Pharmacology of the Methamphetamine Enantiomers

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Presentation Outline

- Epidemiology
- Chemistry
- Regulation
- Our Experiment
  - Pharmacokinetics
  - Subjective Effects
  - Cardiovascular Results
- Future Directions
Onward

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Methamphetamine

- Methamphetamine is the most widely used, illegally manufactured and distributed, abused stimulant drug in the world. A big problem in
  - Asia (Taiwan, Japan)
  - Europe (Scandinavia)
  - North America (West Coast)
- In San Diego, methamphetamine associated with more deaths than cocaine
History of Amphetamines

- Amphetamine first synthesized in 1887 in Germany
- Methamphetamine first synthesized in 1919 in Japan
- CNS effects were recognized in the early part of 20th century

History of the Amphetamines -2

- Use of structurally related phenylisopropylamines may date back to 3000 BC by the Chinese, who used the plant Ma-Huang which contains various pharmacologically active amines, including ephedrine.
Methamphetamine vs. Amphetamine

- Methamphetamine thought to have more central and less peripheral effects than amphetamine
- Amphetamine enantiomers extensively investigated
  - PK CI d>I, CNS d>I, CV I>d
- Very little data on methamphetamine enantiomers

Use in the USA

- In 1994
  - 3.8 million had used at least once
  - 1.8% of the US population
- In 1996
  - 4.9 million had used at least once
  - 2.3% of the US population

Data from the NIDA household surveys of 1994 and 1996
Changing Populations

- In California MA traditionally used by
  - White males, blue collar workers
  - Motorcycle gang members
  - People living in rural areas
  - Gay men in urban areas
- Use spreading to Hispanics (especially Mexicans) and kids in suburbia

Abuse and HIV Transmission

- IV abuse is common.
- Men having sex with men are more likely to report methamphetamine as the primary drug they injected.
- Approximately 16% of IDUs with AIDS report amphetamine or methamphetamine as the primary drug injected.
Structure-Function

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The DEA and Methamphetamine

- Epidemiology
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The Precursor Issue

- Methamphetamine is synthesized - not a plant product
- Decreasing supply requires control of an essential synthetic step (precursor, equipment, training)
- Because most clandestine labs use same recipes precursor control is logical

History of the Precursors

- 1950’s Phenyl 2-Propanone starting material
  - Produces racemic methamphetamine
- 1980 DEA moves 2-P-2 to Schedule II
- Clandestine labs switch to ephedrine and pseudoephedrine
  - Produces only d-methamphetamine
Driving Force for Experiments

- 1996 DEA increases control of ephedrine and pseudoephedrine
  - We expect clan labs to switch to new starting materials that will most likely yield racemic methamphetamine
- Our goal - be there before the drug dealers

Regulation of Precursors

- Article 12 of the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances
  - known as the Vienna Convention
- The basis for international cooperation in control of precursors
In 1988, the US adopted the comprehensive Chemical Diversion and Trafficking Act (CDTA).

This act instituted a control system for 20 chemicals thought to be essential for the synthesis of illicit drugs.

Domestic Chemical Diversion Control Act of 1993 specifically targeted the illicit production of methamphetamine.

Brought over-the-counter, single-entity ephedrine products under DEA regulatory control.
More Laws

- The Comprehensive Methamphetamine Control Act (MCA) of 1996 broadened controls on listed chemicals used in the production of controlled substances
- Removed remaining exemptions for combination ephedrine, pseudo-ephedrine and phenylpropanolamine

The Big Stick

- The recent Methamphetamine Anti-Proliferation Act of 2000 and Ecstasy Anti-Proliferation Act of 2000 enhanced (INCREASED) the federal sentencing guidelines for these two substances.
Those Pesky Canadians

- Sounds impressive but the big loophole is Canada, where you can still purchase all needed precursors in almost any quantity and walk them into US.
- Almost daily someone is arrested at a border crossing with thousands of pseudoephedrine tablets

Human Pharmacology

- Epidemiology
- Chemistry
- Regulation
- Our Experiment
  - Pharmacokinetics
  - Subjective Effects
  - Cardiovascular (2D Echo)
- Future Directions
Methods

- **Subjects**
  - 12 IV Meth users, not dependent
  - Use 2X per year to weekly
  - Ages 18 to 45

- **Procedure**
  - 6 admits to GCRC
  - Double blind, placebo controlled partially balanced Latin Square design

Methamphetamine doses

- d-methamphetamine 0.25 mg/kg
- d-methamphetamine 0.5 mg/kg
- l-methamphetamine 0.25 mg/kg
- l-methamphetamine 0.5 mg/kg
- Racemic methamphetamine 0.5 mg/kg
  - 0.25 d- and 0.25 l-methamphetamine
- Placebo (saline)
### Measures

- **PK**  
  - Methamphetamine and amphetamine  
  - 4-OH metabolites (meth and amph)
- **PD**  
  - Physiologic  
  - Subjective  
  - Echocardiographic
- **After study, determine CYP 2D6 phenotype with dextromethorphan**

### Pharmacokinetic Hypothesis

- I-isomers will be metabolized more slowly than d-isomers
- I-4OH isomers will accumulate in plasma and urine
Cardiovascular Hypothesis

- Both isomers will increase heart rate, blood pressure and rate pressure product but
- L-methamphetamine will be more potent than d-methamphetamine

Subjective Effects Hypothesis

- D-methamphetamine will have more CNS effects than l-methamphetamine
- L-methamphetamine will be less desirable than d-methamphetamine
- Racemic methamphetamine will have less CNS effects than d-methamphetamine
How did we do?

- Not well
- L-methamphetamine had more CNS effects than predicted
- L-methamphetamine is intoxicating and is rated as a good drug
- Racemic methamphetamine has same effects as d-methamphetamine

Echocardiography

- Transthoracic 2D echos obtained before any methamphetamine and 2 hours after dose
- Standard measures
- Calculated SV, CO, EF, Wall Stress
  - In a prior study MDMA increased wall stress more than dobutamine
Echo Hypothesis

- Both d- and l- will increase contractility, l- might be more potent
- No wall motion abnormalities expected

Conclusions

- d-methamphetamine increases CO and EF and is a positive inotrope
- l-methamphetamine has little effect on the heart and may be a cardiodepressant
- Isomers have markedly different cardiac effects
Overall Conclusions

- l-methamphetamine psychoactive with some (although low) abuse potential
- l-methamphetamine metabolized slower than d-methamphetamine
- l-methamphetamine may be a cardiodepressant

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Vick’s Projects

- 12 normotensive and 12 HTN subjects in dose escalation study
- Inhale 2, 4 and 8 times recommended dose every 2 hours for 6 hours
- Measure CO, SVR with Impedance Cardiography

Other Choices

- Methamphetamine isomers and Paroxetine interactions
  - Possible addiction therapy and 2D6 inhibitor
- Effects of subchronic racemate administration
  - Possible interesting metabolic interactions
The Talent - Staff of the DDRC

– MDs, PhDs
  • Tom Everhart, Emilio Fernandez, Elyse Foster, Elizabeth Gray, Debra Harris, Peyton Jacob III, Reese Jones, Rajneesh Nath, Jayant Nath, Kendra Shih and Naoto Uemura

– Professional Staff (including a few ABDs)
  • Dolores Cannon, Polly Cheung, Bob Jimison, Adriana Manari, Tina Melby, Tina Panganiban, Stephanie Rogerson, Kirsten Sanford, Peter Schwonek, Patricia Southard, Gina Sequeria and Kaye Welch