

Profiling Hydrocodone and Metabolites in Urine

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Publication/Presentation

- SOFT 2014 Poster
 - Prescription Opioid Abuse. II. Profiling Hydrocodone and Metabolites in Urine
 - C. P. LoDico*(presenter), R. R. Flegel, R. Heltsley, D. L.Black, J. M. Mitchell, and E. J. Cone
- JAT, Vol 37, October 2013
 - Prescription Opioids. II. Metabolism and Excretion Patterns of Hydrocodone in Urine Following Controlled Single Dose Administration.
 - E. J. Cone, R. Heltsley, D. L. Black, J. M. Mitchell, **C. P. LoDico**, and R. Flegel

Introduction to Study Design

- Hydrocodone (HC) and other semi-synthetic opioids have become commonly misused prescription drugs in the U.S. The combination product, HC with acetaminophen, is the most frequently prescribed opioid drug in the U.S., with more than 136 million prescriptions dispensed in 2011.
- Currently, HC is not tested in U.S. federal workplace programs, but there is considerable interest in adding it and other semi-synthetic opiate analgesics (i.e., hydromorphone, oxycodone, oxymorphone) to the test panel because of their widespread abuse and impairing effects.
- The objective of this study was to delineate the time course of HC and metabolites in human urine following controlled administration with a single 20 mg oral dose of HC bitartrate.

Primary Metabolites of Hydrocodone

- Hydrocodone metabolites
 - Norhydrocodone
 - Hydromorphone
 - Dihydrocodeine

Methods

- **Subjects:** 12 healthy adult volunteers who met the inclusion/exclusion criteria, provided informed consent, had not used opioids in the last 3 months and had not ingested food products containing poppy seeds within the last week.
- **Dosing:** A 20 mg dose of HC bitartrate (two Norco[®] tablets) with 240 mL of room-temperature water
- **Urine Collection:** Specimens were collected before dosing (baseline [BL]) and as pooled collections from each subject on 3 separate days post-dosing.
 - Collection times 0, 4, 8, 12, 16.....24, 28, 32, 36.....48, 52 h
 - **141** urine specimens were collected; 73 (52%) of these were single voids.

Methods (con't)

- **Analysis:** liquid chromatography/tandem mass spectrometry (LC–MSMS) for free (unconjugated) analyte and for total analyte following hydrolysis with β -glucuronidase.
- **Limit of quantitation (LOQ)** = 50 ng/mL
- **LC/MS/MS Analytes**

Hydrocodone (HC)	Noroxycodone
Hydromorphone (HM)	Noroxymorphone
Norhydrocodone (NHC)	Codeine
Dihydrocodeine (DHC)	Morphine
Oxycodone	Norcodeine
Oxymorphone	Normorphine

Results

- HC and NHC were initially detected in the majority of subjects' specimens within 2 hours of drug administration. HC was most frequently detected in combination with NHC.
- NHC was the most abundant metabolite and was often present in higher concentration than HC.
- Total HM and DHC generally became detectable in the 2-4 h collection period.
- HC and metabolites' concentrations peaked within 3-9 h post-dosing, then declined.

Mean Excretion of HC and Metabolites in Urine(Hydrolyzed)

- Mean excretion (ng/mL) versus collection period midpoints (h)

Hours	HC, ng/mL	HM, ng/mL	NHC, ng/mL	DHC, ng/mL
1	417	15	536	0
3	2016	391	2999	144
5	1102	280	1989	115
7	538	164	1211	76
9	395	127	1096	61
11	249	57	584	28
13	274	91	714	57
19	176	85	533	35
26	60	84	288	7
30	5	51	174	0
34	4	26	100	0
50	0	6	29	0

Mean Detection Time by Cutoff

- Analyte cutoff (ng/mL) vs. analyte mean detection time (h)

Cutoff, ng/mL	HC	HM	NHC	DHC
2000	2.8	--	4.5	--
1000	4.0	0.3	9.3	--
500	9.0	2.0	17.3	--
300	12.2	5.2	21.7	1.3
150	18.2	12.0	29.0	4.8
100	20.5	14.3	33.0	7.3
50	27.7	25.5	39.7	16.3

Cutoff Evaluation by Total Analyte(s)

- Analyte cutoff (ng/mL) vs. number of specimens greater than or equal to the cutoff (n)

Cutoff, ng/mL	HC	HM	NHC	DHC	HC/HM	HC/HM/ NHC
50	100	82	126	51	108	126
100	82	43	109	23	88	109
150	74	35	99	13	77	99
300	53	17	82	4	54	82
500	37	8	67	0	37	67
1000	15	1	33	0	15	33
2000	9	0	17	0	9	17

Conclusion

- Hydrolyzed versus non-hydrolyzed results indicated that HC, NHC, and DHC were excreted nearly completely in the unconjugated form, and HM was excreted primarily in the conjugated form.
- Detection times for HC and metabolites were less than 5 h using a 2000 ng/mL cutoff concentration. Use of a 50 ng/mL cutoff concentration extended detection time for HC to approximately 28 h.
- Overall, these data suggest that drug testing requirements for HC should include tests for HC and HM in hydrolyzed urine.
- Some consideration should also be given to allowing testing for NHC as a routine confirmatory test analyte or, alternately, as a special test to assist in results interpretation (i.e., to distinguish HC from HM use).