

Opiates : Drug Metabolism and Disposition

James A. Bourland, Ph.D., D-ABFT
Alere Toxicology

This presentation was modified from its original format for 508 compliancy.

Opium Poppy

- Opiate
- Opioid

Model Opioid

- Morphine chemical structure
 - Modified from – Pain Physician 2008: Opioid Special Issue: 11

Morphine

- Schedule II
- 1804- Morphinum
- “Soldiers Disease”
- M_{μ} Agonist
- $t_{1/2} \sim 2$ h (1.3-6.7h)
- Metabolites
 - Normorphine
 - Mor-3- Glucuronide
 - *Mor-6-Glucuronide*

Morphine Biotransformation

- Morphine - Normorphine
- Morphine - glucuronide and sulfate conjugates
- Normorphine - glucuronide and sulfate conjugates

Morphine Minor Metabolite

- Morphine – (Morphinone) - Hydromorphone

Codeine

- Schedule II, III
- Weak Opioid Analgesic
- Pro-Drug –Analgesia
- $T_{1/2} \sim 3$ h (1.9-3.9h)
- CYP2D6
- Nursing Mothers –
- Metabolites
 - Morphine
 - Norcodeine
 - Conjugates

Codeine Biotransformation

- Codeine - Morphine – conjugation
- Codeine – Norcodeine – conjugation
- Codeine - conjugation

Codeine Minor Metabolism

- Codeine – (Codeinone) - Hydrocodone

Hydrocodone

- Lortab[®], Vicodin[®]
- Most Rx Opioid
- Schedule II,III
- Weak μ agonist
- Prodrug
- Metabolites
 - Hydromorphone
 - Norhydrocodone
 - Hydrocodol
 - Hydromorphol
 - Conjugates

Hydrocodone Biotransformation

- Hydrocodone – Norhydrocodone
- Hydrocodone – Hydromorphone – conjugation
- Hydrocodone – Hydromorphone – Hydromorphol – conjugation
- Hydrocodone – Hydrocodol - Hydromorphol – conjugation

Hydromorphone

- Dilaudid®
- Schedule II
- 7-11X Potency –MOR
- Highly H₂O Soluble
- t_{1/2} – 1.5-3.8h
- Onset 30min
- Duration 4 h
- Metabolites
 - Hydromorphol
 - Conjugation – HM3G

Hydromorphone Biotransformation

- Hydromorphone - Hydromorphol - conjugation
- Hydromorphone - conjugation

Oxycodone

- Oxycontin[®], Percocet[®]
- $t_{1/2}$ 4-6 h
- Schedule II
- High bioavailability p.o.
- CYP2D6
- Metabolites
 - Oxymorphone
 - Noroxycodone
 - Conjugates

Oxycodone Biotransformation

- Oxycodone – Oxymorphone – conjugation
- Oxycodone – conjugation
- Oxycodone - Noroxycodone

Oxymorphone

- Numorphan[®], Opana[®]
- High Affinity μ Receptor
- 10 X –Potency
- CYP 2D6/ 3A4
- Metabolites
 - 6-Oxymorphol
 - Conjugates

Oxymorphone Biotransformation

- Oxymorphone - 6-Oxymorphol - conjugation
- Oxymorphone - conjugation

Opiates : Interpretation Issues

We're not in Kansas anymore!

Opiates:
Minor Metabolites or Process
Impurities?

Opiates: Minor Metabolites

- Morphine – (Morphione) – Hydromorphone
- Codeine – (Codeinone) - Hydrocodone

Process Impurities?

Drug	Potential Process Impurities
Codeine	Morphine*
Hydrocodone	Codeine
Hydromorphone	Morphine, Hydrocodone
Morphine	Codeine
Oxycodone	Hydrocodone
Oxymorphone	Hydromorphone, Oxycodone

The United States Pharmacopeia

The National Formulary

By authority of the United States Pharmacopeial Convention
Prepared by the Council of Experts and its Expert
Committees

2011, USP 34, NF 29, Volume 3

Official from May 1, 2011

Oxycodone Hydrochloride Impurities

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Oxymorphone	0.31	0.15
Noroxymorphone	0.33	0.15
10-Hydroxyoxycodone	0.53	0.15
6-alpha-Oxycodol	0.67	0.25
7,8-Dihydro-8-beta-14-dihydroxycodone	0.71	0.15
Hydrocodone	1.19	0.15
Individual unspecified impurity	--	0.10

Opiates: Findings in Oral Fluid vs. Urine

Disposition of Oxycodone in Oral Fluid: Study Design

- 12 subjects
- Oxycontin (160 mg), every 12 hours
- Naltrexone (50 mg), every 24 hours
- Oral Fluid collected (Quantisal[®]) 6 hours post-dose time point after 3 and 4 days
- Analyzed by LC-MS/MS for Oxycodone, Oxymorphone and Noroxycodone
- A. Collins, J. Bourland and R. Backer. Disposition of oxycodone in oral fluid, *Society of Forensic Toxicologists: Program and Abstracts*, October 2009

Oxycodone, Oxymorphone and Noroxycodone in Oral Fluid in 12 Patients after 160 mg daily dose (day 4)

Drug	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	Mean
Oxycodone	350.6	318.8	327.9	623.7	172.2	255.5	192.7	635.4	369.7	635.5	439.9	332.6	358
Oxymorphone	1	0	0.7	3.1	3.2	0	1.2	4.3	5.6	1.7	9.4	3.4	2.5
Noroxycodone	65	80.9	105.3	105.6	92.9	168.7	83.4	227.5	105.5	143.6	75.4	107.9	113

- ng/mL
- A. Collins, J. Bourland and R. Backer. Disposition of oxycodone in oral fluid. *Society of Forensic Toxicologists: Program and Abstracts*, October 2009

Oxycodone in Plasma and Oral Fluid of Cancer Patients: Study Design

- 43 participants
- 139 paired plasma/saliva samples
- Oxycontin (5-300 mg),
- Oral Fluid collected (Salivette[®]) ;mean 3-4 hours post-dose range (15 min - 20 h)
- Analyzed by LC-MS/MS for Oxycodone, Oxymorphone and Noroxycodone

- J. Hardy, R. Norris, H. Anderson, A,O'Shea and B. Charles. Is saliva a valid substitute for plasma pharmacokinetic studies of oxycodone and its metabolites in patients with cancer? *Supportive Care Cancer*, Published Online: 15 April 2011

Oxycodone in Plasma and Oral Fluid of Cancer Patients: Conclusions

- Lack of correlation between plasma and oral fluid
- Oral Fluid Oxycodone : mean = 336 ng/mL range = 0.93-3620 ng/mL
- Oral Fluid Noroxycodone: mean = 91.4 ng/mL, range = 1.4-1980 ng/mL
- **No Oxymorphone In Oral Fluid Reported**
- J. Hardy, R. Norris, H. Anderson, A,O'Shea and B. Charles. Is saliva a valid substitute for plasma pharmacokinetic studies of oxycodone and its metabolites in patients with cancer?
Supportive Care Cancer, Published Online: 15 April 2011

Oral Fluid Positive Drug Prevalence Rates:

- Retrospective Study: 6441 pain patients
- ELISA screen & LC-MS/MS confirmation
- Drug and Metabolite Concentrations Recorded
- Number of specimens positive for specific drug or metabolites recorded
- Compares prevalence of opiate metabolites in oral fluid relative to parent drug
- Compares prevalence of opiate parent to metabolite percentages in oral fluid versus urine

- R. Heltsley, A. DePriest, D. Black, T. Robert, L. Marshall, V. Meadors, Y. Caplan and E. Cone. Oral fluid drug testing chronic pain patients. I. Positive prevalence rates of licit and illicit drugs. *J. Anal. Toxicol.* **35**: 529-540 (2011).

Opiate Drug and Metabolite Prevalence and Mean Concentrations in Oral Fluid of 6441 Pain Patients

Drug	Mean, ng/mL	N
Oxycodone	613.2	1847
Oxymorphone	24.7	1046
Noroxycodone	135.7	1952
Hydrocodone	178.4	1843
Hydromorphone	305.6	304
Norhydrocodone	23.3	1454
Codeine	127.4	136
Morphine	416.8	619
619Norcodeine	32.1	55

- R. Heltsley, A. DePriest, D. Black, T. Robert, L. Marshall, V. Meadors, Y. Caplan and E. Cone. Oral fluid drug testing chronic pain patients. I. Positive prevalence rates of licit and illicit drugs. *J. Anal. Toxicol.* **35**: 529-540 (2011).

Oxycodone, Oxymorphone and Noroxycodone mean concentrations in Oral Fluid specimens : 3 studies

Drug	Study 1	Study 2	Study 3
Oxycodone	388	336	613.2
Oxymorphone	2.5	0	24.7
Noroxycodone	113	91.4	135.7

- Study #1: Collins *et al.* N=12; Study #2: Hardy *et al.* N =139; Study #3 Hetsley *et al.* N= 2445

Relative Percentage of Parent and Metabolites of Oxycodone and Hydrocodone found in Oral Fluid (N= 6441) and Urine (N= 20,089) based on Median Concentrations

Drug	Oral Fluid	Urine
Oxycodone	69.7%	26.9%
Oxymorphone	2.4%	19.2%
Noroxycodone	27.9%	53.8%
Hydrocodone	83.8%	39.2%
Hydromorphone	3.3%	11.9%
Norhydrocodone	12.9%	49.0%

- R. Heltsley, A. DePriest, D. Black, T. Robert, L. Marshall, V. Meadors, Y. Caplan and E. Cone. Oral fluid drug testing chronic pain patients. I. Positive prevalence rates of licit and illicit drugs. *J. Anal. Toxicol.* **35**: 529-540 (2011).

Opiates: Urine vs. Oral Fluid

Parent	Urine metabolite	Oral Fluid metabolite
Oxycodone	Oxymorphone	Noroxycodone
Hydrocodone	Hydromorphone	Norhydrocodone
Codeine	Morphine	Norcodeine

Questions?