Metabolic Dysfunctions associated with Pharmacological Treatment of Schizophrenia

Pharmacokinetics, pharmacodynamics and pharmacogenetics of aripiprazole and olanzapine in healthy subjects

Dr. Francisco Abad Santos

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Atypical antipsychotics or second generation antipsychotics

 SGAs are 5HT$_{2A}$ Antagonists
 Clozapine was the first SGA.
 Very high affinity for 5-HT$_{2A}$
 Lower D$_2$ affinity than haloperidol

Less extrapyramidal symptoms than typical antipsychotics
Atypical antipsychotics or second generation antipsychotics

Broad Receptor Activity Results in a Wide Range of Effectiveness

- **Olanzapine**
- **Clozapine**
- **Quetiapine**
- **Risperidone**
- **Ziprasidone**
- **Haloperidol**
- **Aripiprazole**

Atypical antipsychotics

Olanzapine

Aripiprazole
Clinical Research Unit

Contacto

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# Bioequivalence studies

Healthy volunteers  
Single-dose fasting studies  
**Aim:** demonstrate that T is bioequivalent to R

<table>
<thead>
<tr>
<th>Sequence 1</th>
<th>Period 1</th>
<th>Sequence 2</th>
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<tr>
<td></td>
<td>T</td>
<td>R</td>
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<td><strong>Washout period</strong></td>
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<td><strong>Period 2</strong></td>
<td>R</td>
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<td>T</td>
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</table>
Parameters for evaluation of bioequivalence

Main parameters: AUC and Cmax
Secondary parameters: Tmax and half-life

AUC

Cmax

Concentration

Time (horas)

0 12 24 36 48 60 72

AUC extrapolated
Other uses of these data

• Evaluation of pharmacokinetics
  – Comparison of men and women

• Evaluation of pharmacodynamics
  – blood pressure
  – heart rate
  – ECG: PR, QTS and QTc
  – prolactin

• Evaluation of safety
  – Adverse events

• Evaluation of pharmacogenetics
  – Polymorphisms in enzymes: CYP450
  – Polymorphisms in transporters: ABCB1
  – Polymorphisms in receptors
Olanzapine

- 2 clinical trials: 66 subjects
- 5 mg single dose
- **Pharmacokinetics**
  - well absorbed: Tmax 6 hours
  - eliminated extensively by first pass metabolism (40%)  
  - metabolized primarily by direct glucuronidation and CYP1A2 and to a lesser extent by CYP2D6 and CYP3A4
  - metabolites are inactive
  - half-life: 21 to 54 hours (mean of 30 h)
Olanzapine pharmacokinetics

- Tmax: 4.00 (2.00-6.00) hours
- half-life: 31.3 ± 7.1 hours
- No differences between men and women after adjusting for weight
• No effect of CYP1A2 and CYP2D6

Effect of GSTM3 polymorphisms

- Cmax
- AUC/10
- Half-life
- Cl

*A/*A
*A/*B or *B/*B
The most frequent
• somnolence (100%)
• fatigue (30.2%)
• hypotension (28.6%)
• dizziness (25.4%)
### Antipsychotic adverse reactions

**Pharmacogenomics 2013; 14(10): 1203–1214**

- Related to DRD2

<table>
<thead>
<tr>
<th></th>
<th>General</th>
<th>DRD2</th>
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<td>Olanzapine</td>
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<td>A1/A1</td>
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<td>4/5</td>
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<td>A1/A2</td>
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<td>5/18</td>
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<td>A2/A2</td>
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</tbody>
</table>
DRD2 Taq1A Polymorphism Modulates Prolactin Secretion Induced by Atypical Antipsychotics in Healthy Volunteers

Rosario López-Rodríguez, PhD,*†‡; Manuel Román, MLT,*†; Jesús Novalbos, PhD,*†; Maria Laura Pelegrina, MD,*†; Dolores Ochoa, MD,*†; and Francisco Abad-Santos, PhD*†‡

Increase in prolactin

FIGURE 1. Prolactin concentration versus time curve after the administration of a single dose of 1 mg risperidone, 5 mg olanzapine, or 25 mg quetiapine to healthy volunteers.
Olanzapine increase in prolactin


Related to gender and DRD2, but not DRD3
Olanzapine increase in prolactin

Related to gender, 5-HTR2A and DRD2

Table 3. Association of gender and polymorphisms with prolactin $iC_{\text{max}}$ and $iAUC$ after administration of olanzapine ($t$ test) (pharmacodynamic parameters expressed as unadjusted data)

<table>
<thead>
<tr>
<th></th>
<th>$N$</th>
<th>$iC_{\text{max}}$ (ng/mL)</th>
<th>$iAUC$ (ng/mL h)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>$p$</td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>33</td>
<td>12.73 ± 10.41</td>
<td>0.019</td>
</tr>
<tr>
<td>Women</td>
<td>30</td>
<td>18.89 ± 9.85</td>
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<tr>
<td>5-HTR2A</td>
<td></td>
<td></td>
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<tr>
<td>C/C</td>
<td>21</td>
<td>20.60 ± 11.91</td>
<td>0.007</td>
</tr>
<tr>
<td>C/T, T/T</td>
<td>42</td>
<td>13.20 ± 8.94</td>
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</tr>
<tr>
<td>DRD2</td>
<td></td>
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</tr>
<tr>
<td>A2/A2</td>
<td>34</td>
<td>12.41 ± 9.39</td>
<td>0.024</td>
</tr>
<tr>
<td>A1/A2, A2/A2</td>
<td>23</td>
<td>18.59 ± 10.59</td>
<td></td>
</tr>
</tbody>
</table>

5-HTR2A, serotonin receptor 2A; AUC, area under the curve; DRD, dopamine receptor D.
Aripiprazole

- 6 clinical trials: 148 subjects
- 10 mg single dose
- **Pharmacokinetics**
  - well absorbed: Tmax 3-5 hours
  - metabolized extensively in the liver primarily by CYP3A4 and CYP2D6
  - major metabolite (dehydroaripiprazole) contributes to overall activity (40% of plasma concentration)
  - half-life: 75 h aripiprazole
    
    94 h dehydroaripiprazole
Aripiprazole pharmacokinetics

- **Tmax**: 3.00 (1-12) hours
- **half-life**: 50.8 ± 14.8 hours
Aripiprazole pharmacokinetics

- Tmax: 24-72 hours
- It is not possible to calculate half-life for metabolite
Aripiprazole pharmacokinetics

- **ARI**: women show higher AUC, Cmax, T1/2 and Vd
- **DHARI**: no influence of gender on PK.

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<tbody>
<tr>
<td><strong>AUC (ng·h/mL)</strong></td>
<td>1631.8±404.1</td>
<td>1557.9±400.6</td>
<td>1731.4±390.1**</td>
<td>405.6±157.2</td>
<td>375.9±130.5</td>
<td>442.8±182.0</td>
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<tr>
<td><strong>Cmax (ng/mL)</strong></td>
<td>49.3±11.1</td>
<td>46.5±9.7</td>
<td>53.1±11.7***</td>
<td>7.2±2.6</td>
<td>6.7±2.2</td>
<td>7.7±3.0</td>
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<tr>
<td><strong>Tmax (h)</strong></td>
<td>3.2±1.6</td>
<td>3.0±1.6</td>
<td>3.3±1.7</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>T1/2 (h)</strong></td>
<td>52.2±20.7</td>
<td>48.2±18.2</td>
<td>57.7±22.7**</td>
<td></td>
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<tr>
<td><strong>Vd/W (L/kg)</strong></td>
<td>4.2±0.8</td>
<td>3.9±0.7</td>
<td>4.6±0.8***</td>
<td></td>
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<tr>
<td><strong>Cl/W (mL/h·kg)</strong></td>
<td>63.3±21.4</td>
<td>63.1±20.2</td>
<td>63.7±23.0</td>
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</tbody>
</table>

*p≤0.05, **p≤0.01 y ***p≤0.001 vs men
Aripiprazole pharmacokinetics

CYP2D6

PM vs UM expose to +68% [ARI] and -45% [DHARI] → +36% [ARI+DHARI]
Aripiprazole adverse reactions

Incidence of ADR

- No: 27%
- Si: 73%

Most common ADRs

- Mareo: 38.5%
- Náuseas/vómitos: 30.4%
- Cefalea: 19.6%

Relation sex-ADR

- RAM
  - Hombres: 69.4%
  - Mujeres: 77.8%
  - P = 0.005

- Náuseas/vómitos
  - Hombres: 21.2%
  - Mujeres: 42.9%
Aripiprazole adverse reactions

CYP3A5*3 - neurologic ADR (dizziness)

Related to:
- AUC_{0-t} : direct relation
- CYP3A5: higher in *1/*1

CYP2D6 - Nausea/vomits

Related to:
- AUC_{0-t} : direct relation
- C_{max} : direct relation
- CYP2D6: higher in PM and IM
- Sex: higher in women
Aripiprazole pharmacodynamics


• decrease of BP (9.3 mmHg SBP - 6.2 mmHg DBP)
• increase in HR (12.1 beats per minute)
• increase QTc interval (9.1 ms)
• sex differences in BP, HR, and QTc interval but the effect of aripiprazole was similar in men and women
• AUC was related with SBP and DBP decrease and HR increase but not with QTc increase

• Prolactin: pending
• Pharmacogenetics: pending
TREATMENT collaboration

- **Phase I clinical trial**
  - 24 healthy volunteers (men and women)
  - Multiple dose (five days of continuous treatment)
  - Aripiprazole and olanzapine
  - Samples for biomarkers

- **Analytics**
  - Aripiprazole, dehydroaripiprazole and olanzapine

- **Pharmacogenetics**
  - Pharmacokinetics: CYP, transporters
  - Pharmacodynamics: DA and 5-HT receptors
Questions???