FORENSIC PATHOLOGY

Sara Acree, M.D. (PGY-4)
LAC+USC Medical Center
History

- 71-year-old Caucasian female
- Homemaker, wife to business executive
- Past Medical History:
  - Rheumatoid Arthritis
  - Parkinson’s disease
  - Psychiatric disorder (not specified)
- Non-ambulatory for the past 5 years
- Found unresponsive at home
  - Rexford Drive, Beverly Hills
History (cont.)

- Taken to CSMC
- Pronounced dead at hospital
- Identified by husband
Why a Coroner’s Case?

Select Criteria

• “Sudden deaths of persons appearing to be in good health.”

• “All cases in which the attending physician is unable or unwilling to certify the cause of death.”
Autopsy Findings

- Caucasian female
- Appeared younger than 71 years
- Height 60”, Weight 115 lbs
- No evidence of external trauma
Anatomical Summary

• Marked deformity of all joints
  – Including lumbar lordosis

• Atherosclerotic Cardiovascular Disease
  – Coronary artery atherosclerosis
  – Severe aortic atherosclerosis
  – Calcific mitral valve disease
  – Cardiomegaly (410g)

• Toxicology “C screen” ordered
Medication List

- Symmetrel (Amantadine)
- Artane (Trihexyphenidyl)
- Navane (Thiothixene)
- Depakote (Divalproex)
- Benadryl (Diphenhydramine)
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Toxicology Results

Autopsy Blood

• Amantadine = 12 mg/L
Toxicology Results

Autopsy Blood

• Amantadine = 12 mg/L

• Toxicity = > 2 mg/L
Amantadine

- First described in 1964
- Synthetic tricyclic amine with adamantane backbone
- 1966: approved for Influenza A
  - Orthomyxoviridae family
  - Multiple subtypes (H_N_)
  - 2009 flu pandemic (“swine flu”) caused by mutant “novel” H1N1
  - 2010: CDC reports resistance
Amantadine

- In 1969, introduced to treat Parkinson disease (PD)
- Discovered to have indirect and direct effects on dopaminergic neurons
- Serious adverse reactions: depression, psychosis and reports of suicidal ideation
# Amantadine Overdose

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<th>Admission [Blood]</th>
<th>Signs &amp; Symptoms</th>
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Investigation (cont.)

- Severe RA for years
  - Bilateral hip and knee replacements
  - Left elbow and wrist, & right ankle prostheses

- “Deformed feet” per hospital admission

- Unable to self-medicate
Manner of Death?

- Natural
- Non-natural
  - Accident
  - Suicide
  - Homicide
Homicide

California Law

• First-degree murder
• Second-degree murder
• Voluntary manslaughter
• Involuntary manslaughter
• Vehicular manslaughter
Homicide

California Law

- First-degree murder
- Second-degree murder
- Voluntary manslaughter
- Involuntary manslaughter
- Vehicular manslaughter

Premeditation

Gross Negligence
Investigation (cont’d)

• Medication was administered by caretaker only

• Caretaker was middle aged Hispanic woman employed for several years

• No motive or evidence of wrongdoing. No evidence of financial or other gain.

• No evidence to implicate husband
Toxicology Revisited

AMANTADINE LEVEL

- Heart blood 12 mg/L
Toxicology Revisited

AMANTADINE LEVEL

- Heart blood: 12 mg/L
- Femoral blood: < 0.08 mg/L
- Vitreous humor: < 0.08 mg/L
Toxicology Explained

• Postmortem Drug Redistribution
Postmortem Redistribution (PMR)

• Before 1980’s, toxicologists assumed:
  \[\text{[postmortem]} = \text{[antemortem]}\]
Postmortem Redistribution (PMR)

• Before 1980’s, toxicologists assumed:
  \[ \text{postmortem} = \text{antemortem} \]


Liver and blood postmortem tricyclic antidepressant concentrations.

Apple FS, Bandt CM

Clinical Laboratories, Hennepin County Medical Center, Minneapolis, Minnesota 55415
Concentration vs Postmortem Interval

Amitriptyline

Nortriptyline

Desipramine

Doxepin
[Liver]/[Blood] Ratio

• Fatal Overdose: 37
• Therapeutic ingestion: 39
PMR: Basic Principle

- Where the distribution is non-uniform before death, it becomes uniform after death
Candidate Drugs?

HEPARIN

0.05-0.1 Vd/kg
Remains localized in bloodstream

OTHER DRUGS

Variable (non-uniform) distribution

CHLOROQUINE

200 Vd/kg
Entire body load lies outside of bloodstream
Drug Characteristics that Influence PMR

• Vd calculation:

\[ V_D = \frac{\text{total amount of drug in the body per body weight unit (Kg) (i.e. Dose)}}{\text{drug blood concentration}} \]

• Antemortem distribution pattern is dependent on the interplay between:
  – Lipophilicity
  – pKa
  – Molecular size
  – Affinity for various organs
PMR: Basic Principle (cont.)

- Uniformity is achieved via diffusion down concentration gradient

- 2 major scenarios:
  - Bound drug
  - Free drug
Mechanisms of PMR

I. Diffusion of Bound Drug
   - Release (then diffusion) from highly concentrated organs, secondary to:
     • Changes in pH
     • Depletion of energy stores

II. Diffusion of Free drug
   - Simple diffusion from a drug depot
Postmortem Redistribution

Mechanism #1

• Drugs can preferentially bind to certain organs
  – Properties of the organ
  – Properties of the drug

• Therefore, a drug’s concentration depends on the sampling site
Overdose Distribution Study

- Suicide case study: overdose by 25yo/F
- 40 total specimens
- 10 ligated blood sites
- 28 tissue sites & fluids
- Multiple drugs:
  - Acetaminophen
  - Alcohol
  - Codeine
  - Diphenhydramine
  - Imipramine

Variability of [drug] by site

GR Jones, 1987
Postmortem Redistribution

Mechanism #1

- “High-affinity” organs:
  - Lungs
    - Capillary-rich organ
    - Rich in lipoproteins
  - Liver
    - Site of metabolism
Postmortem Redistribution

- Heart is next major culprit
  - [Cardiac] > [subclavian] > [femoral] > [antemortem]
  - Increases concentration several-fold greater than antemortem concentrations
Common Foxglove
Common Foxglove
Common Foxglove
Amantadine & Heart [blood]

• Does Amantadine have similar high affinity for cardiac myocytes?
• Known to prolong QT interval and cause CHF
• May explain the extremely high [cardiac] compared to [femoral]: 150x greater
A COMPARISON OF DRUG CONCENTRATIONS IN POSTMORTEM CARDIAC AND PERIPHERAL BLOOD IN 320 CASES

M. DALPE-SCOTT, M. DEGOUFFE, D. GARBUPTT and M. DROST

Determined C/P ratios for 113 drugs across 320 cases.
Drugs with higher Vd had largest C/P ratios.
Potentially useful indicator that a drug is subject to PMR.
Femoral Blood Collections

- Peripheral blood is least subject to PM elevations
- Femoral V. is ideal site
  - Also from antecubital fossa and humeral vessels
- Best collection method:
  - Ligate vessel proximally
  - Draw small sample (2-10 mL)
  - Avoids more central blood
Alternatives to Blood

• Ideal to sample multiple sites and tissue types.
• When tissue is desired or only option…
Postmortem Redistribution

Mechanism #2

- Simple diffusion of free drug from drug depot:
  - Gastric contents
  - Transdermal patches
  - Intravenous infusions
Postmortem Redistribution

Mechanism #2

• Simple diffusion of free drug from drug depot:
  – Gastric contents
    • Diffusion or traumatic release
    • Vomiting and aspiration
Postmortem Redistribution

Mechanism #2

• Simple diffusion of free drug from drug depot:
  – **Transdermal patches**
    • Postmortem diffusion continues at slower rate
    • Locally high concentrations
Postmortem Redistribution

Mechanism #2

• Simple diffusion of free drug from drug depot:
  – **Intravenous infusions**
    • May continue to be pumped after death
    • Causes large local increase in [blood]
What about death after hospitalization?

• Usually, drugs present on admission are metabolized after several days

• Hence, critical to obtain:
  – hospital blood samples
  – blood bank samples
* A Special Request *

From the Los Angeles County
Department of Coroner

Attention all Pathologists and Laboratory Directors

The Coroner’s office asks that the following information be incorporated into standard operating procedure. Please share this information with the appropriate individuals at your institutions, including:

- Hospital Administration
- Nursing Director
- ER staff
- Decedent Affairs Office

A. The Coroner/ME has a need for admission blood samples on all deaths accepted as Coroner’s cases.

Initial admission blood samples collected on patients in the Emergency room (preferably before the initiation of therapies) and sent to the Laboratory and/or Blood Bank should be saved for the Coroner’s Office. Any serum/plasma samples will also be useful for specialized testing. Such samples will be picked up by the Coroner’s Office staff when they come to remove the decedent. This will help with comprehensive Quantitative and Qualitative toxicology testing. These requests will be made by the Coroner’s Office personnel to the hospital staff making the initial call to report a case.

B. The Coroner/ME will appreciate getting results on all toxicology screening tests ordered by Emergency Room personnel.

C. The Coroner/ME requests Hospital Laboratory (Microbiology) personnel follow through with cultures taken on patients suspected of an infectious disease process.

(Some hospitals terminate cultures and serologic testing for infectious diseases soon after a patient’s demise). We kindly ask that you complete such testing.

Thank you for your cooperation.

Yours sincerely,

Dr. Lakshmanan Sathyavagiswaran
CME-Coroner,
LA County

Chief Medical Examiner-Coroner:
Lakshmanan Sathyavagiswaran, MD

Director:
Anthony T. Hernandez

Los Angeles County Department of Coroner
1104 N. Mission Road, Los Angeles, CA 90033
Contact/visit us at: 323.343.0522
http://coroner.lacounty.gov/htm/Coroner_Home.htm
Coroner/ME Office Request

A. Provide admission blood samples on all deaths accepted as Coroner’s cases.

B. Provide results on all toxicology screening tests ordered by ER personnel.

C. Complete microbiology work-up on patients suspected of an infectious disease process.
Case Follow-up: Summary

- Ruled out that drugs did NOT play a role in causing or hastening her death
- Autopsy revealed **clinically unknown** CVD
  - >90% occlusion of coronaries
  - Severe aortic atherosclerosis
  - Cardiomegaly (410 grams)
  - Mitral valve disease
- Physically overexerted herself on same day likely triggering a terminal cardiac event
Case Follow-up: Medical Report

DEATH WAS CAUSED BY:
Atherosclerotic cardiovascular disease

OTHER CONDITIONS CONTRIBUTING BUT NOT RELATED TO THE IMMEDIATE CAUSE OF DEATH:
Cardiomegaly, mitral valve disease, rheumatoid arthritis

MANNER OF DEATH:
Natural
Key Points to Remember…

• Single [conc] can be dangerously misleading

• Toxicology must be performed on blood from more than one site (ie, femoral, vitreous)

• Consider C/P ratio

• Correlate with other investigative findings:
  – PMH, autopsy findings, circumstances of death

• For hospital deaths, antemortem samples are critical for analysis
References

• Drummer OH. Forensic toxicology. EXS. 2010;100:579-603.
Acknowledgements

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Chief Medical Examiner/Coroner
Thank You