



Overdose, Adverse Effects, and Safety of Oral Medications

SHAHROKH C. BAGHERI, DMD, MD; MEHRAN MEHRABI, DMD, MD; HUSAIN ALI KHAN, DMD, MD; AND DEEPAK KADEMANI, DMD, MD

ABSTRACT Overdose of oral medications can be a major concern. This article reviews the clinical presentations, toxic dosages, adverse effects, and the recommended treatments for the most commonly used oral medications in dentistry.

Clinicians need to be aware of the toxicities and adverse effects of the most commonly used oral medications, and recognize the signs and symptoms as early as possible for expedient treatment and referral.

AUTHORS

Shahrokh C. Bagheri, DMD, MD, is in private practice, Atlanta Oral and Facial Surgery, Atlanta, and a clinical assistant professor of surgery at Emory University, Division of Oral and Maxillofacial Surgery, in Atlanta.

Mehran Mehrabi, DMD, MD, is an oral and maxillofacial surgeon stationed with the United States Air Force Base in Biloxi, Miss.

Husain Ali Khan, DMD, MD, is in private practice, Atlanta Oral and Facial Surgery, Atlanta.

Deepak Kademani, DMD, MD, is an assistant professor of oral and maxillofacial surgery, Mayo Clinic, Rochester, Minn.

Pharmacological treatment is a major modality of therapy in dentistry. Not surprisingly, overdose of oral medications can be a major concern. Antibiotics, analgesics and anxiolytics are the most commonly used oral medications in dentistry, the latter two being common causes of adult hospital admissions in the United States.¹ This article outlines the clinical presentations, adverse effects, toxic dosages, and the recommended treatments for commonly encountered oral medications in dentistry.

In the United States there are many systemic analgesics almost all of which contain aspirin, acetaminophen, ibuprofen, or other nonsteroidal anti-inflammatory drugs, or a combination of these agents with other ingredients including opioids. Clinicians frequently recommend or prescribe these medications based on their training or experience. One can safely assume the public is confused and overwhelmed with the tremen-

dous oversupply of such medications.

Prescription anxiolytic medications such as benzodiazepines are relatively safe; however, the margin of safety is clearly decreased when combined with other medications or readily available agents such as ethanol. Antibiotics are uncommonly associated with overdosage, and the lethal dose of most antibiotics are not established. However, mild hypersensitivity reactions are commonly encountered in the dental practice, and even life-threatening anaphylaxis can occur.

It is important for dental professionals to be familiar with the clinical presentations and toxicity of the most commonly encountered oral medications, and provide adequate recommendations for treatment in cases of suspected toxicity.

Analgesics

The toxic effects of NSAIDs are usually as a result of prolonged exposure presenting with acute or chronic systemic manifestations such as renal failure,

gastrodeuodenal damage, and colitis.^{2,3} Acute overdoses are usually mild and self-limited.⁴ NSAIDs are widely used in the treatment of dental pain and chronic temporomandibular joint disorders. In 1989 the Food and Drug Administration required all NSAID bottles to have special warnings regarding potential gastrointestinal and bleeding complications.

The toxic dosage of most NSAIDs is not available and our toxicological knowledge is predominantly based on single acute case reports of massive overdosage or chronic exposures. The most frequently used nonopioid analgesics in dentistry include acetaminophen, ibuprofen, and naproxen. Nonprescription aspirin remains in common use. After an acute ingestion of 20 grams of ibuprofen, which is equivalent to 100 ibuprofen tablets 200 mg each (more than seven times the maximum recommended daily dose), a 48-year old man developed profound metabolic acidosis and coma but subsequently survived.⁵ Symptoms are mostly gastrointestinal (nausea, vomiting, epigastric pain, abdominal pain), but can include tinnitus or in more severe cases renal failure. In one large series of 1,033 inquires regarding ibuprofen ingestion, 705 (65 percent) of patients were asymptomatic; 199 (18 percent) experienced mild symptoms; and 23 (2 percent) experienced moderate symptoms.⁶ Ibuprofen fatalities have been mostly reported in children.⁶ Fortunately, the incidents have decreased, and it is attributed to the development of child-resistant bottles.⁷

The toxic effects of naproxen are similar to ibuprofen. A 25 gram adult naproxen overdose (38 times the maximum daily dosage) produced only transient nausea and indigestion.⁸ Renal failure and severe metabolic acidosis with seizures are also reported with naproxen overdose.^{9,10} Ibuprofen and

naproxen overdose are not uncommon, but serious toxic effects are unusual.

Aspirin and nonaspirin salicylates overdosage and fatalities have been widely documented.¹¹ Salicylates were the most common agent responsible for single drug deaths in Ontario, Canada, from 1984 to 1986.¹² Acute toxicity is usually seen in young suicidal adults with a mortality rate of about 2 percent.¹³ In addition,

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the use of aspirin during pregnancy has been associated with increased risk of congenital defects, neonatal hemorrhage, and other metabolic abnormalities.¹⁴⁻¹⁶ In the study by McGuigan, the presentation of patients on arrival to the emergency services were variable ranging from dead (31 percent) or comatose (22 percent), to alert but symptomatic (45 percent).¹² The consequences of acute overdose are systemic (respiratory alkalosis, metabolic acidosis) and can prove fatal by ingestion of as little as 2 grams to 4 grams by children, or 10 grams to 30 grams by adults.¹⁷ Bronchospasm is also a known complication of aspirin in patients with asthma or airway hypersensitivity.

This is particularly seen in a condition known as Samter's triad (asthma, aspirin sensitivity, and nasal polyposis). The etiology consists of inhibition

of the enzyme cyclooxygenase 1 and subsequent overactivation of the lipoxygenase pathway. This results in an increased production of leukotriene B₄, C₄, and D₄.¹⁸⁻²⁰ The primary etiologic agent is the release of leukotriene C₄ by bronchial mast cells and inflammation of nasal polyps resulting in obstructive airway disease due to bronchospasm.

Clinically large acute overdoses of nonsalicylate NSAIDs only produces mild gastrointestinal upset and central nervous system depression. Effective treatments include emesis within several hours postingestion or administration of activated charcoal immediately postingestion.¹³

Acetaminophen is the most widely used and recommended nonprescription analgesic and antipyretic medication in the United States.²¹ In the last three decades it has gained popularity with emphasis placed on its reduced gastrointestinal side effects when compared to NSAIDs. Acetaminophen-induced hepatic necrosis is well-documented and occurs after ingestion of massive doses.^{22,23,13} The drug is metabolized almost entirely by the liver glucuronide conjugation and hepatic microsomal enzyme pathway.¹⁷ However, a small amount of the drug is metabolized via N-acetyl-p-benzoquinoneimine, NAPQI, which is a toxic intermediate that causes hepatocellular necrosis. At therapeutic doses, NAPQI is rapidly conjugated by hepatic glutathione and excreted, while at toxic doses glutathione stores are depleted with subsequent accumulation of NAPQI, resulting in oxidative damage and hepatocellular necrosis. Drugs that are metabolized by the alternative liver cytochrome P450 oxidation pathway such as cimetidine, ranitidine, and codeine do not affect the metabolism of acetaminophen.^{6,24,25} Conversely, ethanol and barbiturates potentiate acetaminophen hepatotoxicity, probably by utilizing the

hepatic microsomal enzyme system.²⁶

The maximum daily recommended dose of acetaminophen in adults is 4 grams and 75 mg/kg in children. The adult lethal dose ranges from 13 to 25 grams (26 to 50 tablets of 500 mg each); however, hepatotoxicity can be seen with ingestion of as little as 5 grams, especially when the liver metabolic pathway is compromised by the abuse of other substances such as ethanol or barbiturates.¹³ The first reported case of acetaminophen fatality was in 1966.²² Fatalities after acute acetaminophen overdose have been well-documented.^{27,28}

As clinicians, dentists need to be aware of the delayed onset of clinical symptoms even after ingestion of lethal doses of acetaminophen. Symptoms may not be apparent until three to five days postingestion with development of fulminate hepatic necrosis, encephalopathy, coma, and subsequent death. If the damage done to the hepatocytes is reversible complete resolution of hepatic function can occur. A patient may continue to self-treat dental pain by ingestion of greater amounts without being aware of the progressive liver damage. It is important to carefully question the patient on the exact dosage and chronology of self-medication, and have a low threshold of immediate referral to an emergency room for subsequent treatment. Emergency treatment constitutes of determination of plasma acetaminophen levels, gut decontamination, and administration of the antidote N-Acetylcystine and/or activated charcoal.

Several prescription oral narcotics are available on the market (codeine, hydrocodone, oxycodone), the majority of which are structurally similar of morphine and therefore, have potential for abuse and the development of tolerance. Patients with toxic overdose can present with a

range of symptoms including decrease in body temperature, respiratory depression, hypotension, constipation, euphoria, stupor, and pinpoint pupils. Fatal intoxications resulting from ingestion of these medications alone are rare. A recent study of postmortem databases from the medical examiners' and coroners' (ME/C) offices in 23 states over a five-year period revealed that of the 919 drug abuse cases,

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the vast majority (N=889, 96.7 percent) were multiple drug abuse deaths.²⁹ Lethal doses of most narcotics are not well-established. However, the symptoms of narcotic overdose need to be addressed promptly since they are frequently coingested with other agents that can drastically increase the toxicity. The effect of opioids can be rapidly and effectively reversed with the opioid antagonist naloxone. Fatalities and poisonings with ingestion of preparations that combine narcotics with acetaminophen or aspirin are documented.^{30,31}

While there is no magic combination, it has been found that the combination of an opioid and a NSAID, or acetaminophen are not only more efficacious but also reduce the prevalence of side effects compared to higher doses of individual drugs given to achieve the same analgesic effect.³²⁻³⁵

Benzodiazepines

Benzodiazepines are potent anxiolytic and hypnotic agents with anticonvulsant and muscle relaxant properties, commonly prescribed in dentistry for the treatment of dental anxiety prior to procedures and for the treatment of myofascial pain dysfunction. There appears to be a large number of people who use benzodiazepines chronically and a significant amount of abuse/nonmedical use is evident.³⁶ In 2005, McCabe published a survey correlating the nonmedical use of prescription benzodiazepine anxiolytics in a cohort of U.S. college students. They reported that the lifetime prevalence of nonmedical prescription benzodiazepine anxiolytic use was 7.8 percent; past year prevalence was 4.5 percent; and past month was 1.6 percent.³⁷

Caution must be taken when prescribing benzodiazepines for the treatment of chronic temporomandibular disorders or MPD. Abuse and dependence with benzodiazepines is well-established.

In 1991, an estimate of 50,792 reports of abuse involving anxiolytics (mostly alprazolam and diazepam) was reported.³⁸

The lethal dose of benzodiazepines has not been established. Death from oral administration of benzodiazepines alone is very uncommon; however, their toxicity is synergistically increased when taken in combination with other toxicologic agents such as ethanol.^{39,40} In one case, a healthy male fully recovered after ingesting 2 grams of diazepam (200 to 1,000 times the recommended dose for sedation) and required only observation.⁴¹ Two individuals who attempted suicide with alprazolam also recovered with minimal clinical manifestations of toxicity after oral ingestion of 30 mg and 60 mg, respectively (therapeutic dose is 0.25 to 1.0 mg/tid).⁴²

Most overdose patients require only observation in a health care facility and

consideration for psychiatric counseling. Acutely, the sedative effects of diazepam can be reversed with the shorter acting benzodiazepine antagonist flumazenil.

Ethanol

A discussion of ethanol is included in this article because of the potential hazards of simultaneous alcohol abuse and the already mentioned medications. Ethanol is a central nervous system depressant with preferential suppression of inhibitory neurons causing the excitation seen at low ethanol concentrations. The degree of neurologic impairment is dependent on many variables including coingestion of other drugs. The lethal dose is reported to be 5 to 8 g/kg for adults and 3 g/kg in children.¹³ In a healthy 70-kg male, this would translate into approximately an acute dose of 1,250 ml of vodka (40 percent ethanol); 4,200 ml of wine (12 percent ethanol); or 12.5 liters of beer (4 percent ethanol). Therefore, it becomes very uncommon for fatalities to occur exclusively from elevated ethanol concentrations, but rather occur due to accidents secondary to neurologic impairment. In addition, alcoholics who consume large amounts of ethanol develop tolerance and subsequently require larger quantities of the agent to produce similar toxic effects.⁴³

The adverse interactions of alcohol with the most commonly used medications is well-documented. An additive effect with increased gastrointestinal bleeding is observed with salicylates and other NSAIDs.⁴⁴ The increased bleeding time observed with ingestion of NSAIDs can be exaggerated when compounded by thrombocytopenia and decreased liver coagulation factors seen in alcoholic cirrhosis. The increased production of toxic metabolites in chronic alcohol abuse can lead to increased acute hepatotoxicity

with the consumption of acetaminophen, decreasing the toxic dose.^{45,46} A synergistic increase in central nervous system depression is seen with the use of benzodiazepines, causing potentially dangerous levels of sedation.^{39,40}

Alcohol is the most commonly abused CNS depressant in the world. It is more prevalent among men in lower socioeco-

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nomic groups; however, it cuts across all ethnic, cultural, educational, and geographical boundaries.⁴⁷ The need to be aware of the potential increased side effects of commonly prescribed medications when a positive history of alcohol abuse is apparent.

Antibiotics: The Penicillins and Clindamycin

Penicillin was discovered by Fleming in 1928, but was not commercialized until World War II. This low-cost, age-proven, and highly efficacious agent against oral pathogens is the most commonly prescribed antimicrobial in dentistry.⁴⁸⁻⁵⁰ Compared to other antibiotics, it has a low side effect profile making it very attractive to clinicians and patients. The toxic dose of oral penicillin is not established and toxicity is uncommon, even with ingestion of quantities

well above the therapeutic dose.

The usual adult dose of oral penicillin V is 1-2 grams/day in divided doses (25 to 50 mg/Kg in children), with an effective maximum dose of 4 grams/day. The peak plasma concentration following oral dose is reached in 30 minutes to one hour.

The majority of penicillin is eliminated via the kidneys with a half-life of 30 minutes to one hour. In patients with renal failure, the half-life is drastically increased to 12 hours to 20 hours, and a higher dose is achieved rapidly. Lethal doses of the penicillin and other beta lactams are not established. There are no established doses or blood levels consistent with the development of toxic clinical manifestation such as myoclonic seizures. Both recent and historic reports of seizure activity with the use of massive amounts of intravenous beta lactam antibiotics are available, however; the authors found no reports with oral administration.^{51,52}

The hypersensitivity observed with penicillins is not dose-dependent. Fortunately, the feared Immunoglobulin E (IgE) mediated anaphylactic reactions to penicillins are uncommon, occurring in less than 20 per 10,000 courses of treatment with a fatality of 1 per 100,000, usually secondary to intravenous administration.⁵³ This life-threatening reaction is initiated with the release of histamine from mast cells secondary to binding of penicillin metabolites to the IgE receptors on mast cells. This results in increased bronchial secretion, edema, and subsequent respiratory distress accompanied by generalized vasodilatation and hypotension. This condition untreated can result in respiratory and cardiovascular arrest and subsequent death. A milder hypersensitivity manifesting as a skin rash may be present in as many as 10 percent of population.^{54,55} This is

also far more common with intravenous routes compared to oral administration.

Lincomycin, the parent substance leading to the development of clindamycin was discovered in 1962 in Lincoln, Neb. The dose range of oral clindamycin for the treatment of odontogenic infections is 150 mg to 450 mg three times a day (pediatric dose 8 to 20 mg/kg/day). It has a half-life of three hours and it is cleared via the renal and hepatic pathways. Patients with renal and/or hepatic diseases will have an increased bioavailability and half-life. Toxic dosages for humans remains to be determined. However, convulsions, depression, and death have been reported in mice receiving intravenous administration of 855 mg/kg, and death has been reported in rats receiving oral administration of 2618 mg/kg of clindamycin.⁵⁶

Clindamycin is a broad spectrum antibiotic with greater coverage compared to penicillin. This high spectrum of antibiotic coverage is also responsible for its most feared side effect: pseudomembranous colitis.⁵⁷ This condition is not exclusive to clindamycin, and can be seen with any broad spectrum antibiotic such as cephalosporins (a common causative agent), or extended spectrum penicillins such as amoxicillin. Also, pseudomembranous colitis needs to be differentiated from antibiotic-associated diarrhea, which is far more common. In pseudomembranous colitis, loss of normal flora will allow for selective growth of *Clostridium difficile*, the bacteria responsible for the production of the toxin. The symptoms include fever, abdominal pain and cramps, leukocytosis, along with a green-colored diarrhea, or blood in the stool.

Pseudomembranous colitis is confirmed by a *Clostridium difficile* toxin enzyme linked immunoassay or tissue culture assay. Upon confirmation, clindamycin should be discontinued and the pa-

tient referred to a physician for treatment with metronidazole or oral vancomycin. The frequency of pseudomembranous colitis with clindamycin has been reported as 0.1 percent to 10 percent of cases, and is found to be dose-independent with both oral and intravenous administrations.^{58,59} Diarrhea without pseudomembranous features is also seen in 2 percent

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to 20 percent of patients.⁶⁰ Therefore, development of diarrhea is not synonymous with pseudomembranous colitis.

Conclusion

In this brief article, the authors reviewed the overdose, adverse effects, toxicities, and characteristics of the most commonly used oral medications in the dental practice. Careful patient history and a high index of suspicion are essential to identify patients at risk. General knowledge of the toxic doses and recognition of symptoms of these medications will allow for expedient referrals and treatment of patients.

TABLE 1 summarizes the commonly prescribed oral medications in the dental practice, their therapeutic, toxic and/or lethal doses, along with the symptoms, and recommended treatment. ■■■■

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TABLE 1

Most Commonly Encountered Oral Medications in the Dental Practice

	Daily Therapeutic Dose	Toxic/Lethal Dose	Clinical Symptoms of Overdose	Treatment
ANALGESICS				
Aspirin	40-60 mg/kg/day	LD 0.07-0.1g/Kg	Vomiting, hyperapnea, tinnitus, lethargy, coma, seizures, death	Induced emesis if in first 3 hrs. Activated charcoal, alkalinize urine, hemodialysis
Ibuprofen	3200 mg (maximum daily recommended dose)	LD Unknown LD ₅₀ rat 1g/kg	Dizziness, nausea, vomiting, tinnitus, epigastric pain, coma, renal failure	Supportive care. Treat seizures and hypotension, activated charcoal, induced emesis, gastric lavage in massive OD
Naproxen	1500 mg (maximum daily recommended dose)	LD Unknown LD ₅₀ rat 543 mg/kg LD ₅₀ dogs >1g/kg	Dizziness, nausea, vomiting, tinnitus, epigastric pain, edema, diarrhea, headache	As above
Celecoxib	400 mg (maximum daily recommended dose)	Unknown	Abdominal pain, flatulence, diarrhea, dyspepsia, nervousness, tinnitus, rash	As above
Acetaminophen	4000 mg (maximum daily recommended dose)	LD 13-25g Toxic dose 5-15 g	Early: None or minor GI symptoms 24-72 hrs: Encephalopathy, ARF, liver failure, coma, death	Activated charcoal, N-Acetylcystine, induced emesis, dialysis
NARCOTICS				
Codeine	Not to exceed 360 mg in 24 hrs. Usually 60 mg q 6 hours. Can develop tolerance	LD ₅₀ 5 mg/kg LD rat 600 mg/kg Estimated fatal dose in humans is 1.5 g	Decreased temperature, respiration and blood pressure. Euphoria, stupor, pinpoint pupils, death	Supportive care /ACLS Naloxone
Hydrocodone	Usual oral dose: 5-10 mg q 6 hrs. Can develop tolerance	Unknown	As above	Supportive care /ACLS Naloxone
Oxycodone	Usual oral dose: 5-10 mg q 6 hrs. Can develop tolerance	Unknown	As above	Supportive care /ACLS Naloxone
BENZODIAZEPINES				
Diazepam	For anxiety 2-10 mg PO bid to qid.	LD ₅₀ 50 mg/kg	Respiratory depression, lethargy, drowsiness, cardiovascular collapse, bradycardia, death	Supportive care/ACLS Flumazenil
Alprazolam	Therapeutic dose is 0.25-1 mg	Unknown	Respiratory depression, lethargy, drowsiness, cardiovascular collapse, bradycardia, death	Supportive care/ACLS Flumazenil
Triazolam	Therapeutic dose is 0.125-0.25 mg per day. Maximum dose is 0.5 mg/day	Unknown	Respiratory depression, lethargy, drowsiness, cardiovascular collapse, bradycardia, death	Supportive care/ACLS Flumazenil

TABLE 1 CONT.

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	Daily Therapeutic Dose	Toxic/Lethal Dose	Clinical Symptoms of Overdose	Treatment
ANTIBIOTICS				
Penicillin	Effective maximum dose of 4g/day	LD unknown Toxic P.O. dose unknown Toxic dose for IV penicillin: 10 million units/d or CSF>5 mg/L	Seizure with single high dose (IV) or chronic excessive doses in patients with renal failure	Supportive care/ACLS Treat seizures as needed
Amoxicillin	Effective maximum dose 3g/day	Unknown	Minimal with acute oral overdose Acute renal failure caused by crystal deposition in excessive IV administration	Supportive care/ACLS Treat ARF as needed
Clindamycin	600-1800 mg/day in divided doses	Unknown	Minimal with acute oral overdose Hypotension and cardiopulmonary arrest reported after rapid IV administration	Supportive care/ACLS

ACLS: Advanced cardiac life support

ARF: Acute renal failure

GI: Gastrointestinal

LD: Lethal dose

LD₅₀: Lethal dose IN 50 percent of the populationLD_{LO}: Lowest lethal dose

OD: Overdose

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