Use of Intravenous Sedation in Periodontal Practice: A National Survey

Tingey BT, Clark SH, Humbert LA, Tingey JD, Kummet CM
J Periodontol 2012;83(7):830-835

Commonly Reported Drugs Used for Sedation

<table>
<thead>
<tr>
<th>IV Sedation</th>
<th>Oral Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Narcotics</td>
<td>Triazolam</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Lorazepam</td>
</tr>
</tbody>
</table>

Midazolam 68.9%
Narcotics 64.3%
Diazepam 37.8%
Diazepam 52.0%
Triazolam 43.0%
Lorazepam 24.7%
Nitrous Oxide/Oxygen (N₂O-O₂)

**Actions**
- produces numbing of extremities
- produces sedation at low levels
- produces tingling sensation
- produces analgesia at high levels

**Advantages**
- rapid onset of action
- easily titratable
- pleasant, non-irritating odor
- produces sense of heaviness, floating, warmth
- sounds appear distant
- rapidly cleared from the body

**Disadvantages**
- may cause nausea and vomiting
- cumbersome to the operator
- requires scavenging

**Route of Administration**
- inhalation

**Benzodiazepines**

- effects:
  - anxiolytic
  - anticonvulsant
  - sedative
  - hypnotic
  - muscle relaxant

- low dose
- high dose
Benzodiazepines

- Radiation generally provided without inducing significant respiratory or cardiovascular depression.
- Intensity of effects dependent upon blood level determined by:
  - Drug dose administered
  - Rate of administration
- CNS depressant effects potentiated by the presence of other anesthetic agents (e.g., nitrous oxide).
- Sedation generally provided without inducing significant respiratory or cardiovascular depression.
- Degree of amnesia (anterograde) varies among individual agents.

Pharmacokinetics

- Highly lipid soluble
- Highly protein bound
- Undergo biotransformation in liver
- Eliminated by the kidney
- Duration of action dependent on redistribution affected by:
  - Age
  - Sex
  - Enzyme induction
  - Hepatic or renal disease.

Cardiovascular and Respiratory Effects

- Cardiovascular and respiratory effects generally not clinically significant.
- When titrated to sedation endpoint, relatiely safe drugs with a large therapeutic index.
Benzodiazepines

Cardiovascular Effects
- Minimal decrease in:
  - arterial blood pressure
  - myocardial contractility
  - systemic vascular resistance

Respiratory Effects
- Respiratory depressant effects dose-related
  - secondary to direct CNS depression
  - mild reduction in ventilatory response to retained CO2 in healthy patients
  - apnea 2° to rapid administration of midazolam

Side Effects
- Few side effects with low doses
- Most common:
  - lightheadedness
  - mild psychomotor impairment
  - nausea / vomiting when used alone < 3%
- Benzodiazepines possess mild anti-emetic property
- Evidence from studies of benzodiazepine antagonist

Adverse Effects/Contraindications
- Thrombophlebitis (diazepam)
- Paradoxical reactions
  - excitation
  - prolonged psychomotor impairment
  - vertigo
- Prolonged sedation/inadvertent general anesthesia
- Excessive dosing
  - Cimetidine

Mechanism of Action
- Benzodiazepine receptor occupancy
  - <20% induction of anxiolysis
  - 30-50% sedation
  - >60% loss of consciousness

Benzodiazepine receptor occupancy
- Reduction of anxiety
- Induction of analgesia
- Sedation
- Loss of consciousness
Specific Receptor Antagonists

- Reverse spectrum of benzodiazepine effects
- Competitive, high affinity interaction with benzodiazepine receptor
- Antagonist has no intrinsic activity
  - Does not cause change in nerve membrane
  - Does not open chloride channels
  - Reduces number of receptors occupied by agonist
  - Can titrate reversal of benzodiazepine effects

Titrated dose can awaken an unresponsive patient without reversing analgesia
- Decrease degree of receptor occupancy enough to only reverse hypnosis
- Improves safety of IV benzodiazepines
- Not for routine use
- Concern with re-sedation
- Better to titrate agents to safe and effective endpoint

Intravenous Administration

- Titrated method most appropriate for IV administration of benzodiazepines
- Slow injection of drug to specific endpoint
- Moderate sedation endpoint defined by:
  - Calm appearance
  - Slurred speech
  - Ptosis of eyelids
  - At no time should the "conscious" patient become unresponsive to verbal command
Precautions Regarding Use in Elderly Patients

- Aging process results in:
  - Increased sensitivity to benzodiazepines
  - Less plasma volume as muscle mass declines
  - Changes in glomerular filtration rate and benzodiazepine excretion
  - Delay in onset of clinical effects
  - Reduction in cardiac output results in increased circulation time

- Need to titrate slowly to avoid overdose
- Impaired clearance may increase duration following chronic administration

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Diazepam

- Prototypical benzodiazepine
- Highly lipid soluble & water insoluble
- 99% bound to plasma protein
- Rapid onset: 1-3 minutes following IV administration
- Duration of action:
  - 40-60 minutes
  - Rate of distribution out of central nervous system

- "Hangover" after very large doses
- Composed of metabolic degradation results in prolonged elimination half-life 20-70 hours slow & variable
- Production of active metabolites which can themselves produce sedation
  - Desmethyldiazepam
  - Temazepam
  - Oxazepam

- Prototypical benzodiazepine
- High lipid solubility & water insolubility
- 99% bound to plasma protein
- Rapid onset 1-3 minutes following IV administration
- Duration of action:
  - 45-120 minutes
  - Rate of distribution out of central nervous system

- Biotransformation may lead to second sleep effect
- Irritating upon intravenous administration
- May lead to thrombophlebitis
- Reduction of incidence
  - Administration through large veins
  - Formulation dissolved in sterile emulsion
  - Diazemuls™ (available in Canada)

- Average adult dose approximately 5-10 mg
- Vary in response occurred for titration
- 5 mg/minute maximum rate of injection
- Avoid exaggerated CNS depressant effects
- Extreme incidence of vomiting
- Profound anxiolytic effects at this dose
- Amnesia unreliable and of short duration

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Diurepam

- Routes of Administration:
  - Intravenous
  - Oral
  - Rectal

Midazolam

- When first introduced
  - Thought to be twice as potent as diazepam
  - 57 deaths in first 18 months on market
  - Now considered 3-4 times more potent
  - Pacing without objectively defined
  - Same spectrum of dose-dependent effects
  - Relatively less outward signs of sedation although
    much more predictable amnesia

WARNING:
Intravenous midazolam has been associated with respiratory depression and respiratory
arrest, especially when used for sedation in noncritical care settings. In some cases, where
this was not recognized promptly and treated effectively, death or hypoxic encephalopathy
has resulted.

Midazolam

- Water soluble formulation
- Becomes lipid soluble after injection
- Risk of venous irritation
- Rapid onset of action
Midazolam

- Rapid onset = 30-60 seconds
- Peak effect = 3-5 minutes
- Distribution half-life = 6-15 minutes
- Elimination half-life = 1.5-3 hours
- Duration of action:
  - short (50-30 minutes)
  - dose-dependent
- Short elimination half-life
- Rapid excretion of metabolites
- Biotransformation → no active metabolites
- Thrombophlebitis virtually eliminated

Midazolam

- Availability:
  - 5 mg/ml (green packaging)
  - 1 mg/ml (orange packaging)
  - 2 mg/ml (HCl syrup)

Midazolam

- Routes of administration:
  - Intravenous
  - Intramuscular
  - Oral
    - Doses 1-3 mg/kg, maximum dose of 30 mg
    - For use in children

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Midazolam

- Recommended rate of injection: 1.0 mg/minute
- Rapid administration associated with severe respiratory depression
- Amnesia persists for 20-30 minutes

Midazolam HCl syrup is indicated for use as a single dose for procedural sedation and analgesia in pediatric patients.

- Rapidly absorbed after oral administration
- Subject to substantial intestinal and hepatic first-pass metabolism

Diazepam vs. Midazolam

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diazepam</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active metabolites</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Distribution half-life</td>
<td>30-60 min</td>
<td>6-15 min</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>20-70 hr</td>
<td>1.5-3 hr</td>
</tr>
<tr>
<td>Onset</td>
<td>1-3 min</td>
<td>30 sec</td>
</tr>
<tr>
<td>Duration</td>
<td>45-120 min</td>
<td>20-35 min</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unique effects</td>
<td>Thrombophlebitis</td>
<td>Mild hypotension</td>
</tr>
<tr>
<td>Potency</td>
<td>5 mg</td>
<td>1-2 mg</td>
</tr>
<tr>
<td>Concentration</td>
<td>5 mg/ml</td>
<td>1 and 5 mg/ml</td>
</tr>
<tr>
<td>IV increment</td>
<td>2.5-5 mg</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

Triazolam

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“If the only tool you have is a hammer, you tend to see every problem as a nail.”

Abraham Maslow

Anesthesia Guides Get Update

Today’s News
Nov. 5, 2002
Anesthesia guides get update
House OKs changes to Association’s policy on oral sedative agents

“...in the last several years, there [had] been a proliferation of CE courses where the technique being touted calls into question good anesthetic principles with regard to the use of these medications...”

Robert M. Peskin, D.D.S.

http://www.ada.org/prof/pubs/daily/0211/1105sed.html

“...What apparently is being taught is that following the initial administration of a certain medication, if in the practitioner’s judgment the desired effect has not been attained, additional doses are added...”

“In recommending changes to the guidelines, it was the Committee’s opinion that orally administered drugs cannot be treated safety in that manner.”
Titration

The administration of small incremental doses of a drug until a desired clinical effect is observed. In accord with this particular definition, titration of oral medication for the purposes of sedation is unpredictable.

Titration

Repeated dosing of orally administered sedative agents may result in an alteration of the state of consciousness beyond the intent of the practitioner. Except in unusual circumstances, the maximum recommended dose of an oral medication should not be exceeded.

Triazolam

- Effective anxiolytic and amnestic agent
- Rapid onset of action
- Peak blood levels in 1.3 hours
- Short elimination half-life
- T½ = 2-3 hours
- Biotransformed into inactive metabolites

Characteristics

- Eight (8) times more effective than diazepam
- Very little effect on circulatory or respiratory system
- Several studies have shown no changes in blood pressure, pulse or O₂ saturation and only a slight change in respiratory rate
Triazolam

- Short duration of action is ideally suited to dentistry
- Allows for rapid recovery
- Important for outpatient procedures
- Shown to be as effective as intravenous diazepam for conscious sedation

- Significant adverse reactions widely publicized in the lay press are associated with repeated use of high doses, particularly in the elderly
- Behavioral abnormalities

Peak plasma concentration
- Within 1.3 hours
- Occurs more rapidly in daytime than at night
- As much as 2 times quicker after 12 hour fast
- Absorbed 2.86 times faster when administered sublingually

*range 0.5 - 4.0 hours after dose

Metabolized in the liver by CYP 3A substrate
- Hydroxylation
- Oxidation
- 90% in the urine
- 9% in the feces
- Reacts adversely when taken with cimetidine
- Tagamet®

Availability (as Halcion®)
- 0.125 mg tablets
- 0.25 mg tablets

Routes of administration
- Oral

Usual adult dose
- 0.125 - 0.25 mg (30 - 45 minutes pre-op)
The Triazolam Controversy

- No published studies evaluating the safety of incremental sublingual administrations

- No published studies evaluating the reversal of triazolam by intramuscular injection of the competitive antagonist flumazenil

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Pharmacokinetics and Clinical Effects of Multi-Dose Sublingual Triazolam in Healthy Volunteers

Jackson DL, Milgrom P, Heacox GA, Kharasch ED

J Clin Psychopharm 2006;26:4-8

Objectives

- Evaluate CNS depression by repeated dosing of sublingual triazolam
- To determine if triazolam plasma concentrations are time-dependent
- Compare efficacy of single flumazenil dose (0.2 mg) at reversing sedative effects of triazolam
- Intranasal
- Intramuscular
- Intravenous
Summary

- Incremental dosing of triazolam (1 mg, total) over 90 minutes produced highly variable levels of CNS depression in ASA I subjects over the course of 180 minutes.
- While many of the subjects were within the range of moderate sedation, a level of CNS depression consistent with deep sedation was induced in some of the subjects.
- A single dose of flumazenil was unable to completely reverse the sedative effects of triazolam short term (within 20 minutes of administration).
- All subjects experienced some amount of rebound sedation within 60 minutes.

Benzodiazepine Elimination

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Elimination Half-Life (hr)</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>1-2 hr</td>
<td>a-hydroxyalprazolam</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5-6 hr</td>
<td>desmethyldiazepam</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1-6 hr</td>
<td>none</td>
</tr>
<tr>
<td>Midazolam</td>
<td>2-3.6 hr</td>
<td>a-hydroxymidazolam</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>1-4 hr</td>
<td>none</td>
</tr>
<tr>
<td>Triazolam</td>
<td>1.2-2 hr*</td>
<td>a-hydroxytriazolam</td>
</tr>
</tbody>
</table>

* peak concentration is 28% faster when given sublingually

Flumazenil

- Specific benzodiazepine antagonist
- High affinity
- Easily reversible weak inhibition of delta receptors
- Zero efficacy

Mechanism of action:
- Unconsciousness
- Sedation
- Amnesia
- Psychomotor dysfunction
Flumazenil

- Less lipid soluble, low binding to plasma proteins
  → rapid distribution of free drug
- Short onset of action = 1-2 minutes
- 80% response in 3 minutes
- Peak effect = 6-10 minutes

- Duration of action
  - Intravenous
    → 20-35 minutes
  - Biotransformation in liver
  - Distribution half-life = 7-15 minutes
  - Short elimination half-life = 54 minutes

- Rapid hepatic biotransformation and renal secretion

- Titrating 0.2-0.5 mg usually sufficient for prompt reversal of unarousable patient
- 0.1 mg/minute if not respiratory emergency
- Profound re-sedation more likely if:
  - Reverse diazepam or lorazepam
  - Cumulative dose of midazolam > 10 mg

Comparison of Routes of Flumazenil Administration to Reverse Midazolam-induced Respiratory Depression in a Canine Model

Heniff MS, Moore GP, et al
*Acad Emerg Med* 1997;4:1115-1118
Results

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous (IV)</td>
<td>120 seconds</td>
<td>± 24.5 seconds</td>
</tr>
<tr>
<td>Sublingual (SL)</td>
<td>202 seconds</td>
<td>± 94.5 seconds</td>
</tr>
<tr>
<td>Intramuscular (IM)</td>
<td>310 seconds</td>
<td>± 133.7 seconds</td>
</tr>
<tr>
<td>Rectal (PR)</td>
<td>542 seconds</td>
<td>± 84.4 seconds</td>
</tr>
</tbody>
</table>

Opioid Analgesics

Classification

- Agonist: specifically stimulates opioid receptor
- Partial Agonist: intermediate efficacy
- Agonist-Antagonist: between 0 - 100%
- Antagonist: drugs that bind with high affinity and zero efficacy

Mechanism of Action:
through stimulation of opioid receptor

Opioid receptors for endogenous opioids
- Enkephalins
- Endorphins
- Dynorphins

Opioid receptor classification
- mu
- delta
- kappa
- sigma (?)

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[Acad Emerg Med 1997;4:1115-1118]
**Mu (μ) Receptor Actions**

- Analgesia (supraspinal and spinal)
- Euphoria
- Sedation
- Catalepsy
- Altered locomotion
- Tolerance and withdrawal
- Alteration of seizure activity
- Alteration of pituitary hormone release
- Ocular effects (mydriasis or miosis)

**Delta (δ) Receptor Actions**

- Spinal analgesia
- Withdrawal
- Anticonvulsant effects
- Luteinizing hormone inhibition
- Decrease in bladder motility
- Respiratory depression
- Hypertension
- Catecholamine inhibition

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Kappa (κ) Receptor Actions
- Analgesia (primarily spinal but also supraspinal)
- Sedation
- Constipation
- Tolerance
- Seizure induction
- Vasopressin inhibition
- Bradycardia
- Psychotomimetic and dysphoric actions

Opioid Analgesics: CNS Effects
- Analgesia
  - Primary effect of all opioids due to:
    - Increased pain threshold
    - Increased pain tolerance
- Sedation
  - Drug-dependent
  - May be potentiated by other CNS depressants
  - Mediated by mu and kappa receptors
- Euphoria/Dysphoria
  - Euphoria mediated by mu receptors
  - Potential for dysphoria mediated by kappa receptors
- Tolerance
  - Decreased response to the same dose of a drug over time
  - Mediated by all opioid receptors
- Physical dependence
  - Drug withdrawal produces spontaneous disturbance
  - May be supplemented by replacement
  - Mediated by all opioid receptors
- Addiction
- Antitussive effect
- Nausea and vomiting
  - Exacerbated in ambulatory patient
- Opioid Analgesics: CNS Effects
- Physical dependence
  - Drug withdrawal produces spontaneous disturbance
  - May be supplemented by replacement
  - Mediated by all opioid receptors
- Addiction
- Antitussive effect
- Nausea and vomiting
  - Exacerbated in ambulatory patient
Opioid Analgesics: Respiratory Effects

- All mu receptor agonists depress respiration
  - 2nd degree depression occurs in response of respiratory center to CO2
  - Alveolar ventilatory response to CO2
    - decreased
    - shifted to right
  - High doses can block spontaneous respiration
    - may be seen in susceptible patients with lower doses
    - potentiated by other CNS depressants (except diphenoxylate)
  - Manifestations
    - decreased respiratory rate with increased tidal volume
    - apnea (in high enough doses), although the patient retains the ability to respond to a command to initiate breathing
    - PCO2 is elevated
    - administration to patients with COPD with caution

Opioid Analgesics: Other Effects

- Gastrointestinal
  - constipation
  - biliary tract smooth muscle spasm
- Other effects
  - histamine release
  - miosis
  - chest wall rigidity

Opioid Analgesics

- Agonists
  - morphine sulfate
  - meperidine hydrochloride
  - fentanyl citrate
  - alfentanil hydrochloride
  - sufentanil citrate
  - remifentanil hydrochloride
- Agonist/antagonists
  - pentazocine lactate
  - nalbuphine hydrochloride
  - butorphanol tartrate
- Other effects
  - nausea
  - vomiting
  - pruritus
  - miosis
  - respiratory depression
Meperidine

- Demerol
- Synthetic narcotic
- One-tenth as potent as morphine
- Not nauseogenic
- May produce hypotension

Most frequently used opioid in dentistry
- Minimal atropine-like effect
- 0 salivary secretions
- Localized histamine release
- "Tracking phenomenon"
- Not an allergic reaction!
- Self-limiting over 10-15 min.

Onset: 2-4 min.
Duration: 30-45 min.
Availability: 50 mg/ml
Dosage: 25-50 mg

Fentanyl

Sublimaze
- Rapid onset: <1 min., but max. effect does not occur for several min.
- Short duration: 30-60 min.
- 100x more potent than morphine
- 100 μg fentanyl = 10 mg morphine
**Fentanyl**

- Recovery:
  - Respiratory depression activity outlasts analgesia
  - Respiratory depression:
    - peaks in 5-15 min
    - may last up to 4 hr.

- Cardiovascular system:
  - Remains stable
  - May see bradycardia

**Indications:**
- Short procedures
- Supplement to GA
- Premedication & maintenance
- Chest wall (truncal) rigidity – dose/rate dependent
- Managed by assisted or controlled ventilation
- Neuromuscular blockade

**Precautions:**
- Not recommended < age 2
- Pregnancy (risk/benefit ratio?)
- Patients w/ COPD, liver & renal dysfunction
- No narcotics within 14 days of MAOI's
- Severe & unpredictable potentiation of narcotic effect

**Sublization:**
- Rapid onset: < 1 min, but max effect does not occur for several min.
- Short duration: 30-60 min
- 100x more potent than morphine,
  - 0.1 mg 100 µg fentanyl = 1 mg morphine
Fentanyl

- Parenteral Availability:
  - 50 μg/ml
  - Dosage: 25-100 μg
- Fentanyl Patch:
  - 12 - 100 μg/hr
- Fentanyl Lollipop:
  - 200 - 1600 μg

Morphine Sulfate

- Classical narcotic agonist
- Duration: 1½ - 2 hr.
- Rarely used in outpatient sedations
  - Parenteral dose should not exceed 8 mg
  - Dilute to 1 mg/ml
  - Drug of choice in treating MI pain

Naloxone Hydrochloride

- Narcotic antagonist
- Soluble in water, dilute acids and strong alkali
- Routes of administration:
  - Intravenous
  - Intramuscular
  - Subcutaneous
- Prevents or reverses effects of opioids:
  - Respiratory depression
  - Sedation
  - Hypotension
- Reverses effects of agonist-antagonists
  - Psychotomimetic effects
  - Dysphoric effects
Naloxone Hydrochloride
- Pure narcotic antagonist with no other pharmacologic activity
- Onset of action: within 2 minutes
- Duration of action: dependency on dose and route of administration
- Serum half-life: 30-81 minutes

Anticholinergics/Antisialogues
- Advantages:
  - Reduce excessive secretions
  - Vagolytic
- Disadvantages:
  - Onset of action may be longer than procedure
  - Atropine shorter than glycopyrrolate

Routes of Administration
- Oral
- Intramuscular
- Intravenous
- Examples:
  - Atropine
  - Glycopyrrolate
  - Scopolamine

Agents that are Inappropriate for Moderate Sedation
- Narcotics
  - Remifentanil
- Neuroleptics
  - Phentolamine
  - Butyrophenones
- Dissociative Anesthetics
  - Ketamine
- Barbiturates
  - Methohexital
  - Althesin
- Propofol
- Muscle Relaxants
  - Depolarizing
  - Nondepolarizing