Olaf H. Drummer,[1] Ph.D.; Marie L. Syrjanen,[1] B.Sc.; Michael Phelan,[1] B.App.Sc.; and Stephen M. Cordner,[1] FRCPA

A Study of Deaths Involving Oxycodone

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ABSTRACT: Nine deaths involving oxycodone were investigated to assess the contribution of this opiate to these fatalities. All except one of the bodies were subjected to a full autopsy by specialist pathologists with a subsequent thorough toxicological examination. No significant anatomical pathology was found at autopsy. All deaths gave concentrations of oxycodone in femoral blood higher than expected following normal therapeutic use. In three cases no other drug in toxic concentrations was detected. Two cases involved the presence of a high concentration of a benzodiazepine and in a further two cases a high concentration of alcohol in addition to other drugs in therapeutic concentrations were present. One case involved methamphetamine in significant concentrations and another involved high concentrations of oxazepam in combination with pethidine. In all cases the presence of oxycodone was given as a factor contributing to the death. In only one case were there circumstances clearly indicating suicide. Our observations suggest that oxycodone is at least as toxic as other opiates and will cause deaths if misused.

KEYWORDS: pathology and biology, oxycodone, opiates, death, toxicity, adverse reactions

Oxycodone is a semi-synthetic opiate with a pharmacological potency similar to morphine and an elimination half-life of 2 to 5.5 hours [*1*]. Oxycodone is orally bioavailable and is indicated for the treatment of moderate to severe pain. It is administered either orally as 5 mg tablets or rectally as 30 mg suppositories.

There are no published complete case reports of deaths involving oxycodone in the medical and forensic toxicological literature. Unpublished reports include the death of a man scuba diving who also apparently took an overdose of oxycodone, and brief reports of two other suicidal deaths [*2*].

Over the last three years we have experienced 22 sudden deaths in which oxycodone was detected in postmortem tissues. Eighteen of these were drug-related and included oxycodone as a contributory factor to death. We report a detailed account of nine of these deaths in which oxycodone was a significant contributory factor.

Subjects and Methods

The Victorian Institute of Forensic Pathology is a statutory body with responsibility to oversee and provide forensic pathology and related services in Victoria. The Institute

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[1] Victorian Institute of Forensic Pathology, and Department of Forensic Medicine, Monash University, South Melbourne, Victoria, Australia.

conducts some 2500 postmortem examinations each year at its own facilities where it also performs the toxicological analyses in these cases as well as in those examinations performed in Victorian country centers. In the nine cases included in this report, one was examined externally only, however the others were autopsied by full time pathologists either at the Victorian Institute of Forensic Pathology (n = 6) or at a regional hospital in Victoria (n = 2). Autopsy included macroscopic and microscopic examination of all the major organs. Femoral blood was collected in tubes containing 1% sodium fluoride/oxalate as preservative and anticoagulant and were stored frozen until use except for the blood specimens taken for ethanol estimation which were stored at 4°C. Police reports were used to obtain information as to the circumstances of death and any other relevant information obtained by way of statements was also made available at the State Coroner's Office.

All cases were subject to a full toxicological examination. This involved a urine screen for opiates, amphetamines, cannabinoids, cocaine metabolites, benzodiazepines, and barbiturates. Blood extracts were also analyzed on a capillary column gas chromatographic screen using a nitrogen-phosphorus detector for basic and neutral drugs [*3*]. An additional screen was conducted by gradient elution high performance liquid chromatography (HPLC) using photo-diode array detection [*4*]. Further tests for alcohol in blood and urine, morphine in blood and bile (where available) and the chloral hydrate metabolite, trichloroethanol, in blood were separately conducted. Only positive findings are reported in the following case summaries. Involvement of other drugs at less than the therapeutic concentrations can therefore be excluded. When drugs were present at a scene that would not otherwise be identified by the described techniques, tests were conducted to include these drugs in any screening tests.

Oxycodone was quantified by combined gas chromatography-mass spectrometry (GC-MS) using selected ion monitoring (SIM). The method involved the extraction of 1 mL of blood (or tissue homogenate in water) with redistilled 1-chlorobutane in silanized glass extraction tubes after alkalinization with 0.5 mL of 2 M TRIS buffer, pH 9.0. Internal standard (hydrocodone) was added prior to alkalinization. Following extraction, the solvent (upper layer) was transferred to a fresh glass extraction tube and evaporated to dryness in a sample concentrator (Savant Industries). When dry, the residue was reconstituted into 100 μL of methanol. An aliquot (usually 1 μL) was injected into the GC-MS.

Standards were prepared by spiking drug-free blood (or tissue homogenate) with known amounts of oxycodone to concentrations of 100, 200, 500, 1000, and 2000 ng/mL. These standards, and blank cases, were subject to the same procedure as for the unknown cases. As a consequence, recovery losses were automatically corrected for.

The column used was a 25 m × 0.2 mm I.D. × 0.33 μm HP-Ultra-2 capillary column (Hewlett Packard). Flow rate (helium) was approximately 0.8 mL/min. GC conditions consisted of a starting temperature of 90°C, initial hold time of 2 min, followed by a 15°C/min programmed rise to a temperature of 310°C. A final hold time of 15 min was used prior to cooling back to the initial temperature.

A HP-5970 B "bench-top" GC-MS was used (Hewlett Packard) operating in the electron impact mode. Mass spectral parameters included: source temperature 310°C, electron voltage 70 eV and electron multiplier voltage 2000 V. A split of 40:1 was used. Monitored ions were m/z 315, 230 and 140 for oxycodone and m/z 299, 242 and 214 for hydrocodone. The respective retention times were 18.1 and 17.6 min.

Case Summaries and Findings

Case 1—This 23-year-old, 58 kg female was a heavy amphetamine user and had no obvious fresh needle marks on her body. The deceased was found at her premises together with numerous empty bottles of alcohol and an empty bottle of temazepam capsules. She

had apparently taken oxycodone suppositories the night before her death although the packet was not located at the scene.

The autopsy showed no significant signs of natural disease other than a lymphocytic infiltrate of portal tracts. Toxicology showed high concentrations of oxycodone and methamphetamine as well as low therapeutic concentrations of diazepam and temazepam. The cause of death was given as mixed drug toxicity.

Case 2—This 34-year-old, 95 kg male was found dead in his bed by his wife the morning after he arrived home appearing drunk. The afternoon prior to his death he had lunched with a friend and had been to an interview.

The autopsy was unremarkable showing no evidence of significant natural disease except for approximately 50% stenosis of the left anterior descending coronary artery.

Toxicology showed apparently high concentrations of oxycodone in blood and liver and therapeutic concentrations of diazepam and oxazepam in blood. The cause of death was given as mixed drug toxicity.

Case 3—This 49-year-old, 72 kg female had been suffering from a long term respiratory tract infection and was taking a number of medications for this condition. The deceased was found dead in her flat. A large number of prescription drugs were also located at the scene. These included cyproheptadine, diazepam, dothiepin, indapamide, oxazepam, paracetamol, and temazepam. No oxycodone exhibits were found at the scene.

No significant pathology was detected at autopsy except for evidence of terminal aspiration. Toxicology showed apparently high concentrations of oxycodone in femoral blood and liver in addition to therapeutic concentrations of dothiepin, temazepam and propranolol. The cause of death was given as toxic effects of drugs in association with aspiration of gastric contents.

Case 4—The deceased was a 24-year-old, 116 kg male who was known to be a drug addict and had been receiving medication from various doctors including diazepam, thioridazine, and benzhexol. Statements from his father suggested that he may have taken from three to eleven 30 mg oxycodone suppositories on the evening before his death. The deceased was found dead the following morning.

The autopsy showed a heart weighing 495 g with apparent left ventricular hypertrophy and congested and oedematous lungs. Toxicology showed toxic concentrations of oxycodone and clonazepam in blood as well as diazepam and thioridazine in concentrations consistent with therapeutic use. The cause of death was given as mixed drug toxicity.

Case 5—This 21-year-old, 86 kg female was a heroin addict and believed she suffered from terminal cancer. The deceased was found dead fully clothed in her bed in the morning. The previous night she had been placed in bed by her mother because she fell asleep watching television. Empty bottles of oxazepam and dextropropoxyphene were located at the scene.

Autopsy showed pulmonary congestion and intra-alveolar hemorrhages and the bronchi contained mucus and cellular debris. The liver showed a dense chronic inflammatory infiltrate in the portal tracts. Her serum reacted positive to antibodies for hepatitis C. Toxicology showed apparently high concentrations of oxycodone in blood and liver and oxazepam in blood as well as significant amounts of pethidine. The cause of death was given as mixed drug toxicity.

Case 6—This 28-year-old, 65 kg male died while in police custody at the City Watch House. Death occurred approximately 4 hours after detention. The deceased suffered from acquired immune deficiency syndrome (AIDS) and had been a heroin addict. He had

apparently taken flunitrazepam and oxycodone suppositories and possibly also some heroin and wine during the 24-hour period prior to his death. The police had assumed the deceased was acutely intoxicated with alcohol.

The autopsy showed generalized lymphadenopathy and metastatic Kaposi's sarcoma. Toxicology showed toxic concentrations of oxycodone in blood and liver and flunitrazepam in blood, but neither alcohol nor morphine was detected in his tissues. The pathologist concluded that the deceased died from the combined toxic effects of oxycodone and flunitrazepam, the metastatic Kaposi's sarcoma being regarded as a contributory factor.

Case 7—This 57-year-old, 60 kg female was found dead by her husband in the morning. She had apparently consumed five to six glasses of Riesling wine and an unknown number of prescribed drugs the night before her death.

The autopsy showed moderate atherosclerosis for age in the cerebral vessels, coronary arteries and aorta. The mitral valve showed a degree of old rheumatic shortening and fusing of the chordae tendinae and valve leaflets and the lungs were moderately congested.

Toxicology showed high concentrations of oxycodone and alcohol in femoral blood. A small amount of oxycodone was detected in gastric contents. Therapeutic concentrations of quinine, doxepin, oxazepam, and temazepam were also detected in femoral blood. The cause of death was given as mixed drug and alcohol toxicity, the old rheumatic mitral valve disease not being regarded as significant in relation to her death.

Case 8—This 44-year-old, 45 kg woman had a history of previous suicide attempts. She was found dead in her bed in the morning. A number of empty packets of medication were found in the bedroom as well as a suicide note.

Autopsy showed only moderate congestion of the lungs. Toxicology showed toxic concentrations of alcohol, oxycodone and clonazepam as well as therapeutic concentrations of propoxyphene, doxepin and paracetamol. Cyproheptadine was also detected in significant amounts in blood and stomach contents. The cause of death was given as mixed drug toxicity.

Case 9—This 37-year-old, 60 kg male had been suffering from AIDS for which he had been receiving treatment for about four years. The deceased had previously abused drugs and was found dead in bed at his premises. Drugs located at scene included oxycodone suppositories, domperidone, temazepam, dapsone, ketoconazole, and sodium valproate.

The case only involved an external inspection only by the pathologist.

Toxicology showed high concentrations of oxycodone in femoral blood and vitreous humor and a therapeutic concentration of temazepam. The cause of death was given as mixed drug toxicity, with the proviso that it was only a "reasonable cause of death" because the absence of a complete autopsy prevented the assessment of any accompanying natural disease.

Results and Discussion

A summary of the toxicology findings are shown in Table 1. In these nine cases femoral blood oxycodone concentrations range from 0.6 to 1.4 mg/L (mean = 0.90 mg/L). In none of the five cases in which gastric contents were analyzed was there a large amount of oxycodone. In only one case (7) was oxycodone detected at all in the gastric contents. Other drugs were detected in all of the cases investigated. Cases 2, 3 and 9 also involved drugs which, in our view were present in concentrations consistent with normal therapeutic use. Cases 4 and 6 involved the additional presence of a benzodiazepine (clonazepam and flunitrazepam as their respective 7-amino metabolites) in concentrations at which significant toxicity might be expected [*5*]. The remaining cases (1, 5, 7 & 8) involved significant

TABLE 1—*Summary of toxicological findings in drug-related deaths in which oxycodone was a contributing poison.*[a]

Case	Sex/Age	Oxycodone concentration	Other Drugs (femoral blood concentration)	
1	F 23	B = 0.6	Methamphetamine	1.0
		S.C. = 0	Diazepam	0.2
			Temazepam	0.1
2	M 34	B = 0.6	Diazepam	0.4
		L = 0.4	Oxazepam	0.1
		S.C. = 0		
3	F 49	B = 0.7	Dothiepin	0.3
		L = 1.4	Temazepam	0.3
		S.C. = 0	Propranolol	0.1
4	M 24	B = 0.7	7-Aminoclonazepam	0.3
		S.C. = 0	Diazepam	0.3
			Thioridazine	0.2
5	F 21	B = 0.7	Oxazepam (S.C. = 16)	4.5
		L = 0.8	Pethidine	0.3
6	M 28	B = 1.2	7-Aminoflunitrazepam	0.1
		L = 1.9		
7	F 57	B = 1.0	Alcohol	1700
		S.C. = 2	Quinine	5.7
			Doxepin	0.3
			Oxazepam	0.4
			Temazepam	0.2
8	F 44	B = 1.4	Alcohol	2300
		L = 3.6	Propoxyphene	0.3
			Doxepin	0.2
			7-Aminoclonazepam	0.3
			Cyproheptadine	Detected
9	M 37	B = 1.2	Temazepam	0.1
		V = 1.8		

[a] All results in mg/L for blood and vitreous, mg/kg for liver and mg total contents of stomach. B = femoral blood, L = liver, S.C. = stomach contents, V = vitreous humor.

amounts of other drugs including methamphetamine (1), oxazepam and pethidine (5), and alcohol (7 & 8).

Published pharmacokinetic studies involving oxycodone show that plasma concentrations are generally much less than 0.1 mg/L. For example a single oral dose of 4.5 mg results in peak plasma concentrations of 0.009 to 0.037 mg/L [*6*]. Intravenous administration of single doses of oxycodone (3.1 to 4.7 mg) gave plasma concentrations less than 0.1 mg/L [*1*]. Blood or plasma concentrations following prolonged chronic administration are not known.

A summary of our own postmortem cases in which oxycodone was an incidental finding in deaths not directly caused by drug toxicity is shown in Table 2. These show femoral blood oxycodone concentrations ranging upto 0.3 mg/L. Postmortem intervals of these three cases were similar to the other nine cases included in Table 1. The circumstances of these three unrelated deaths suggested that drugs were not deliberately misused prior to death. As a consequence these data would suggest that postmortem femoral blood concentrations of upto 0.3 mg/L may be associated with normal therapeutic use of oxycodone. The reason for the higher levels seen postmortem may be due to a build-up of oxycodone concentrations

TABLE 2—*Blood oxycodone concentrations in deaths unrelated to oxycodone toxicity.*

Case No.	Sex/Age	Femoral blood oxycodone (concentration (mg/L)	Cause of Death
10	F 66	0.1	Disseminated carcinoma of the pancreas
11	F 25	0.2	Suicide by Hanging
12	M 61	0.3	Acute congestive cardiac failure

following repeated use and/or due to postmortem redistribution in which oxycodone bound to neighboring tissue leaches out into the surrounding blood [*7*].

The phenomenon of postmortem redistribution is not relevant in the analysis of the liver. Concentrations in the liver in the five cases where data was available ranged from 0.4 to 3.6 mg/kg (mean 1.6 mg/kg.). This was, on average, 1.6 times the corresponding femoral blood concentration. There was also a significant correlation between femoral blood and liver concentration ($r^2 = 0.86$). Vitreous humor concentrations also appear to be similar to blood concentrations as shown in case 9. Vitreous may therefore be a useful alternative (or addition) to blood and liver specimens in toxicological investigations.

Suicidal ingestion of an overdose of oxycodone clearly occurred in case 8. In the other cases there was no direct evidence to suggest that a deliberate overdose of oxycodone was taken although this possibly cannot be entirely dismissed. In the absence of obvious suicidal intent in the remaining 8 cases, the question arises as to why the oxycodone concentrations were as high as they were. The possibilities of accidental over-medication to relieve pain or an unexpected accumulation of oxycodone as a consequence of a reduced clearance or too frequent administration must be considered. Since the elimination half-life in healthy subjects may range upto 5.5 h [*1*] too frequent dosing may cause an accumulation of drug similar to that observed for methadone [*8*].

It was of interest that ketoconazole was used by the deceased in case 9. This drug is known to impair microsomal P450 oxidation of drugs and to cause liver toxicity [*9,10*]. While the possibility of ketoconazole-induced oxycodone toxicity cannot be proven in this case the possibility of an adverse reaction with this drug, or indeed with other drugs, should always be considered in multi-drug cases.

An inquest into the death of case 5 found that the labeling on the packaging did not convey any warning that the drug is dangerous if misused, or if used in combination with other drugs that dependence may occur with repeated use. It seems to us an important first step that such warnings be included on such medications in future so that serious side effects and deaths may be reduced. The Coroner's findings in the other deaths did not add to the conclusions already presented.

In any event, these case summaries show that oxycodone in femoral blood concentrations of 0.6 mg/L or higher may cause death. As always, postmortem drug levels must be interpreted with care taking into account the autopsy findings, the circumstances, the toxicological literature and the experience of the toxicology laboratory. Extreme care in the prescription and use of this synthetic opiate is warranted as it is for the other potent opiate analgesics.

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References

[1] Pöyhiä, R., Olkkola, K. T., Seppälä, T., and Kelso, E., "The Pharmacokinetics of Oxycodone After Intravenous Injection in Adults," *British Journal of Clinical Pharmacology,* Vol. 32, 1991, pp. 516–518.

[2] Baselt, R. C. and Cravey, R. H., "Disposition of Toxic Drugs and Chemicals in Man," 3rd edition, Year Book Medical Publishers, 1989, pp. 626–627.

[3] Drummer, O. H., Kotsos, A., and McIntyre, I. M., "A Class-Independent Drug Screen in Forensic Toxicology Using a Photodiode Array Detector," *Journal of Analytical Toxicology,* Vol. 17, 1993, pp. 225–229.

[4] Drummer, O. H., Syrjanen, M. L., and Cordner, S. M., "Deaths Involving the Benzodiazepine Flunitrazepam," *American Journal of Forensic Medicine and Pathology,* Vol. 14, No. 3, 1993, pp. 238–243.

[5] Drummer, O. H., Horomidis, S., Kourtis, S., Syrjanen, M. L., and Tippett, P., "Capillary Gas Chromatographic Drug Screen for Use in Forensic Toxicology," *Journal of Analytical Toxicology,* in press.

[6] Renzi, N. L. and Tam, J. N., "Quantitative GLC Determination of Oxycodone in Human Plasma," *Journal of Pharmaceutical Sciences,* Vol. 68, 1979, pp. 43–45.

[7] Prouty, R. W. and Anderson, W. H., "The Forensic Science Implications of Site and Temporal Influences on Postmortem Blood-Drug Concentrations," *Journal of Forensic Sciences,* Vol. 35, 1990, pp. 243–270.

[8] Drummer, O. H., Opeskin, K., Syrjanen, M. L., and Cordner, S. M., "Methadone Toxicity Causing Death in Ten Subjects Starting on a Methadone Maintenance Program," *American Journal of Forensic Medicine and Pathology,* Vol. 13 No. 4, 1992, pp. 346–350.

[9] Report in "Ketoconazole and the Liver," *Australian Adverse Reactions Bulletin,* February 1987.

[10] Ketoconazole in *Drug Evaluations Annual 1991,* American Medical Association, Milwaukee, pp. 1488–1490.

Address requests for reprints or additional information to
Olaf H. Drummer, Ph.D.
Dept. of Forensic Medicine, Monash University
57–83 Kavanagh St.
South Melbourne, Victoria 3205
Australia