

Oxymorphone Distribution in Biological Matrices: A Collection of Case Studies

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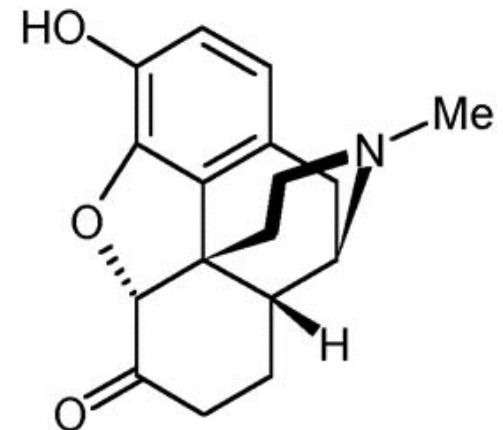
Introduction

■ What is oxymorphone?

- 4, 5 α -epoxy-3, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride
- Semi-synthetic opioid analgesic; agonist for the μ -opiate receptor
- Used in patients with around-the-clock pain
- Metabolite of oxycodone
- Schedule II
- Toxicity leads to: hypotension, bradycardia, apnea, coma, circulatory collapse, and cardiac arrest¹

■ Properties:

- Sparingly soluble in alcohol or ether
- Freely soluble in water
- MW = 337.80²



Introduction

- Emergence:
 - Original Approval by FDA: April 2, 1959.
 - Manufactured by Endo Pharms
 - Available in an injectable form as well as a suppository under the name Numorphan ®
 - Oral dosage approved by FDA on June 22, 2006; again produced by Endo Pharms and given the trade name Opana ®
 - Extended release also available
 - Standard form available in 5mg and 10mg dosage; Extended release available in 5, 10, 20, and 40 mg²



Methodology

- Ways to determine presence of oxymorphone in case work:
 - Investigator's / Officer's Reports – *"Your First Line of Defense"*
 - Previous History Reports
 - Hospital Records
 - Medication Inventory
 - Laboratory standard screening protocol
 - Immunalysis® ELISA Screen for drugs of abuse (Ex. Opiate Pack)
 - Immunalysis® ELISA Specific Screen (Ex. Oxycodone Specific Pack)

Methodology

- Montgomery County Coroner's Office Screening Techniques
 - Immunalysis® ELISA Screening kit
 - Problems with Cross-Reactivity for oxymorphone
 - ~2 % cross-reactivity with most ELISA packs¹
 - Important to screen urine where higher concentrations are present if oxymorphone is suspected
 - (Ex. 1) Our opiate screen has a 20% cross-reactivity of a 125 ng/mL sample of oxymorphone in comparison to a 100% cross-reactivity of a 25 ng/mL sample of morphine.³
 - (Ex. 2) For the oxycodone specific screen, a 50 ng/mL sample of oxymorphone is equivalent to a 15 ng/mL sample of oxycodone and has a cross-reactivity of 30%.⁴

Methodology



Methodology

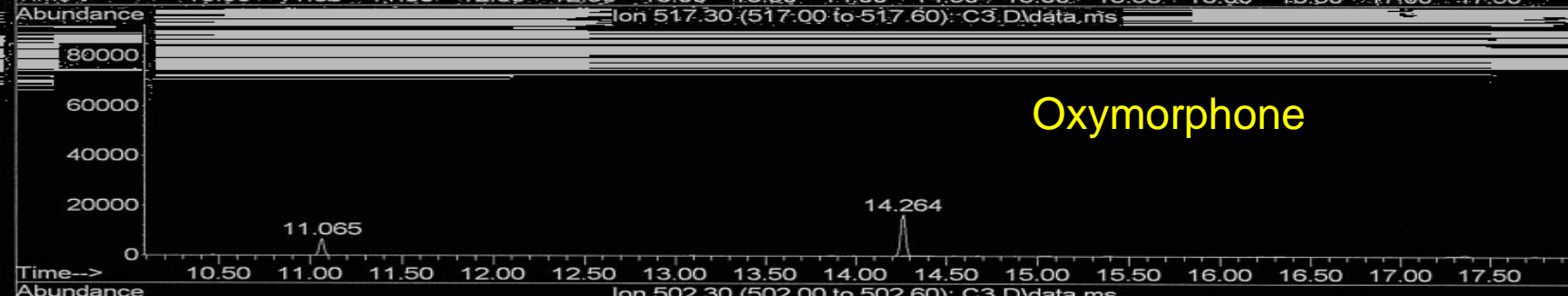
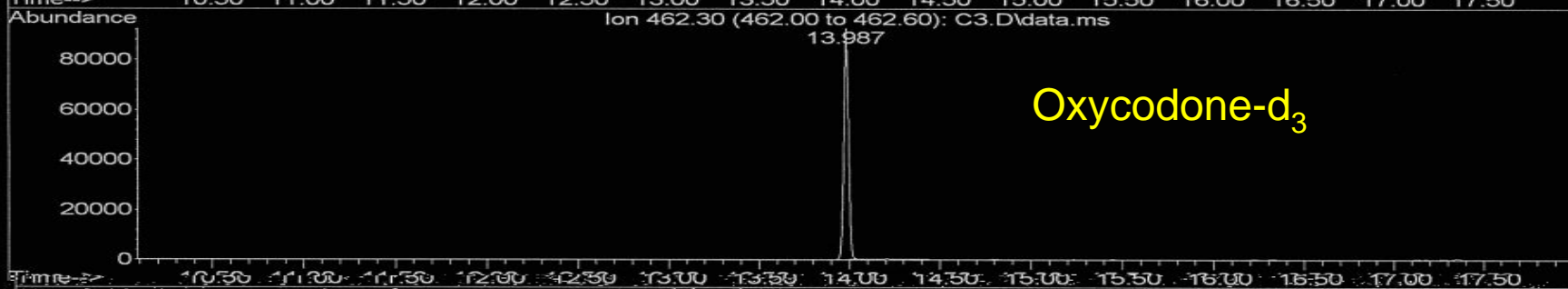
■ Opiate Extraction Technique:

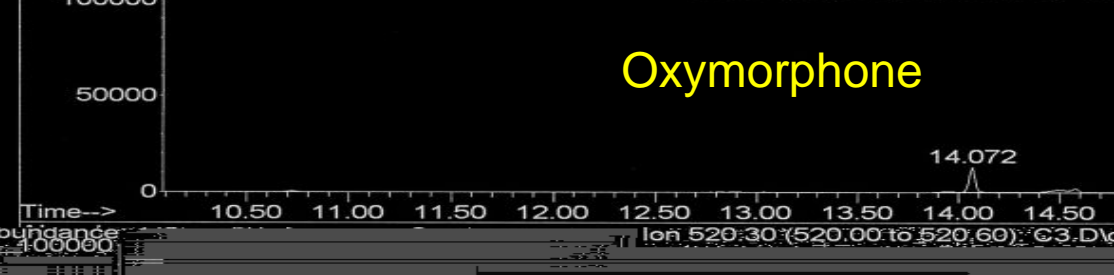
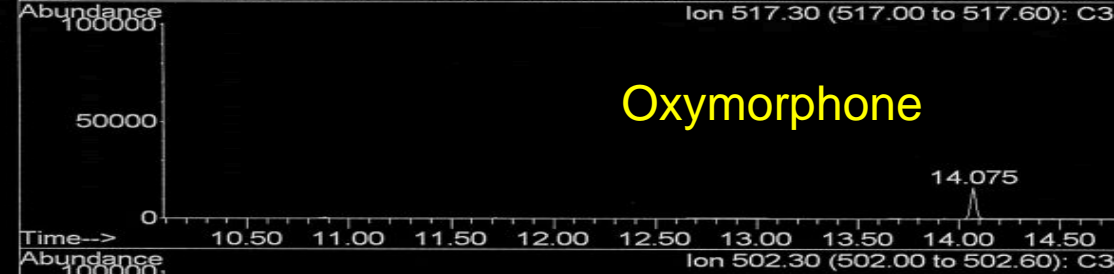
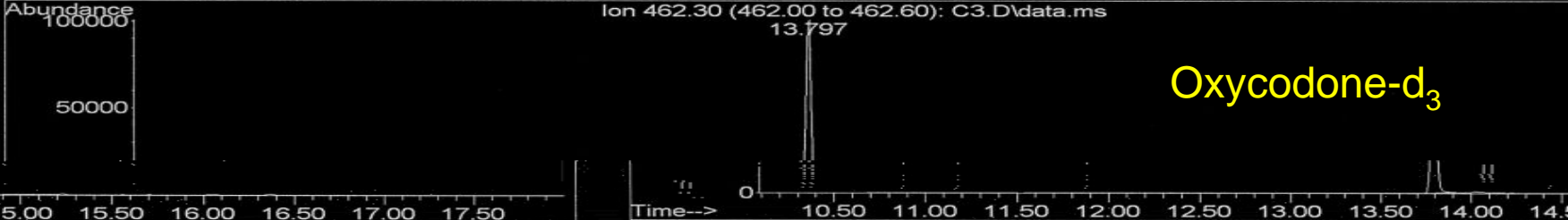
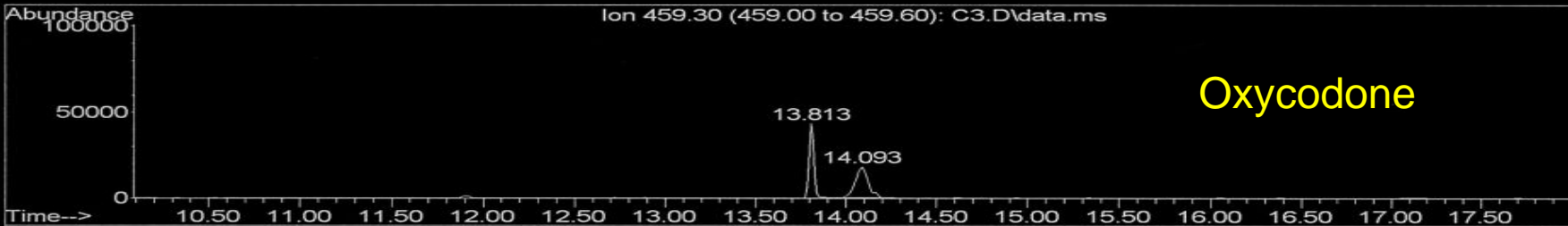
- Phosphate buffered samples loaded onto solid phase extraction columns with co-polymeric bonded phase
 - Hydrophobic, reverse phase
 - Ion exchanger
 - Extract with ammoniated ethyl acetate
 - Derivatization with 1:1 BSTFA/1% TMS and ethyl acetate
-
- Method used to quantitate morphine, 6-monoacetylmorphine, hydrocodone, hydromorphone, codeine, oxycodone, and oxymorphone with deuterated internal standards



Methodology

- Instrumentation:
 - Samples were shot on one of two GC/MS instruments based on availability:
 - 6890 inert source
 - 7890 inert source
 - Column: DB-5MS, (J & W Scientific)





Methodology

- Data reviewed for presence and quantification of 7 different opiates
 - Calibration curves must have $R^2=0.99$ or greater
 - Controls must be within 20% or 2 standard deviations of the expected value
 - Calibration Range from 0.01 – 0.50 $\mu\text{g/mL}$ and shown to be linear up to 1.0 $\mu\text{g/mL}$.
- Oxymorphone identified by 2 ions (517.30 and 502.30) and currently compared to oxycodone- d_3
 - Ion ratios must be within 20% of ratios calculated for calibrators
- Since oxymorphone is a metabolite of oxycodone, we should expect to see it in conjunction with oxycodone. However, if the oxymorphone exists by itself or in an equal or greater quantity than the oxycodone, it should be explored as to whether or not the person consumed the oxymorphone separately.
- Additional testing has led to identification of oxymorphone in all of the following matrices: blood, urine, vitreous, cerebrospinal fluid (CSF), liver, brain, and hair.

Case Studies

■ Case #1:

- 21 yr old, white male
- Out drinking heavily with friends, then was reported to have taken several white pills marked “E-40”
- Last known to be asleep ~1:00 AM, found dead the following morning. No medical history or drug paraphernalia at scene.
- Drugs:
 - Oxymorphone:

□ Femoral Blood = 40 ng/mL	Brain = < 40 ng/g
□ Vitreous = 50 ng/mL	Liver = 60 ng/g
□ CSF = 40 ng/mL	Urine = Positive (720 ng/mL)
 - Other drugs present:
 - Urine:
 - 11-COOH-THC = Positive
- Death ruled: Accident by acute oxymorphone intoxication

Case Studies

■ Case #2:

- 59 yr old, white female.
- History includes stroke, multiple cancers. Meds include: Clonazepam, Cyclobenzaprine, Lyrica, Opana, Hydrocodone, Promethazine, Topomax, and Bupropion.
- Discovered by daughter lying on the floor next to bed in disoriented state. Placed back in bed and found unresponsive the following morning.
- Drugs:
 - Oxymorphone:
 - Femoral Blood = 30 ng/mL
 - Brain = 80 ng/g
 - Liver = 240 ng/g
 - Urine = Positive (450 ng/mL)
 - Other drugs present:
 - Femoral Blood:
 - Topiramate = 13 µg/mL
 - Citalopram = 0.13 µg/mL
 - Promethazine = 0.14 µg/mL
 - Bupropion = 0.08 µg/mL
 - Hydrocodone = 0.02 µg/mL
 - Pregabalin = 3.4 µg/mL
 - Cyclobenzaprine = 0.05 µg/mL
- Death Ruled: Accident by drug intoxication (oxymorphone, hydrocodone, promethazine, and others)

Case Studies

■ Case #3:

- 48 yr old, white male
- Last known alive when observed sleeping and snoring loudly in bed by wife.
- Medical history included COPD, emphysema, HTN, chronic back pain, morbid obesity. It was reported that the decedent had no family doctor and would frequent the emergency room for treatment. Meds: Opana, Valium, Hydrocodone
- Drugs:
 - Oxymorphone:

□ Femoral Blood = 90 ng/mL	Brain = 110 ng/g
□ Vitreous = 160 ng/mL	Liver = 460 ng/g
□ CSF = 390 ng/mL	Urine = Positive (4600 ng/mL)
 - Other drugs present:
 - Heart Blood
 - Diphenhydramine = 0.15 µg/mL
 - Diazepam = 0.46 µg/mL
 - Nordiazepam = 0.79 µg/mL
 - Temazepam = 0.05 µg/mL
 - Oxazepam = 0.05 µg/mL
- Death Ruled: Accident by multiple drug intoxication

Case Studies

■ Case #4:

- 24 yr old, white male
- Single car accident where decedent struck a tree at a high rate of speed (~105-112 mph). Pronounced dead at the scene.
- Drugs:
 - Oxymorphone:
 - Heart Blood = 20 ng/mL Brain = not detected
 - Vitreous = 20 ng/mL Liver = not detected
 - Urine = not detected
 - Other drugs present:
 - Heart Blood:
 - Hydrocodone = 0.02 µg/mL
 - THC = 11 ng/mL 11-COOH-THC = 107 ng/mL
 - Femoral Blood:
 - Ethanol = 0.07 GM%
- Death Ruled: Accident, blunt force injury to head

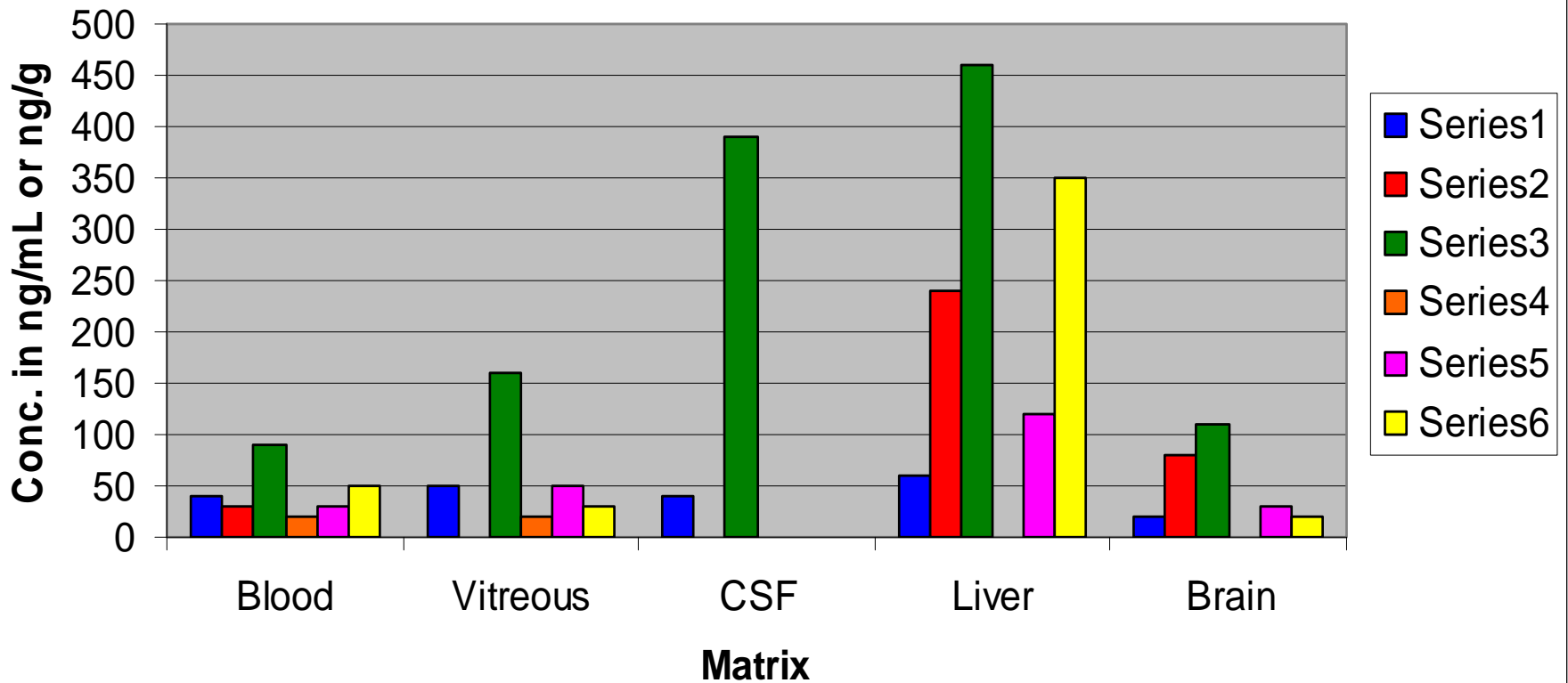
Case Studies

Case	Blood	Vitreous	CSF	Liver	Brain	Urine
1	40	50	40	60	20	720
2	30	X	X	240	80	450
3	90	160	390	460	110	4600
4	20	20	X	ND	ND	ND
5	30	50	X	120	30	2200
6	50	30	X	350	20	2200

- Values are represented in ng/mL
- X indicates where specimens were not available
- *ND* indicates where specimens were available but not detected

Case Studies

Oxymorphone Distribution in Sample Matrices



Case Studies

- A case from outside the Coroner's Office:
 - 25 yr old, white female
 - Found sleeping in vehicle on the side of the road. Field sobriety performed and suspect arrested.
 - Reportedly a recovering heroin addict
 - Drugs:
 - Oxymorphone:
 - Urine = Positive (30 ng/mL)
 - Other drugs present:
 - Urine:

■ Codeine	Cocaine
■ Morphine	Benzoylecgonine
■ 6-MAM	Ecgonine Methyl Ester

Future Work

- Comparing oxymorphone with its deuterated internal standard vs. oxycodone-D₃
- Lowering calibration curve and internal standard values to better reflect drug range
- Compile enough data to determine possible distribution patterns of oxymorphone in biological matrices

References

- 1. R.C. Baselt. *Disposition of Toxic Drugs and Chemicals in Man, Seventh Edition*. Biomedical Publications, Foster City, CA, 2004, pp 833-834.
- 2. Opana, Package Insert, <http://www.endo.com/>. February, 2008.
- 3. Opiates Direct Elisa Kit. Immunalysis Corporation. Ver: 06/2001. February, 2008.
- 4. Oxycodone Blood Direct Elisa Kit. Immunalysis Corporation. Ver: 01/2005. February, 2008.

Questions?

