New Concerns for an “Old” Drug? Dihydrocodeine: Two Fatalities in Northeast Ohio.

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Abstract

Introduction: Dihydrocodeine (6-alpha-hydrocodol, DHC) is an opioid agonist, prescribed for moderate to severe pain. In European countries DHC has been used to treat opioid addiction in place of methadone or buprenorphine. In the US, DHC is formulated with caffeine and acetaminophen (APAP) or aspirin (i.e. Synalgos®, Panlor®), but is not available as an isolated drug. Until recently, detection of DHC at The Cuyahoga County Medical Examiner’s Office (CCMEO) has only been attributed to hydrocodone (HC) metabolism. This study describes two cases of DHC toxicity which are not consistent with HC exposure.

Case Histories:
Case #1: A 51 year-old male, reported as a sudden death at home, with a previous stroke history and prescriptions for Nucynta® (Tapentadol) and morphine for chronic pain, and also medications for hypertension and depression.
Case #2: A 56 year-old male, found deceased at home on the bathroom floor. He was known to abuse prescription pills.

Objective: To inform toxicologists of two recent deaths related to possible DHC intoxications, and the need to include this analyte in opiate procedures.

Materials/Methods: Specimens collected at autopsy were kept refrigerated until analyzed. Blood samples were screened using ELISA (Immunalysis® Opiates Direct Kit 207-480). Extraction of DHC was by solid phase extraction (UCT Clean Screen® ZSDAU020) followed by derivatization with MSTFA (UCT). Analytes were separated, detected and quantified using an Agilent GC/EI-MS in the SIM mode with a Restek Rxi®-5ms, 30 m X 0.25 mm i.d., 0.25 µm film thickness, analytical column. Toxicological analyses were also performed by outside reference laboratories for drugs other than DHC.

Results:

Table 1. Concentration of DHC detected in specimens from two postmortem cases.

Case	Heart Blood (ng/mL)	Femoral Blood (ng/mL)	Liver (ng/g)	Vitreous Humor (ng/mL)	Urine (qualitative)	Bile (qualitative)
Case #1	238	277	448	270	Positive	Positive
Case #2	1951	1160	1824	1454	Positive	Positive

Additional Toxicology:
Case #1: Femoral blood contained 1447 ng/mL codeine, 125 ng/mL morphine, 32 ng/mL hydrocodone*, 18 ng/mL cyclobenzaprine*, 1500 ng/mL citalopram*, 96 ng/mL bupropion*, 740 ng/mL hydroxybupropion*, 350 ng/mL tapentadol**, 33 ng/mL gabapentin**, 507 ng/mL atenolol**, 110 ng/mL hydrochlorothiazide**, 45 mg/L APAP and caffeine positive.

Case #2: Femoral blood contained 12 ng/mL hydrocodone, 80 ng/mL alprazolam and bromazepam positive**.
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Discussion/Conclusion: Prior to these cases, DHC has been detected in many cases at CCMEO, but only in conjunction with HC. Although both of these cases contain HC, the ratio of DHC to HC is not consistent with HC usage. DHC:HC ratios resulting from HC exposure are typically < 0.5. The ratio of DHC to HC in femoral blood for these two cases was 8.6 and 96.6, respectively. A five year retrospective analysis of a CCMEO database revealed 75 cases in which the average femoral blood DHC:HC ratio was 0.26 ± 0.23. Similar results were found by Franklin County Coroner’s Office, Columbus, Ohio, with an average femoral DHC:HC ratio of 0.32 ±0.19 from 14 cases during the past three years. In no cases previously observed was the DHC:HC ratio > 2. DHC was considered to be a contributing factor of death in both cases presented in this study. Previous reports indicate DHC intoxications are fatal at concentrations ranging from 1900 ng/mL-12,000 ng/mL. Detection of caffeine and APAP in Case #1 supports the possibility that the decedent had been prescribed DHC in the US (although case history does not include a prescription). A pill slurry collected from the gastric contents of Case #2 tested positive for DHC with no HC; absence of any other analytes suggests the DHC consumed may have been purchased outside of the US or over the Internet. The observation of two fatalities at CCMEO in which DHC seemingly played a role in cause of death demonstrates the need for laboratories to include DHC in their opiate procedures.

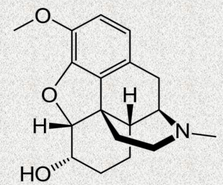
Keywords: Dihydrocodeine, Opiates, Postmortem, United States

Objective

The objective of this poster is to inform toxicologists of two recent deaths related to possible DHC intoxications, and to encourage laboratories to include this analyte in opiate procedures.

Introduction

- Dihydrocodeine (6-α-hydrocodol, DHC) is a semi-synthetic opioid agonist, prescribed for moderate to severe pain.
- DHC was first prepared in 1920 by the hydrogenation of codeine[1-3].



Dihydrocodeine

- In some European countries (i.e. United Kingdom, Germany) DHC has been used to treat opioid addiction in place of methadone or buprenorphine, although its effectiveness for this purpose is controversial[2,4,5].
- In the United States, DHC is a schedule II substance[2] and is formulated with caffeine and acetaminophen (APAP) or aspirin[6] (i.e. Synalgos®, Panlor®), but is not available as an isolated drug.
- Metabolism of DHC is similar in nature to that of codeine: O-demethylation to dihydromorphine, N-demethylation to nordihydrocodeine and nordihydromorphine and conjugation of parent drug with glucuronic acid[7].
- Presence of DHC may be detected after use of DHC containing medications or as a product of hydrocodone (HC)[3,8,9] or codeine metabolism[8].
- The 6-keto-reduction of HC results in the formation of both stereoisomers 6-α-hydrocodol (DHC) and 6-β-hydrocodol[9].

Case Histories

Case #1:

- 51 year-old, single, white male, reported as a sudden death at home, with a previous stroke history and prescriptions for Nucynta® (Tapentadol) and morphine for chronic pain, and also medications for hypertension and depression.
- A monthly pill organizer was found on scene containing the following tablets/capsules (number present indicated by parentheses): 75 mg Nucynta® (12), 60 mg Morphine Sulfate (12), 4 mg Tizanidine (30), 300 mg Gabapentin (55), 20 mg Citalopram (8), 150 mg Bupropion (8), 5 mg Warfarin (3), 80 mg Atorvastatin (4), 10 mg/25 mg Lisinopril/Hydrochlorothiazide (4), 50 mg Atenolol (4), 160 mg Fenofibrate (4), 81 mg Aspirin (4), 40 mg Omeprazole (5), 100 mg Docusate (18), 20 mg Senokot® (5) and 16 miscellaneous vitamins.

Case #2:

- 56 year-old, single, white male, with a history of depression and prescription pill abuse (Valium®) was found deceased at home on the bathroom floor.

Methods

- Heart blood, femoral blood, liver, vitreous humor, urine and bile specimens were collected at autopsy and kept refrigerated until analyzed.
- Femoral blood samples were screened using ELISA (Immunalysis® Opiates Direct Kit 207-480).
- Extraction of DHC was achieved by solid phase extraction (UCT Clean Screen® ZSDAU020) followed by derivatization with MSTFA (UCT).
- DHC was separated, detected and quantified using an Agilent GC/EI-MS in the SIM mode with a Restek Rxi®-5ms, 30 m X 0.25 mm i.d., 0.25 µm film thickness, analytical column.
- Full toxicological analyses were performed on both cases at CCMEO.
- Additional toxicological analyses were performed by outside reference laboratories (AIT Laboratories, NMS Labs) for quantification of a number of miscellaneous drugs.
- Retrospective analysis was performed on a CCMEO database and a similar database used by the Franklin County Coroner’s Office to reveal all cases containing both DHC and HC.
- The CCMEO and Franklin County databases provided information from January 1, 2009-July 23, 2013 and January 1, 2011-July 23, 2013, respectively.
- Calculations were performed to determine the average DHC:HC ratio in cases where HC was consumed.

Results

CASE #1

Cause of Death: Mixed drug intoxication
Manner of Death: Accidental

DHC Results:
Heart Blood: 238 ng/mL; Femoral Blood: 277 ng/mL; Vitreous Humor: 270 ng/mL; Liver: 448 ng/g; Urine: Positive; Bile: Positive

Femoral DHC:HC ratio = 8.6

Additional Toxicology Findings in the Femoral Blood:
32 ng/mL hydrocodone*
1447 ng/mL codeine
125 ng/mL morphine
18 ng/mL cyclobenzaprine*
1500 ng/mL citalopram*
96 ng/mL bupropion*
740 ng/mL hydroxybupropion*
350 ng/mL tapentadol**
33 ng/mL gabapentin**
507 ng/mL atenolol**
110 ng/mL hydrochlorothiazide**
45 mg/L APAP
caffeine positive

*NMS Labs, **AIT Laboratories

CASE #2

Cause of Death: Acute intoxication by the combined effects of dihydrocodeine and hydrocodone
Manner of Death: Undetermined

DHC Results:
Heart Blood: 1951 ng/mL; Femoral Blood: 1160 ng/mL; Vitreous Humor: 1454 ng/mL; Liver: 1824 ng/g; Urine: Positive; Bile: Positive

Femoral DHC:HC ratio = 96.6

Additional Toxicology Findings in the Femoral Blood:
12 ng/mL hydrocodone
80 ng/mL alprazolam
bromazepam positive**

*NMS Labs, **AIT Laboratories

Results

Table 2. Concentration of hydrocodone and dihydrocodeine in 75 postmortem femoral samples obtained from a five-year retrospective analysis of a CCMEO database, ratio of dihydrocodeine to hydrocodone was also calculated.

Case #	HC Conc. (ng/mL)	DHC Conc. (ng/mL)	DHC:HC Ratio	Case #	HC Conc. (ng/mL)	DHC Conc. (ng/mL)	DHC:HC Ratio
1	436	108	0.25	39	113	39	0.35
2	45	10	0.22	40	127	14	0.11
3	415	85	0.20	41	364	54	0.15
4	167	22	0.13	42	23	10	0.43
5	124	23	0.19	43	23	13	0.57
6	18	22	1.22	44	178	32	0.18
7	393	57	0.15	45	212	14	0.07
8	65	11	0.17	46	84	14	0.17
9	125	19	0.15	47	208	12	0.06
10	300	34	0.11	48	681	60	0.09
11	172	41	0.24	49	285	24	0.08
12	124	16	0.13	50	55	14	0.25
13	49	12	0.24	51	319	36	0.11
14	76	11	0.14	52	494	32	0.06
15	79	17	0.22	53	117	15	0.13
16	40	15	0.38	54	64	22	0.34
17	44	12	0.27	55	42	11	0.26
18	82	24	0.29	56	64	21	0.33
19	466	87	0.19	57	97	11	0.11
20	208	20	0.10	58	17	12	0.71
21	93	11	0.12	59	150	54	0.36
22	223	49	0.22	60	70	13	0.19
23	84	18	0.21	61	108	21	0.19
24	1102	134	0.12	62	510	39	0.08
25	150	35	0.23	63	74	19	0.26
26	23	22	0.96	64	98	16	0.16
27	102	11	0.11	65	19	28	1.47
28	50	10	0.20	66	75	17	0.23
29	77	19	0.25	67	328	45	0.14
30	42	19	0.45	68	54	10	0.19
31	94	22	0.23	69	554	66	0.12
32	37	14	0.38	70	38	11	0.29
33	222	58	0.26	71	136	28	0.21
34	253	23	0.09	72	30	12	0.40
35	27	11	0.41	73	80	14	0.18
36	168	35	0.21	74	149	16	0.11
37	221	18	0.08	75	799	164	0.21
38	51	16	0.31		Avg. Ratio: 0.26	Ratio SD:0.23	

Green highlighted cells indicate a DHC:HC ratio of ≥ 0.5; SD = Standard Deviation

Table 3. Concentration of hydrocodone and dihydrocodeine in 14 postmortem femoral samples obtained from a three-year retrospective analysis of a Franklin County (Ohio) Coroner’s Office database, ratio of dihydrocodeine to hydrocodone was also calculated.

Case #	HC Conc. (ng/mL)	DHC Conc. (ng/mL)	DHC:HC Ratio	Case #	HC Conc. (ng/mL)	DHC Conc. (ng/mL)	DHC:HC Ratio
1	59	29	0.49	8	56	42	0.75
2	68	20	0.29	9	332	38	0.11
3	196	38	0.19	10	181	68	0.38
4	290	60	0.21	11	41	24	0.59
5	39	19	0.49	12	250	56	0.22
6	86	23	0.27	13	159	36	0.23
7	228	40	0.18	14	280	38	0.14
					Avg. Ratio: 0.32	Ratio SD: 0.19	

Green highlighted cells indicate a DHC:HC ratio of ≥ 0.5; SD = Standard Deviation

Discussion / Conclusion

- Previous studies reported fatal blood DHC concentrations ranging from 1900 ng/mL-12,000 ng/mL[3,5,10].
  - In **Case #1**, the femoral DHC concentration of 277 ng/mL in conjunction with the numerous other medications (in particular the codeine) contributed to the cause of death.
  - **Case #2** contained 1160 ng/mL DHC in the femoral blood, which appeared to have been a lethal dose when paired with the benzodiazepines present.

Discussion / Conclusion

Where is the DHC *really* coming from?

- **Ingestion of DHC containing drug?**
  - **Case #1** contained DHC, APAP and caffeine; this combination of drugs is commonly found in the DHC formulations prescribed in the United States[6], and may indicate the decedent consumed a DHC containing drug.
  - **Case #2** gastric contents contained a pill slurry from which an aliquot was diluted with methanol and injected onto a GC/MS. The slurry was found to contain DHC only, supporting the theory that this individual did in fact consume a DHC containing drug, and that it was not a formulation prescribed in the US. Further investigation indicated the decedent was known to purchase medications over the Internet.
- **HC Metabolism?**
  - In the past, DHC has been detected in many CCMEO cases, but always in conjunction with HC. An earlier study reported a DHC:HC range of 0.0-2.9 for 47 cases specifically involving HC exposure[11].
  - The data in **Tables 2 & 3** (from cases where HC was presumed to have been consumed) indicate an average femoral blood DHC:HC ratio of 0.26 ± 0.23 for the CCMEO cases and 0.32 ± 0.19 from the Franklin County cases.
  - No cases examined in this retrospective study exhibited a DHC:HC ratio > 2.0.
  - The DHC:HC ratios of the two cases presented in this study **(Case #1 = 8.6, Case #2 = 96.6)** are *not* consistent with the DHC:HC ratios seen in cases involving HC usage.
  - Although the possibility exists that these two individuals may metabolize HC differently than the general population, the facts surrounding the two cases do not support this scenario.
  - It is also worth mentioning that HC is a known minor metabolite of DHC[3,7,8], which may explain the presence of HC in these cases.
- **Codeine Metabolism?**
  - It has been reported that both HC[9] and DHC are minor metabolites of codeine[8].
  - It is plausible based on the large concentration of codeine in **Case #1** that the DHC and HC detected in the case are due to codeine metabolism.
  - No codeine was present in **Case #2** and therefore is not a viable explanation for the presence of DHC.
- **Final Thoughts:**
  - It is important to test for DHC in an opiate procedure because the drug is a prescription narcotic analgesic that is easily abused, can be purchased over the Internet and is also detected as an active metabolite of both HC and codeine.

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