnancy test, subjects were randomized and began treatment on menstrual cycle day 1 or 2
  - Treatment administration continued for 3 menstrual cycles (90-102 days in amenorrheic women)
- FSH, ACTH, cortisol, LH levels measured every 2 weeks
- Participants recorded vaginal bleeding and other symptoms on a daily calendar
- Participants completed QOL questionnaires initially and 3 months post treatment

- **Treatment options after TX1**
  - No surgery and no extension, or
  - Hysterectomy, or
  - Myomectomy, or
  - 3 additional months of treatment with CDB-2914 (TX2)
    - Women received their earlier CDB dose or were randomized to 10mg or 20mg if they had received placebo
    - Study procedures were identical to TX1
Results

• TX1
  o PLC
    ▪ TFV increased by 7%
  o CDB10
    ▪ TFV decreased by 17%
  o CDB20
    ▪ TFV decreased by 24%

• TX2
  o 12 women entered TX2
  o TFV continued to decrease (TX1: -21%, TX2: -11%, p = 0.014)

• Amenorrhea occurred in 20/28 women taking CDB
• None occurred in PLC group
• Ovulation resumed after CDB
• Fibroid QOL questionnaire only improved in CDB group
  o Symptom severity
  o Energy/mood
  o Overall QOL
• Adverse events were unchanged between TX1 and TX2

Conclusions

• Administration of CDB-2914 for 3-6 months controls bleeding, reduces fibroid size, and improves QOL
• CDB-2914 is well tolerated in this small subset of women, with no serious adverse events

SUMMARY

• Ulipristal- selective progesterone receptor modulator, indicated for pregnancy prevention up to 5 days after unprotected sexual intercourse
• Ulipristal may be a well-tolerated nonsurgical alternative for treatment of uterine fibroids (possible new indication)
• Levonorgestrel- 2nd generation synthetic progestin, indicated for pregnancy prevention up to 3 days after unprotected sexual intercourse
• Labeling, wording, and current political views- fuel current controversy surrounding the definitions of personhood, emergency contraception, and abortion
REFERENCES