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OxyContin[®] Abuse and Overdose

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Abstract

Background: OxyContin[®] (controlled-release oxycodone hydrochloride) (Purdue Pharma, Stamford, CT) was approved in 1995 by the US Food and Drug Administration (FDA) for moderate-to-severe chronic pain. Crushing and snorting the delayed-release tablets results in a rapid release of the drug, increased absorption, and high peak serum concentrations. The propensity for addiction to OxyContin[®] and the trend of increased prescription drug abuse have made it imperative for physicians and health care providers to recognize the clinical presentation of overdose and know how to manage associated complications. **Objectives:** In this review of OxyContin[®], we discuss current trends in its abuse and the clinical presentation of overdose. We review the specific effects of the drug on body systems and the recognition of symptomatology, differential diagnosis, and management. **Discussion:** Many of the clinical findings in acute opioid overdoses are nonspecific, making diagnosis difficult. OxyContin[®] overdose presents with a typical opiate toxidrome, including decreased respirations, miosis, hypothermia, bradycardia, hypotension, and altered mental status. The presence of coingestants can cloud the clinical picture. If OxyContin[®] overdose is suspected, early ventilation and oxygenation should be administered, which is generally sufficient to prevent death. Even in the absence of a confirmation, cautious administration of naloxone—the opiate receptor antagonist and antidote for opioid overdoses—may have both diagnostic and therapeutic effects. **Summary:** With increasing rates of prescription drug abuse, OxyContin[®] will continue to present challenges to physicians and health care providers. Physicians should be aware of potential patients who are seeking OxyContin[®] for recreational use.

Keywords: OxyContin[®]; addiction; substance abuse; overdose; opioid

Introduction

OxyContin[®] (controlled-release oxycodone hydrochloride) (Purdue Pharma, Stamford, CT) was approved in 1995 by the US Food and Drug Administration (FDA) to treat moderate-to-severe chronic pain.¹ Oxycodone, the active ingredient in OxyContin[®], is a schedule II analgesic that acts as a pure opioid agonist on both central and peripheral opiate receptors. It has a high bioavailability when administered orally, with a half-life of 4.5 hours, and is formulated as a sustained-release tablet. It is designed to provide pain relief over a 12-hour period.^{1,2} The controlled-release property of OxyContin[®] was thought to originally deter abuse when compared with other opioids. In fact, because of several preclinical and clinical findings on drugs with slow onsets of action, the 1997 *Physicians' Desk Reference* and the package insert originally stated, "Delayed absorption, as provided by OxyContin[®] tablets, is believed to reduce the abuse liability of the drug."³⁻⁷ More recently, US law enforcement officials have called OxyContin[®] abuse an "epidemic" and referred to the medication and similar formulation drugs as "killers."⁸ Crushing and snorting the delayed-release tablets results in the rapid release of the drug, increased absorption, high peak serum concentrations, and may precipitate a

fatal overdose.^{9,10} The propensity for addiction to OxyContin[®] and the trend of increased abuse have made it imperative for physicians to recognize the clinical presentation and know how to manage complications associated with OxyContin[®] overdose.

Discussion

Trends in Abuse

The first cases of OxyContin[®] abuse were recorded in rural areas, including Maryland, eastern Maine, eastern Ohio, the “rust-belt” regions of Pennsylvania, and the southern Appalachian areas of West Virginia, Virginia, and Kentucky.¹¹ Abuse continues to be concentrated in rural areas, as well as small- to medium-sized urban and suburban areas.⁷ The drug has become known as a “poor-man’s heroin” because of its comparatively lower street price than heroin.⁹ It is commonly known as “hillbilly heroin,” “Oxy,” “OC,” or “OxyCotton.”⁹ Its abuse does not seem to be as prevalent in inner city urban areas where inexpensive heroin is available.⁷ Abusers often obtain the medication in clinics by reporting appropriate complaints of chronic pain or by “doctor shopping,” whereby they visit different medical practitioners to obtain several prescriptions and then get them filled at multiple pharmacies to avoid getting caught.⁹ One study indicated that 70% of OxyContin[®] abusers obtained the drug via a physician’s prescription.⁷ Reports also indicate that some abusers will commit fraud and theft, and adolescent abusers will often steal the drug from their parents.^{12–13}

The US Department of Justice reported that 464 deaths were linked to OxyContin[®] overdoses in 2002 and the Drug Abuse Warning Network (DAWN) stated that there was an estimated 42 810 emergency department (ED) visits from oxycodone use in 2005.^{14–15} A study using a DAWN-based classification scheme to analyze the numbers and demographics of drug abuse deaths involving oxycodone/OxyContin[®] from August 27, 1999 through January 17, 2002 found that the average age of death was 39.7 (\pm 10.6) years (range, 9–88 years); 67.2% of the deaths were males. Of the reported deaths, 92.9% were white and 3.1% were black.¹⁶ Similarly, an analysis of the demographics of OxyContin[®] abuse by Cicero et al found the average age of abuse to be 34 years.⁷ Men were much more likely ($>$ 65%) to abuse the drug than women, and 91% of the users were white. Less than 5% were black and $<$ 3% were Hispanic.⁷

Oxycodone overdoses often involve polysubstance abuse.¹⁷ In one study, of the patients who died from OxyContin[®] abuse and overdose, 96.7% had taken multiple drugs.¹⁶ It was determined via toxicological testing that

56.5% were using concomitant benzodiazepines, 40.1% were taking antidepressants, and 27.1% were abusing illicit drugs.¹⁶ Of those patients who presented to the ED for oxycodone abuse in 2002, 71% of the visits included the simultaneous use of other drugs.¹⁸ The most prevalent coingestions were ethyl alcohol (33%), benzodiazepines (21%), and cocaine (12%).¹⁸

Several studies and surveys have indicated that OxyContin[®] abuse is increasing at an alarming rate.^{7,8,11,13,15,19} The “Monitoring the Future Study” by National Public Radio online and the University of Michigan published an alarming statistic that OxyContin[®] use by 12th graders went up 40% between 2002 and 2005, with 5.5% of 12th graders abusing the drug in 2005.¹⁹ The DAWN report concluded ED visits from nonmedical use of oxycodone increased nearly 15% between 2004 and 2005 while nonmedical use of pharmaceuticals in general increased 21% between those same 2 years.¹⁵ These statistics, along with similar findings in a study on the trends in OxyContin[®] abuse, indicate that OxyContin[®] abuse is substantial but seems to be following the general trend of increased prescription drug abuse.^{7,15} Additionally, $>$ 87% of OxyContin[®] abusers in 1 study had current and past histories of substance abuse, signifying that few legitimate patients become addicted to the drug if used as prescribed.⁷

Clinical Presentation of OxyContin[®] Abuse and Overdose

Pure OxyContin[®] overdose presents with a typical opiate toxidrome, including decreased respirations, miosis, hypothermia, bradycardia, hypotension, and altered mental status. The presence of coingestants can cloud the clinical picture. Further, the route of administration influences the pharmacokinetic and pharmacodynamic effects of the drug and ultimately the clinical presentation and hospital course.

Opioid overdose causes respiratory depression via both reduced hypercarbic and hypoxic respiratory drive.^{20,21} By binding to μ_2 receptors, opioids lower the sensitivity of medullary chemoreceptors to hypercapnea and blunt respiratory response to hypoxia.²² This 2-fold effect, reducing either respiratory rate or tidal volume, leads to apnea.²⁰ The link between acute respiratory distress syndrome (ARDS) and opioids has been known since 1880, although the exact mechanism is still under dispute.²³ The patient will usually regain normal ventilation following respiratory depression, either spontaneously or after administration of an opioid antagonist such as naloxone, and later develop hypoxemia and pulmonary edema over the course of the next few minutes or hours. Frothy, pink sputum may be present in the patient’s

airway or in the endotracheal tube of an intubated patient as a result of sympathetic discharge.²⁰ Convulsions and premature ventricular contractions (PVCs) can also occur as a result of hypoxia and subsequent acidemia.²¹

Hypotension may also be present because of arteriolar and venous dilation caused by histamine release.^{24,25} Although the opioid receptor does not appear to be directly involved in histamine release, there may be some nonspecific ability of opioids to activate mast cell G proteins, which induce degranulation of histamine-containing vesicles.²⁶

Miosis, or pinpoint pupils, is also a sign of opioid overdose.²¹ The mechanism remains controversial, with studies showing that morphine stimulates parasympathetic pupilloconstrictor neurons in the Edinger-Westphal nucleus and increases firing of pupilloconstrictor neurons to light.²⁷ Oxycodone most likely induces miosis via mediation of inhibitory neurotransmission resulting in either hyperpolarization of sympathetic nerves or removal of inhibition in parasympathetic neurons.²⁰

Necrosis of intranasal structures, similar to the damage associated with chronic cocaine use, has been reported as a result of prolonged OxyContin® abuse by snorting crushed tablets. The findings included nasal collapse, septal perforation, palatal retraction, and pharyngeal wall ulceration, which can mimic sinusitis and rhinitis. These conditions are most likely a result of a post-inflammatory response to the crushed powder.²⁸

Unlike normal-release oxycodone, OxyContin® exhibits a pharmacokinetic profile with 2 distinct serum peaks, allowing for rapid onset and a long duration of action (Table 1). Approximately 38% of an orally ingested dose is absorbed with a mean half-life of 37 minutes.²⁹ Serum concentrations normally peak in approximately 3 hours with the oral ingestion of OxyContin®.¹⁷ In the case of a large oral ingestion, the toxicity may be prolonged secondary to slowed gastrointestinal motility and possible pharmacobezor formation. When OxyContin® is crushed and nasally insufflated, the controlled-release mechanism is lost, resulting in the rapid rise of serum concentrations. These abuse and overdose scenarios ultimately result in altered pharmacokinetic parameters and unpredictable clinical scenarios.

Differential Diagnosis and Treatment

Many of the clinical findings in acute opioid overdoses are non-specific, making diagnosis difficult. Hypoglycemia, hypoxia, hypothermia, stroke, head injury, and spinal cord injury may all mimic OxyContin® poisoning or may exist concomitantly. These conditions can be verified by routinely available testing; however, if present, they do not necessarily exclude an OxyContin® overdose. Other overdose symptoms presenting similarly may include clonidine, phenylcyclohexylpiperidine (PCP), phenothiazines, and benzodiazepines. Each of these generally induce unique clues to exclude opioid toxicity, such as nystagmus associated with PCP, electrocardiogram (ECG) abnormalities with phenothiazines, and coma with nearly normal vital signs with benzodiazepines.²⁰ Adding to the difficulty in diagnosis is the low sensitivity and specificity of immunoassay urine drug screens commonly used in the ED. The immunoassay drug screen for opiates is specific for morphine glucuronide and exhibits a 30% cross-reactivity with oxycodone. The cross-reactivity can vary between manufacturers and has been reported to be as low as 5% for some tests.²⁰ Taking this into consideration, a negative urine drug screen for opiates can not necessarily rule out oxycodone ingestion. A confirmatory immunoassay specific for oxycodone should be ordered if the patient's clinical picture remains unclear. Many OxyContin® overdose patients are simultaneously abusing other drugs, making diagnosis even more difficult if there is no definitive confirmation of the patient's abuse of the opioid.

If OxyContin® overdose is suspected, early ventilation and oxygenation should be administered, which is generally sufficient to prevent death. However, even in the absence of a confirmation, cautious administration of naloxone—the opiate receptor antagonist and antidote for opioid overdoses—may have both diagnostic and therapeutic effects.²⁰ Studies have shown that high-dose naloxone therapy is safe in patients with nonopioid-related conditions, such as spinal cord injury or acute ischemic stroke.^{20,30} Although ventilation assistance may still be required because of a delayed response, a small dose of 0.05 mg of naloxone administered intravenously typically leads to a patient reaction. The goal of this treatment is not complete arousal but one of an increased respiratory drive and a return to adequate spontaneous ventilation. This approach of using a small dose is effective in avoiding endotracheal

Table 1. Pharmacokinetic Profile of Oxycodone

Drug Type	Pharmacokinetic Profile	Time to Peak	Duration	Half-Life
Oxycodone Immediate Release (Oral)	Monoexponential	1.4 ± 0.7 hours	4–6 hours	2–3 hours
Oxycodone Extended Release (Oral)	Biexponential	3.2 ± 2.2 hours	8–12 hours	4.5 hours

intubation, enables timely classification of nonopioid causes of the patient's condition, and lowers the risk of acute opioid withdrawal.²⁰ High-dose naloxone treatment or subcutaneous administration often leads to a faster response but may also increase withdrawal symptoms,²⁰ most commonly including confusion, restlessness, and headache, and less often aggressiveness, gastrointestinal complaints, tachycardia, shivering, seizures, sweating, and tremor.³¹

The route of ingestion of oxycodone will influence the pharmacodynamics on the body. Nasal insufflation of oxycodone will result in faster onset and acute toxicity. Small bolus doses of naloxone may be effective, as previously mentioned. We suggest a bolus of 0.05 to 0.2 mg until a desired effect of improving patient hypoventilation. This may be determined by hypoxia or elevated CO₂ levels. When tablets are orally ingested, naloxone and oxygen therapy will have to be administered for a longer period of time. In a large acute ingestion, toxicity may be delayed and prolonged enough to necessitate the use of a naloxone infusion. The typical per-hour infusion rate to start with is 2/3 the dose required to stimulate the patient. For example, if 3 mg were required to maintain the patient's ventilation status, the subsequent infusion would start at 2 mg/hr. The titration endpoint for naloxone infusions is patient respiration.²¹

Specific long-term management of OxyContin® abuse is treated by several medications. Methadone blocks the effects of opioids and if taken regularly prevents withdrawal symptoms. It has been used for decades to treat people addicted to opioids. Other medications include levo-alpha-acetylmethadol (LAAM), an alternative to methadone that blocks the effects of opioids for up to 72 hours. Naltrexone is a long-acting opioid blocker but is not generally used in the acute setting. Other available long-term treatments are buprenorphine and suboxone, which is a combination of buprenorphine with naloxone. Treatment of long-term addiction is not the focus of this article; however, management of these patients also focuses on psychotherapy along with these medications.

Conclusion

With the increasing rates of prescription drug abuse, OxyContin® overdose will continue to be a challenge for physicians to identify and manage. Since the abuse is seen in all ages, all health care providers should be knowledgeable about this chronic pain agent. Increasing illegal purchasing and abuse should also prompt health care providers to be aware of patients who are seeking this drug for recreational use.

Conflict of Interest Statement

Christopher T. Aquina BS, Andreia Marques-Baptista, MD, Patrick Bridgeman, PharmD, and Mark A. Merlin, DO, EMT-P, FACEP disclose no conflicts of interest.

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