A Bibliography of the Forensic Opioid Literature
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Postmortem Changes in Opioid Concentrations – Opioid Necrokinetics

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INTRODUCTION

Laboratory measurements of drug concentrations in blood and tissue samples collected at autopsy are commonly used to determine what role, if any, the drug may have played in causing death. The accurate interpretation of these test results requires an understanding of:

- How and where the sample was collected and stored.
- The analytical methods used and their limitations.
- The relationship between the opioid concentration at the time of death and the concentration in the sample collected for measurement.

The concentrations of many drugs in blood and other tissues either increase or decrease after death occurs. This is important information to be aware of and consider when interpreting postmortem opioid concentrations.

The intent of this bibliography is to provide an up-to-date, comprehensive reference list of literature that should be considered when interpreting postmortem opioid concentrations. It consists of the journal article reference in a standard format followed by a brief annotation summarizing the purpose, methods and results. The primary citations are cross-indexed in the next section by drug, whether the drug was determined to be either the cause of death or contributed to death, whether there were multiple drugs detected, and whether the reports involve animals or humans.

New references will be added go this bibliography as they become available.

Send comments or questions to WatsonW@uthscsa.edu

Opioid Necrokinetics References – July 2001

1. Aderjan R, Hofmann S, Schmitt G, Skopp G. Morphine and morphine glucuronides in serum of heroin consumers and in heroin-related deaths determined by HPLC with native fluorescence detection. J Anal Toxicol 1995;19(3):163-8.

   Purpose: determine morphine glucuronide and morphine concentrations after heroin use in forensic cases. HPLC with fluorescence detection methodology. Patient samples (blood) included 10 fatalities after heroin injection and one oncology patient who died following oral morphine treatment.

2. Anderson DT, Muto JJ. Duragesic®transdermal patch: postmortem tissue distribution of fentanyl in 25 cases. J Anal Toxicol 2000;24(7):627-34.

   Purpose: describe fentanyl concentrations associated with transdermal patch use in series of 25 deaths over 3 years. GC-MS with selective ion monitoring methodology. Patient samples were collected 24 to 72 hours after notification of death and included heart and peripheral blood as well as tissues. Three cases were attributed solely to fentanyl.

3. Beike J, Kohler H, Blaschke G. Antibody-mediated clean-up of blood for simultaneous HPLC determination of morphine and morphine glucuronides. Int J Legal Med 1997;110(4):226-9.

   Purpose: describe method of sample preparation prior to analysis of blood samples for morphine and glucuronides metabolites. HPLC with fluorescence detection methodology. Patient samples (coronary blood) were from 7 patients with heroin related-deaths.

4. Bogusz MJ. Postmortem distribution pattern of morphine and morphine glucuronides in heroin overdose (response to Skopp G et al.: Int J Legal Med (1996) 109:118-124.) Int J Legal Med. 1997;110(2):114-6.

   Purpose: describe the post-mortem distribution of morphine and metabolites. GC-MS with chemical ionization. Patient samples (peripheral and central blood, CSF, vitreous) were collected from 2 cases with evidence of IV heroin abuse.

5. Bourel B, Hedouin V, Martin-Boyer L, Becart A, Tournel G, Deveaux M, Gosset D. Effects of morphine in decomposing bodies on the development of Lucilia sericata (Diptera: Calliphoridae). J Forensic Sci 1999;44(2):354-8.

   Purpose: determine the effect of morphine in decomposing animal bodies on the development of Lucilia sericata (calliphorid fly). 4 rabbits (1 control) were administered morphine HCl and sacrificed. RIA analysis. Concentrations of morphine in central blood and tissue were determined after sacrifice.

6. Cook DS, Braithwaite RA, Hale KA. Estimating antemortem drug concentrations from postmortem blood samples: the influence of postmortem redistribution. J Clin Pathol 2000;53(4):282-5.

   Purpose: compare antemortem blood drug concentrations with postmortem concentrations at peripheral and central blood vessel sites in 6 cases. Analytical methods not described. Opioid cases include methadone and dextropropoxyphene ingestions. Concentrations of methadone and dextropropoxyphene were measured in hemolyzed femoral blood samples, and central/peripheral ratios obtained from the published literature.

7. Druid H, Holmgren P. A compilation of fatal and control concentrations of drugs in postmortem femoral blood. J Forensic Sci 1997;42(1):79-87.

   Purpose: compile a list of postmortem drug concentrations from cases with standardized sampling and analytical methods, grouping results based on role of substance in causing death. HPLC and GC methods were used. Femoral samples were collected with visual isolation of femoral and popliteal veins. 5 opioids were reported in sample sizes ranging from 122 to 415.

8. Drummer OH, Syrjanen ML, Phelan M, Cordner SM. A study of deaths involving oxycodone. J Forensic Sci 1994;39(4):1069-75.

   Purpose: describe detailed account of deaths in which oxycodone was a significant contributory factor. GC-MS with selected ion monitoring was used. Femoral blood was collected from 9 cases that had from 1 to 5 additional drugs present.

9. Ferslew KE, Hagardorn AN, McCormick, WF. Postmortem determination of the biological distribution of sufentanil and midazolam after an acute intoxication. J Forensic Sci 1989;34(1):249-57.

Purpose: case report of death secondary to self-injection of sufentanil and midazolam. GC-MS with electron ionization and HPLC with UV detection methods were used. Cardiac blood was collected along with urine, liver and kidney tissue; time postmortem was not reported.

10. Garriott JC. Skeletal muscle as an alternative specimen for alcohol and drug analysis. J Forensic Sci 1991;36(1):60-9.

Purpose: provide drug and alcohol concentrations in skeletal muscle, and compare to postmortem blood concentrations. GC and GC-MS methods were used. Aorta blood, vitreous humor, and thigh muscle was collected and opioids quantitated in 18 cases; time postmortem was not reported.

11. Gerostamoulos J, Drummer OH. Postmortem redistribution of morphine and its metabolites. J Forensic Sci 2000;45(4):843-5.

Purpose: assess the postmortem redistribution of morphine and metabolites in heroin-related deaths. HPLC with dual UV and ECD method was used to measure morphine, glucuronide metabolites, and normorphine. Femoral, subclavian, and heart blood samples were collected when the body was admitted to the mortuary and a second sample an average of 59 hrs later at autopsy.

12. Goeringer KE, Logan BK, Christian GD. Identification of tramadol and its metabolites in blood from drug-related deaths and drug-impaired drivers. J Anal Toxicol 1997;21(7):529-37.

Purpose: report GC-MS analytical method for tramadol and metabolites and its application to cases of suspected drug-related deaths and drug-impaired driving cases. Results in 12 drug-related deaths were described, with tramadol and metabolite concentrations in unreported biological fluids.

13. Hedouin V, Bourel B, Martin-Bouyer L, Becart A, Tournel G, Deveaux M, Gosset D. Determination of drug levels in larvae of Lucilia sericata (Diptera: Calliphoridae) reared on rabbit carcasses containing morphine. J Forensic Sci 1999;44(2):351-3.

Purpose: measure the morphine concentrations in fly larvae raised on rabbits that received different doses of morphine, and compare fly larvae and rabbit tissue morphine concentrations. RIA method used. Morphine was administered intravenously to 3 rabbits prior to sacrifice. Samples were collected from the rabbit immediately postmortem, and fly larvae collected at times up to 447 hours after egg placement.

14. Hedouin V, Bourel B, Martin-Boyer L, Becart A, Tournel G, Deveaux M, Gosset D. Morphine perfused rabbits: a tool for experiments in forensic entomotoxicology. J Forensic Sci 1999;44(2):347-50.

Purpose: describe morphine kinetics in rabbits that received either single intravenous injections or continuous infusions. RIA method used. 9 rabbits were administered morphine and blood and tissues collected over a 3-hour period postmortem.

15. Hilberg T, Ripel A, Slordal L, Bjorneboe A, Morland J. The extent of postmortem drug redistribution in a rat model. J Forensic Sci 1999;44(5):956-62.

Purpose: describe the postmortem redistribution of drugs compared to their pharmacokinetics and pKa using nortriptyline as a control administered to every rat. Gas chromatography, high performance liquid chromatography, and GC-MS methods were used. 50 rats were administered nortriptyline in addition to 1 of 9 other drugs, with 6 rats receiving codeine. Central and peripheral blood samples and tissues obtained at time of death and 2 hours postmortem.

16. Jitsufuchi N, Kudo K, Imamura T, Kimura K, Ikeda N. Distribution of drugs in various tissues in a brain dead man. Forensic Sci Int 1997;90(1-2):103-9.

Purpose: describe the distribution of local anesthetics, barbiturates, and pentazocine to evaluate the time and progression of brain death in one patient. GC-MS methods were used. Blood and tissue samples were collected 15 hours postmortem

17. Jones GR, Pounder DJ. Site dependence of drug concentrations in postmortem blood – a case study. J Anal Toxicol 1987;11(5):186-90.

Purpose: describe the site dependence of imipramine, acetaminophen, codeine, diphenhydramine and ethanol concentrations in one patient. GC, HPLC, and GC-MS methods were used. Samples were collected 12 hours after death from 10 venous and arterial sites, 34 tissue sites, CSF, vitreous, and bile.

18. Koren G, Klein J. Postmortem redistribution of morphine in rats. Ther Drug Monit. 1992;14(6):461-3.
Purpose: determine whether passive redistribution of morphine occurs postmortem. RIA method used. Cardiac blood samples were collected in 10 rats immediately after sacrifice, 24 hrs and 96 hrs postmortem.

19. Li L. [Detection on morphine concentration changes of postmortem cardiac blood in rats by HPLC]. Fa Yi Xue Za Zhi 1997;13(2):65-7, 76, 128. Chinese.
(From English Abstract). Purpose: determine whether the dose of morphine administered impacted postmortem redistribution. HPLC method used. Rats were administered therapeutic or toxic dose of morphine, and cardiac blood concentrations measured up to 96 hours postmortem.

20. Logan BK, Smirnow D. Postmortem distribution and redistribution of morphine in man. J Forensic Sci 1996;41(2):221-9.
Purpose: evaluate site and time dependent changes in postmortem morphine concentrations. RIA method used. Samples of left ventricular and femoral blood, and CSF were collected at first contact with the body and again at autopsy in 48 cases, including 32 morphine related deaths.

21. McIntyre LM, King CV, Boratto M, Drummer OH. Post-mortem drug analyses in bone and bone marrow. Ther Drug Monit 2000;22(1):79-83.
Purpose: determine drug concentrations in bone and bone marrow collected postmortem. HPLC and GC-MS methods were used. Opioids were detected in both bone and bone marrow. The report did not report correlate bone concentrations to those in blood.

22. Missliwetz J, Vycudilik W. Homicide by strangling or dumping with postmortem injuries after heroin poisoning? Am J Forensic Med Pathol 1997;18(2):211-4.
Purpose: describe a case of morphine detection in a corpse that was approximately 2 years postmortem. GC-MS methods were used. Brain and liver tissue was analyzed, and the death attributed to heroin

23. Moriya F, Hashimoto Y. Distribution of free and conjugated morphine in body fluids and tissues in a fatal heroin overdose: is conjugated morphine stable in postmortem specimens? J Forensic Sci 1997;42(4):736-40.
Purpose: describe the distribution and stability of morphine and the metabolites in a case that died after heroin and methamphetamine injection. Immunoassay screening and GC-MS methods were used. Stability of morphine in blood, urine, CSF, and tissues was determined over 10 days after collection at different storage temperatures.

24. Moriya F, Hashimoto Y. Redistribution of basic drugs into cardiac blood from surrounding tissues during early-stages postmortem. J Forensic Sci 1999;44(1):10-6.
Purpose: describe redistribution of basic drugs (morphine, methamphetamine, amitriptyline, nortriptyline and promethazine) into cardiac blood by comparing data from human autopsy cases to data obtained from animal experiments. GC and GC-MS methods were used. Blood samples were collected from various vessels and cardiac chambers and tissues. In rabbit model sample was collected 6 hr postmortem.

25. Paul D, Gauthier CA, Minor LD, Gonzales GR. The effects of postmortem delay on mu, delta and kappa opioid receptor subtypes in rat brain and guinea pig cerebellum evaluated by radioligand receptor binding. Life Sci 1997;61(20):1993-8.
Purpose: describe the rate that opioid receptor subtypes degrade postmortem. Radioligand binding methods were used to determine changes in binding to opioid receptors. Tissue from rats and guinea pigs were used after storage at different temperatures.

26. Pounder DJ, Yonemitsu K. Postmortem absorption of drugs and ethanol from aspirated vomitus--an experimental model. Forensic Sci Int 1991;51(2):189-95.

Purpose: determine using a human cadaver model whether drugs (ethanol, dextropropoxyphene, paracetamol) in gastric material present in the airways postmortem would result in diffusion of drugs into blood. GC and HPLC methods were used. Samples were collected from various blood vessels 48 hr postmortem.

27. Pounder DJ, Adams E, Fuke C, Langford AM. Site to site variability of postmortem drug concentrations in liver and lung. J Forensic Sci 1996;41(6):927-32.

    Purpose: determine whether postmortem diffusion of drugs into liver and lung occurred in 8 cases of suicide. Drugs involved in deaths included benzodiazepines, cyclizine, tricyclic antidepressants, propoxyphene, paracetamol (acetaminophen), and SSRI antidepressants. GC-MS and HPLC methods were used. Samples were collected from various blood vessels, tissues, vitreous humor, bile, and urine.

28. Prouty RW, Anderson WH. The forensic science implications of site and temporal influences on postmortem blood-drug concentrations. J Forensic Sci 1990;35(2):243-70.

    Purpose: describe the dependence of postmortem drug-concentrations on the collection site and postmortem time interval before sample collection. Samples were collected both by local and regional medical examiners at initial evaluation and autopsy. Opioids evaluated are propoxyphene and metabolite, meperidine, codeine, methadone, morphine, and pentazocine. GC and HPLC methods were used. Samples were collected from both heart blood and peripheral blood vessels at various times postmortem.

29. Scott KS, Oliver JS. Vitreous humor as an alternative sample to blood for the supercritical fluid extraction of morphine and 6-monoacetylmorphine. Med Sci Law 1999;39(1):77-81.

    Purpose: compare vitreous humor and blood concentrations of morphine and 6-monoacetylmorphine concentrations in postmortem samples using supercritical fluid extraction. GC-MS method was used. Samples of vitreous humor and blood (site not identified) were collected in 20 cases involving heroin abuse.

30. Sawyer WR, Forney RB. Postmortem disposition of morphine in rats. Forensic Sci Int 1988;38(3-4):259-73.

    Purpose: determine the antemortem and postmortem distribution of morphine in a rat model. HPLC method was used. Morphine (5mg/kg) was administered intravenously and samples collected from orbital sinus and cardiac blood and various tissues at different times up to 96 hr postmortem.

31. Skopp G, Lutz R, Ganssmann B, Mattern R, Aderjan R. Postmortem distribution pattern of morphine and morphine glucuronides in heroin overdose. Int J Legal Med 1996;109(3):118-24.

    Purpose: determine the postmortem distribution of morphine and metabolites in 4 cases of heroin overdose. HPLC method was used. Blood samples from various vessels and vitreous humor were collected.

32. Skopp G, Lutz R, Potsch L, Ganssmann B, Klinder K, Schmidt A, Aderjan R, Mattern R. An in vitro experiment for postmortem vascular permeation. The passage of morphine and morphine glucuronides across a vascular wall. J Forensic Sci 1997;42(3):486-91.

    Purpose: use an in vitro model of vascular permeation across vascular wall to evaluate the postmortem movement of morphine and metabolites. HPLC method was used. Drug adsorption to and penetration into vascular tissue, and diffusion across vascular walls were all demonstrated as potential mechanisms of changes in postmortem blood drug concentrations.

33. Skopp G, Klinder K, Potsch L, Zimmer G, Lutz R, Aderjan R, Mattern R. Postmortem distribution of dihydrocodeine and metabolites in a fatal case of dihydrocodeine intoxication. Forensic Sci Int 1998;95(2):99-107.

    Purpose: describe the postmortem distribution of dihydrocodeine and metabolites after fatal dihydrocodeine ingestion. HPLC and GC-MS methods were used. Blood was collected from various central and peripheral venous sites as well as brain, liver, kidney, and hair.

34. Xu Z. [Postmortem distribution of morphine in rats.] Fa Yi Xue Za Zhi 1997;13(2):71-2, 74, 128. Chinese.

    Not available

35. Yonemitsu K, Pounder DJ. Postmortem toxico-kinetics of co-proxamol. Int J Legal Med 1992;104(6):347-53.

Purpose: describe four cases of fatality involving dextropropoxyphene and acetaminophen to evaluate postmortem drug redistribution. GC methods were used. Samples were collected from various peripheral blood vessels and tissues at autopsy, and again at least 24 hr later in two cases.

36. Xu Z, Wu J, Wang B, Wang W. [Distribution of morphine in acute morphine-treated rats]. Hua Xi Yi Ke Da Xue Xue Bao. 1998 Mar;29(1):29-32. Chinese.

English abstract only. Purpose: immunohistochemistry (PSP) methods are used to develop a model of morphine distribution in rat after acute dosing. Samples of various tissues were collected 10 to 160 min after administration.

INDEX OF SELECTED TOPICS BY REFERENCE NUMBER

Opioid involved:

codeine – 2, 7, 12, 15, 28
dextromethorphan – 2, 28
dextropropoxyphene – 2, 6, 7, 10, 12, 21, 26, 27, 28, 35
dihydrocodeine – 33
fentanyl – 2
heroin – 1, 3, 4, 11, 22, 23, 29, 31
hydrocodone – 2, 12
meperidine (pethidine) – 2, 7, 10, 28
methadone – 6, 7, 21, 28
morphine – 5, 10, 12, 13, 14, 18, 19, 20, 24, 32, 34, 36
oxycodone – 7, 21
pentazocine – 16, 28
sufentanil – 9
tramadol – 2, 12

Drug caused/contributed to death:

codeine – 7, 10, 17
dextropropoxyphene – 7, 10
dihydrocodeine – 33
fentanyl – 2
heroin – 1, 3, 4, 11, 22, 23, 29, 31
meperidine (pethidine) – 7, 8
methadone – 7
morphine – 10, 20
oxycodone –8
sufentanil – 9
tramadol – 12

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urine – 2, 7, 8, 9, 17, 23, 24, 27
vitreous humor – 2, 4, 7, 9, 10, 15, 27, 28, 29, 30, 31

Timing of Samples

antemortem/perimortem: 6, 15, 18, 24, 30, 34
postmortem, serial: 11, 20, 25, 26, 28, 34, 35, 36

Necrokinetics Reviews and Modeling, Selected Citations

A. Hilberg T, Bugge A, Beylich KM, Morland J, Bjorneboe A. Diffusion as a mechanism of postmortem drug redistribution: an experimental study in rats. Int J Legal Med 1992;105(2): 87-91.
B. Hilberg T, Bugge A, Beylich KM, Ingum J, Bjorneboe A, Morland J. An animal model of postmortem amitriptyline redistribution. J Forensic Sci 1993;38(1):81-90.
C. Hilberg T, Morland J, Bjorneboe A. Postmortem release of amitriptyline from the lungs; a mechanism of postmortem drug redistribution. Forensic Sci Int 1994;64(1):47-55.
D. Hilberg T, Ripel A, Smith AJ, Slordal L, Morland J, Bjorneboe A. Postmortem amitriptyline pharmacokinetics in pigs after oral and intravenous routes of administration. J Forensic Sci 1998;43(2):380-7.
E. Hilberg T, Rogde S, Morland J. Postmortem drug redistribution – human cases related to results in experimental animals. J Forensic Sci 1999;44(1):3-9.
F. Moriya F, Hashimoto Y. Redistribution of basic drugs into cardiac blood from surrounding tissues during early-stages postmortem. J Forensic Sci 1999;44(1)10-6.
G. Moriya F, Hashimoto Y. Determining the state of the deceased during cardiopulmonary resuscitation from tissue distribution patterns of intubation-related lidocaine. J Forensic Sci 2000;45(4):846-9.
H. Pohland RC, Bernhard NR. Postmortem serum and tissue redistribution of fluoxetine and norfluoxetine in dogs following oral administration of fluoxetine hydrochloride (Prozac®). J Forensic Sci 1997;42(5):812-6.
I. Pounder DJ, Smith DRW. Postmortem diffusion of alcohol from the stomach. Am J Forensic Med Pathol 1995;16(2):89-96.
J. Quatrehomme G, Bourret F, Liao Z, Ollier A. An experimental methodology for the study of postmortem changes in toxic concentrations of drugs, using secobarbital as an example. J Forensic Sci 1994;39(5):1300-4.
K. Robertson MD, Drummer OH. Postmortem distribution and redistribution of nitrobenzodiazepines in man. J Forensic Sci 1998;43(1):9-13.
L. Shepherd MF, Lake KC, Kamps MA. Postmortem changes and pharmacokinetics: review of the literature and case report. Ann Pharmacother 1992;26:510-4.

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