Oral Sedation

Edward C. Adlesic, DMD
University of Pittsburgh School of Dental Medicine

Oral Sedation

➢ What is it good for???
➢ Edwin Star 1970s
➢ “Absolutely nothin”
➢ Pediatric dentists
  ➢ the experts in oral sedation
  ➢ take uncontrollable patients 🔄 give them a
    “cocktail” and are able to provide care for 30 mins to
    an hour
  ➢ specialty is dedicated to the safe practice of oral
    sedation

Oral Sedation in Adults

➢ Questionable practice
  ➢ agents can provide safe anxiolysis when they work
    • but it is unpredictable
  ➢ moderate sedation with oral medications
    • controversial on several levels

Oral Sedation

➢ Chloral hydrate (trichloroethanol)
  ➢ synthesized in 1832
  ➢ sedative hypnotic agent
  ➢ CNS depressant
    • respiratory depression as well
  ➢ dose = 20 to 40 mg/kg
    • maximum dose of 1000 to 1500 mg
  ➢ hypnosis in ~ 30 minutes
  ➢ best use in children < 48 months old
    • decreased efficacy in older children
Chloral Hydrate

➢ chloral hydrate + alcohol spirits
  • Mickey Finn or knock out drops
➢ adverse effects
  – myocardial sensitization with volatile agents
  – metabolite is carcinogen
➢ no analgesia
➢ purchase from compounding pharmacy
➢ was used in pediatric dentistry
  – replaced by midazolam

Oral Diphenhydramine

➢ Benadryl
➢ 1.5 mg/kg oral dose in children
  – oral syrup: 12.5 mg/5 ml
➢ 50 to 100 mg oral dose in adults
➢ onset = 1 hour
➢ duration = 4 to 6 hours
➢ onset is slow & duration is too long

Hydroxyzine (Vistaril)

➢ antihistamine agent
  – anxiolytic, analgesic, & antiemetic properties
  – side effect: dry mouth
➢ dose in children
  – 1 to 2 mg/kg PO maximum dose = 50 mg
  – onset = 15 to 30 minutes
  – working time = 45 minutes
  – duration = 2 to 4 hours

Hydroxyzine (Vistaril)

➢ in children
  – often combined with oral Demerol
➢ tablets: 10, 25, 50, & 100 mg
➢ syrup: 10 mg/5 ml & 25 mg/5 ml
Oral Sedation

➢ Barbiturates
  – barbital in early 1900s
  – Amytal, Seconal
  – Thiopental
  – CNS depressants
  – low margin of safety
  – benzodiazepines replaced this class of drugs

Benzodiazepines

➢ are the agents of choice for oral anxiolysis
➢ compared to previous agents
  – equal or greater efficacy
  – greater margin of safety
➢ anxiolytic, sedative, & hypnotic effects
  – dose dependent
➢ CNS effects are mediated by GABA system

GABA

➢ GABA is an inhibitory neurotransmitter in the CNS
  – counteracts the excitatory neurotransmitters
➢ 3 GABA receptors on the post synaptic neuron
  – GABA_A
    • this is the target receptor for many general anesthetic agents
  – GABA_B
  – GABA_C

GABA – A Receptor

➢ consists of 5 glycoprotein subunits
  – α, β, γ ( alpha, beta, gamma )
  – subunits can also have subunits
    • α 1 – 6  β 1 – 3
➢ activation of GABA receptor increases Cl ion transmembrane conduction
  – hyperpolarize the post synaptic membrane
  – inhibit post synaptic transmission
➢ benzodiazepines bind to the GABA_A α subunit
Benzodiazepine Receptors

- benzodiazepines bind to α receptors
  - α1, α2 receptors
  - also called benzodiazepine receptors (BZ receptors)
- BZ1 receptors mediate
  - sedation & anticonvulsant effects
- BZ2 receptors mediate
  - anxiolysis, antergrade amnesia, & skeletal muscle relaxation

Benzodiazepines

- dose dependent CNS depression
  - concentration dependent receptor occupancy
  - 20% occupancy - anxiolysis
  - 30 to 50% occupancy - sedation
  - ≥ 60% occupancy - hypnosis
- high therapeutic index
  - dose required to achieve the desired effect is far less than the dose that produces adverse effects
- shallow dose response curve
  - dose that produces mild to moderate sedation is far less than the dose for inducing hypnosis

➢ benzodiazepine does not open the Cl channel
➢ GABA must bind to its receptor for BZ to have an effect: No GABA – No response
➢ Benzodiazepine then binds to its GABA receptor
  - this enhances GABA's ability to open the Cl channel

Benzodiazepines

➢ dose dependent CNS depression
  - concentration dependent receptor occupancy
  - 20% occupancy - anxiolysis
  - 30 to 50% occupancy - sedation
  - ≥ 60% occupancy - hypnosis

➢ all BZ agents have same efficacy for sedation
➢ varying degrees of antergrade amnesia
➢ all reversible with flumazenil
Effective dose (ED₅₀) for BZ is far less than lethal dose (LD₅₀) ⇒ death from overdose BZ very rare

not so for barbiturates & other sedative hypnotic
   - these agents directly open Cl channels even in absence of GABA

Pharmacokinetics

lipid soluble agents
   - ↑ ability to diffuse from plasma to brain
   - more rapid onset
   - ↓ duration of action by redistribution

metabolism is by hepatic phase I enzymatic reactions
   - metabolite may be active ⇒ that will ↑ duration of effect

elimination half life does not predict anesthetic duration

Elimination of BZ

- triazolam, midazolam, & alprazolam
  - phase I reactions form α hydroxy metabolite which breaks down to inactive glucuronide compound

- lorazepam
  - 1 step conjugation reaction to form inactive glucuronide compound

- diazepam
  - form active metabolite nordazepam, then oxazepam, another active metabolite, then inactive glucuronide compound for excretion by kidney

CVS Effects of BZ

- minimal CVS effects with therapeutic doses
- high doses depress the CVS
  - ↑ HR ↓ BP
- BZ will decrease cardiovascular response to stress (anxiety & pain)
Respiratory Effect of BZ

➢ minimal respiratory depression
➢ high doses can result in
  – depression of hypoxic respiratory drive
  – apnea
➢ COPD & OSA patients
  – BZ can cause airway obstruction by relaxation of airway
  – in OSA anesthetics decrease arousal mechanism

Other Effects

➢ disinhibitory reactions
  – dysphoria
  – idiosyncratic responses from BZ
  – excitement, agitation, confusion, & hostility
  – additional doses of BZ do not resolve the problem
    • will delay recovery
    • may make reaction worse
➢ IV route: venous irritation & phlebitis
➢ mild anticholinergic response
  – dry mouth ↑ IOP

Oral Diazepam

➢ long acting agent
➢ onset 30 to 60 minutes
➢ peak plasma concentration 1 to 2 hours
➢ duration of action 2 to 4 hours
➢ elimination half life 20 to 80 hours

Oral Diazepam

➢ lipid soluble drug
  – final redistribution compartment is fat
  – prolonged drowsiness is due to slow release from fat
➢ active metabolites
  – nordazepam 30 to 100 hours
  – oxazepam 5 to 15 hours
  – adds to drowsiness & “hang over” effects
### Oral Diazepam (Adults)
- **Usual dose**: 10 to 30 mg PO (0.05 to 0.3 mg/kg)
- **Minimal sedation dose**: 5 to 10 mg PO
- **Moderate sedation dose**: 15 to 30 mg PO
- **No repeat dose given**
- **Better alternative BZ available for use**: triazolam

### Oral Diazepam (Children)
- **Usual dose**: 0.25 to 0.5 mg/kg PO
  - Child 2 to 5 yrs.: 2 to 5 mg
  - Child 6 to 10 yrs.: 5 to 10 mg
  - Child 11 to 15 yrs.: 5 to 15 mg
- **Typical working time of**: 45 to 60 minutes

### Oral Midazolam
- **Short acting BZ**
- **Onset of action**: 15 to 30 minutes
- **Peak plasma level**: 20 to 50 minutes
- **t\(_{1/2}\)b elimination**: 1.7 to 2.6 hours
- **Bioavailability from oral route**
  - 35 to 44%
  - Due to gastric acidity in stomach

### Oral Midazolam
- **High degree of liver 1st pass effects**
- Decrease midazolam plasma concentrations
- **Adult dose**:
  - 0.5 mg/kg PO
  - Maximum dose of 20 mg
- **Not a recommended BZ for adult sedation**
- **Used mostly in children**:
  - 0.5 mg/kg maximum of 15 mg
  - Duration of 30 minutes
Oral Lorazepam (Ativan)

- long acting BZ
- onset of action: 60 to 120 minutes
- peak plasma level: 1 to 2 hours
- duration of action: 2 to 4 hours
- oral bioavailability: 83 to 100%
- $t_{1/2}$ elimination: 10 to 20 hours

Oral Lorazepam (Ativan)

- low lipid solubility agent
  - delayed onset of action
    - takes longer to leave plasma & enter CNS
  - prolonged duration of action
    - slow redistribution from CNS
- no active metabolite
  - phase II hepatic metabolism
    - glucuronide conjugation
    - inactive metabolite excreted in urine

Oral Lorazepam (Ativan)

- adult dose: 1 to 3 mg (0.02 mg/kg)
- profound amnesia with lorazepam: “forget the entire day”
- not an agent for children

Triazolam (Halcion)

- short acting sedative hypnotic
- Netherlands 1977 at maximum dose 1 mg
  - reports of hallucinations, amnesia, aggression, depression, & bizarre behavior
- introduced in US in 1983
  - maximum dose: 0.5 mg
- reports of adverse effects continued
  - 0.5 mg tablet removed from market
  - FDA review: 0.125 to 0.25 mg safe to use

Arch Int Med. 1991;151:2003
**Triazolam (Halcion)**

- **current indication for use** is insomnia
  - short term treatment only
  - 0.125 to 0.25 mg PO
  - maximum recommended dose (MRD)
    - **in rare cases 0.5 mg is used**
- minimal sedation = anxiolysis
  - 0.125 to 0.25 mg
- minimal to moderate sedation in dentistry
  - 0.125 to **0.5 mg** PO or SL


**Triazolam (Halcion)**

- drug of choice for anxiolysis in adults
- onset PO 30 minutes
- peak plasma levels ~ 75 minutes
  - peak plasma levels occur 15 to 30 mins prior to CNS effects
- duration of action ~ 2 hours

**Sublingual Triazolam**

- avoids liver 1st pass effect
- increases bioavailability by 28%
- greater anxiolytic effect than PO route
  - no ↑ in adverse side effects by this route
  - no ↑ in psychomotor impairment
- no detectable amnesia
- 0.5 mg SL triazolam should be used cautiously
  - potential ↑ in side effects & recovery

Triazolam prior to Sedation

- 0.25 mg PO (45 to 60 min) prior to IV sedation
- reduced anxiety at time of venipuncture
- reduced doses of intra operative IV drugs

Anesth Progress. 1993;40: 117-121

Triazolam Oral Sedation

- single dose of agent 1 hour prior to surgery
- 0.125 to 0.25 mg PO
  - sublingual route more effective
- MRD maximum recommended dose 0.5 mg
  - manufacturer of drug ➔ unusual circumstances
  - used for moderate sedation in dentistry 0.25 to 0.5 mg
- like any oral medication: unpredictable results

### Table 3. Dose Requirements for IV Conscious Sedation

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (Mean ± SE)</th>
<th>Triazolam Group (Mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam (mg)</td>
<td>6.0 ± 0.9</td>
<td>4.6 ± 0.7</td>
</tr>
<tr>
<td>Fentanyl (ug)</td>
<td>130.5 ± 15.8</td>
<td>97.8 ± 13.8</td>
</tr>
<tr>
<td>Metohexital (mg)</td>
<td>86.8 ± 29.0</td>
<td>43.2 ± 12.8</td>
</tr>
</tbody>
</table>

Differences in dose were not significantly different between treatment groups (ANOVA).

### Triazolam Multiple Dosing

- 188 patients for 270 procedures over 15 years
- age 7 to 78
- weight based dose triazolam
  - based upon sedation scores from 1st treatment
  - 0.25 mg for 1st 40 lbs
  - additional 0.125 mg for each 70 lbs
  - given 1 hour prior to scheduled appointment
  - medical literature ➔ usually not weight based dose
  - use either 0.125 or 0.25 mg

- after 30 minutes: assess the level of sedation
  - if inadequate ➔ give ½ the initial dose

- procedure started after 60 minutes
  - if not sedate ➔ add nitrous oxide 30 to 50%
  - if that fails ➔ reschedule for IV sedation

- SpO2 mean range ➔ 96.5 to 96%
  - multiple patients 90 to 96%
**Triazolam Mutiple Dosing**

- CVS system stable
- dose range was 0.25 mg to 0.75 mg
- 98.4% success rate
- only 9% needed the second dose

Question: if only 9% required a second dose, why not limit the oral sedation to just a single preoperative dose and refer the others for IV

*General Dentistry, 2004 Nov-Dec; 496-501*

**Triazolam & Implant Surgery**

- usual dose 0.125 to 0.25 mg for insomnia
- dental sedation: 0.125 to 0.25 mg PO or SL
  - give a dose the evening before
  - anxiolytic dose 1 hour before surgery
- not a weight based dose
- do not exceed 0.5 mg

*J Oral Implantology, 2004; 30(2): 93-97*

**Incremental Triazolam**

- 0.25 mg PO 1 hour before procedure
- reassess in 30 minutes
  - if sedation inadequate ➔ 0.25 mg SL by dentist
  - additional doses are used ➔ time interval not explained
- during xrays, bite adjustment, or restroom breaks where you need patient cooperation
  - 2.0 ounces of clear fruit juice (do not use grapefruit) through a straw
  - lightens sedation by physiologic stimulation
  - REALLY?????

*General Dentistry, 2005 Jan-Feb; 22-26*
2007 Oral Sedation Survey

- Oral sedation in 1686 cases
  - At home dosing: 10.9% of cases
    - Triazolam 50.4%, Diazepam 46.9%
  - In office dosing: 81.8% of cases
    - Triazolam used 82.9% of the time
      - 54.8% used 1 additional dose
      - 32.3% used 2 additional doses
      - 19.9% used 3 additional doses
      - 6.2% used 4 additional doses
      - Rare to see more than 4 additional doses

2007 Oral Sedation Survey

- Adverse side effects
  - 78.2% no adverse effects
  - 16% DBP decrease > 25% baseline
  - 4% SpO₂ < 90

- Based on the survey, the conclusion was
  - Triazolam used at 1 to 3 doses of 0.125 or 0.25 mg
  - Max dose could be 2 mg as it is 4X as potent as lorazepam

Justifying Total Anxiolytic Dose of Triazolam

- Attempt to recommend oral doses for sedation
- Compared lorazepam to triazolam
  - Statement in paper: lorazepam to triazolam ratio is 4:1
- Used lorazepam doses in ETOH withdrawal
  - ETOH withdrawal: lorazepam total dose PO 8 mg/day
  - Statement in paper: triazolam max dose could be 2 mg/day since it is 4X as potent as lorazepam
- Flawed conclusion
  - ETOH withdrawal symptoms including seizures cannot be compared to procedural sedation

Justifying Total Anxiolytic Dose of Triazolam

- Previous oral sedation literature set maximum anxiolytic dose of triazolam to be 0.625 mg
  - Far below the 2.0 max 24 hour dose
- Arbitrarily picked 200 lbs as maximum weight to dose triazolam & set that dose as 0.5 mg
  - 0.25 mg for 1st 40 lb then 0.125 mg for each 70 lb
- Divide weight by 400 for triazolam & 100 for lorazepam to get max weight based dose for ages 41 to 64
Maximum Cumulative Dose

- paper claims maximum cumulative dose of triazolam is 2.0 mg in 24 hr
- use their weight based formula to set initial dose
- additional doses are given every 90 min as needed
  - no additional dose to exceed 0.25 mg
- no scientific research to validate the above
- Question: should 90 min be the interval for dosing???

Gen Dentistry. 2007 March-Apr: 143-148

Adult Minimal Oral Sedation

- triazolam initial dose PO 0.125 to 0.375 mg
- if sedation not adequate
  - redose after 2 hours
  - use SL route ➔ greater bioavailability
  - maximum total dose 0.5 mg
- limit treatment time to 4 hours
- avoid multiple incremental dosing
- may be reasonable approach

Gen Dentistry. 2012 Jan-Feb: 31 - 43

However

- following statements are of concern
- afternoon cases encourage intake of small amount of clear liquids + dry toast or crackers to "absorb gastric secretions"
- DM patients should take their medications
  - in operatory give them small amounts of apple juice to stabilize blood sugars
- SpO₂ < 92%: take 1 to 2 deep breaths & reverses in few seconds
- Flumazenil 0.2 mg SL will reverses BZ??????

Gen Dentistry 2012

---

**Table 2: Adult minimal oral sedation**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>≤50</th>
<th>51-60</th>
<th>61-65</th>
<th>66+</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-40</td>
<td>0.24</td>
<td>0.28</td>
<td>0.30</td>
<td>0.32</td>
</tr>
<tr>
<td>50-60</td>
<td>0.38</td>
<td>0.42</td>
<td>0.45</td>
<td>0.50</td>
</tr>
<tr>
<td>61-65</td>
<td>0.48</td>
<td>0.52</td>
<td>0.55</td>
<td>0.60</td>
</tr>
<tr>
<td>≥66</td>
<td>0.55</td>
<td>0.58</td>
<td>0.60</td>
<td>0.65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>≤50</th>
<th>51-60</th>
<th>61-65</th>
<th>66+</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-40</td>
<td>0.24</td>
<td>0.28</td>
<td>0.30</td>
<td>0.32</td>
</tr>
<tr>
<td>50-60</td>
<td>0.38</td>
<td>0.42</td>
<td>0.45</td>
<td>0.50</td>
</tr>
<tr>
<td>61-65</td>
<td>0.48</td>
<td>0.52</td>
<td>0.55</td>
<td>0.60</td>
</tr>
<tr>
<td>≥66</td>
<td>0.55</td>
<td>0.58</td>
<td>0.60</td>
<td>0.65</td>
</tr>
</tbody>
</table>

- weight calculations are for age 41 to 64
- age 18 to 40 increase dose by 25%
- age 65 and older decrease by 50%

---

**Table 3: Adult minimal oral sedation**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>≤50</th>
<th>51-60</th>
<th>61-65</th>
<th>66+</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-40</td>
<td>1.20</td>
<td>1.35</td>
<td>1.50</td>
<td>1.65</td>
</tr>
<tr>
<td>50-60</td>
<td>1.80</td>
<td>2.00</td>
<td>2.20</td>
<td>2.40</td>
</tr>
<tr>
<td>61-65</td>
<td>2.40</td>
<td>2.60</td>
<td>2.80</td>
<td>3.00</td>
</tr>
<tr>
<td>≥66</td>
<td>3.00</td>
<td>3.20</td>
<td>3.40</td>
<td>3.60</td>
</tr>
</tbody>
</table>

- following statements are of concern
- afternoon cases encourage intake of small amount of clear liquids + dry toast or crackers to "absorb gastric secretions"
- DM patients should take their medications
  - in operatory give them small amounts of apple juice to stabilize blood sugars
- SpO₂ < 92%: take 1 to 2 deep breaths & reverses in few seconds
- Flumazenil 0.2 mg SL will reverses BZ??????
Pharmacokinetics

- IV route: immediate plasma levels
- PO route: slower to absorb; bioavailability issues; lower plasma concentrations

Anest Progress. 2011; 58: 166

Pharmacokinetics of Triazolam PO

- PO & SL dose have short half-life: 2 to 4 hours
- dose of triazolam determines
  - intensity of anxiolysis
  - duration of effect
- dose of 0.5 mg SL can have sustained sedation beyond 8 hours
  - full recovery can not occur at the completion of a 4 hour appointment – refer back to 2012 paper on time


- demonstrates effect-site equilibration effect
  - time for triazolam to leave plasma & cross blood brain barrier
  - clinical effect of drug delayed 30 mins after T_{max} of 1 hour

Triazolam: single SL dose of 0.25 mg

- 1st dose at 0; 2nd dose at 60 min; 3rd dose at 90 min
- maximum pharmacologic effects at 3 hours
- still exceed 2 ng/ml at 8 hours
  - C_{max} for 0.25 mg triazolam is 2 ng/ml
- expect some sedation past 8 hours

J Clin Psychopharm. 2006
Pharmacokinetics Stacked Doses

- healthy volunteers age 21 to 39
- 3 Groups of SL triazolam 0.25, 0.50, 0.75 mg
- evaluate sedation by BIS & Observer Assessment of Alertness/Sedation (OAA/S) scale

2009 Study

<table>
<thead>
<tr>
<th>Dose</th>
<th>Plasma concentration at end of 6 hours ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 mg</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>0.50 mg</td>
<td>2.9 ± 1.5</td>
</tr>
<tr>
<td>0.75 mg</td>
<td>4.1 ± 1.6</td>
</tr>
</tbody>
</table>

- after six hours
  - groups 0.5 mg & 0.75 mg still had plasma concentrations exceeding the C_max of 0.25 mg of triazolam

**TABLE 1. Treatment Groups and Triazolam Dosing Schedule**

<table>
<thead>
<tr>
<th>Dosing Time, min</th>
<th>Group 1 (Placebo Control)</th>
<th>Group 2 (Total Dose, 0.25 mg)</th>
<th>Group 3 (Total Dose, 0.5 mg)</th>
<th>Group 4 (Total Dose, 0.75 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Placebo</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>60</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Dose | T_max min | C_max ng/ml**

- 0.25 mg | 60 (1 hr) | 2.1 ± 0.8 |
- 0.50 mg | 150 (2+ hr)| 4.0 ± 1.6 |
- 0.75 mg | 240 to 300 (>4 hr) | 5.1 ± 1.6 |

- level of consciousness in 0.25 mg group returned to baseline at 360 min
Pharmacokinetics Stacked Doses

➢ patients should be monitored at least 360 min if the total stacked dose is given in 60 to 90 min
➢ total stacked doses of 0.5 to 0.75 mg of triazolam
   - unsafe to discharge a patient earlier than 6 hours after the first dose
➢ larger doses will require even longer recovery periods

J Clin Psychopharmac. 2009

Summary for Triazolam

➢ no pharmacology data to support the concept of “oral titration”
   - unpredictable
➢ 0.5 mg dose at 90 min had a plasma concentration of ~ 2.5 ng/ml
   - it did not reach $T_{\text{max}}$ until 150 minutes & the $C_{\text{max}}$ was 4.0 ± 1.6 ng/ml
   - at 6 hours the plasma conc is still 2.9 ng/ml
   - you can not re-dose at 60 min intervals and 90 min intervals will not allow for a significant reduction

Summary for Triazolam

➢ using current data
   - an oral triazolam dose of 0.25 to 0.5 mg for adults should be safe
   - repeat dosing schedules still need clinical testing to identify a “safe” increment of time & dose
   - even at 0.5 mg there are still significant plasma levels after 6 hours
➢ the most conservative approach would be to limit the dose to 0.125 to 0.5 mg
   - if that is not sufficient refer for IV anesthesia

Dentist Disciplined for 8 fold Dose of Triazolam

➢ West Virginia dentist administered 17 tablets of triazolam (4.25 mg) for a 5 hour case
➢ Patient admitted to hospital for 3 days for flumazenil treatment
➢ According to officials from DOCS
   - maximum dose of triazolam is 0.5 mg
   - overdose may occur at ≥ 2.0 mg

Case report 2009
Flumazenil

- Flumazenil is a competitive pharmacologic antagonist of BZ at the BZ receptor
- In sufficient doses it will compete for the BZ receptor to displace the BZ from the receptor
- Reverses unconsciousness before hypoxic brain damage from hypoventilation, upper airway obstruction, or apnea occurs

- FDA approval for IV route only
  - Reports of intranasal, rectal, and down ET tube
- Reverse BZ sedation
  - 0.2 mg IV at 1 minute intervals as needed
  - Most patients will respond to 0.6 to 1 mg
- Overdoses of BZ
  - Will need cumulative dose of 1 to 3 mg IV
- Anesthetic situation where patient is hypoxic, apneic, & can not be ventilated
  - 1 to 3 mg IV bolus of flumazenil should be safe
  - Research in volunteers showed no adverse effects from 100 mg

Flumazenil

- 0.1 to 0.2 mg yield plasma conc of 3-6 ng/ml
  - Partial antagonism of BZ
- 0.6 to 1 mg yield plasma conc of 12-28 ng/ml
  - Complete antagonism for typical BZ sedation

- Onset: 1 to 2 minutes
- 80% response: 3 minutes
- Peak effect: 6 to 10 minutes

Flumazenil

- $t_{1/2a}$ distribution half life: 4 to 11 min
- $t_{1/2b}$ elimination half life: 40 to 80 min
- 99% metabolism to inactive metabolites
- 1% excreted unchanged in urine

- Resedation is unlikely if used < 10 mg midazolam
  - > 10 mg midazolam or equivalent may see resedation in ~ 40 minutes
  - Monitor patients for at least 1 hour before discharge

Flumazenil
Flumazenil

Magnitude and Duration of Reversal of Sedation as a Function of Flumazenil Dose
Flumazenil doses of 0.2, 0.6 & 1 mg (blood level in ng/mL)

Minutes after Flumazenil Injection
*sedation produced by midazolam infusion

at a rate of 0.05 – 0.20 mg/kg/hr in healthy volunteers

SM Flumazenil Study

- study used 3 doses of 0.25 mg SL triazolam
  - 1st at 0 min; 2nd at 60 min; 3rd at 90 min
- at 120 min, inject 0.2 mg flumazenil in 2 ml fluid into posterior maxillary vestibule (submucosal) injection
- at 150 min (30 min after flumazenil)
  - transient ↑ in BIS lasting 30 min then return to baseline
  - transient ↑ in sedation score for 30 min then returned to baseline

JADA 2009;140(5): 559-566

SM Flumazenil Study

- demonstrates that moderate to deep sedation from incremental SL triazolam
  - get incomplete and transient reversal
  - reversal lasted no longer than 30 min
  - resedation occurred
  - dose of flumazenil 0.2 mg submucosal injection

- 0.2 mg submucosal is inappropriate for rescue

JADA. 2009;140(5): 559-566

Fallacy of SL Flumazenil

- 0.2 mg flumazenil IV will incompletely reverse conscious sedation
  - do not expect it to reverse unconscious patient

- SL flumazenil will eventually work to a degree
  - light sedation may be partially reversed by 0.2 mg
  - deeper sedation requires ↑ dose of flumazenil
  - will not have enough time to prevent hypoxic brain injury in apneic, obstructed, unconscious patient
Fallacy of SL Flumazenil

➢ BZ overdosed & unconscious patient
  – IV route is still the best & only approved route
  – no IV skills ➢ give 0.6 to 1 mg flumazenil IM
    • volume is 6 to 10 ml
    • too much volume for SL injection
    • IM in divided doses in both deltoid muscles
    • Anest Progress. 2011; 58: 1-2

➢ Personally, SL is unproven ➢ if you want to use stacked doses learn how to start an IV

Ketamine

➢ Structural analog of phencyclidine (“angel dust” – PCP) synthesized in 1962
➢ NMDA: N-methyl-D-aspartate receptor antagonist
➢ IV, IM, PO, or rectal anesthetic agent
➢ Analgesic, amnestic, & cataleptic effects
➢ Been used in anesthesia since 1970’s

Dissociative Anesthesia

➢ ketamine produces a functional dissociation between thalamocortical & limbic systems
  – depresses neuron function in cerebral cortex while simultaneously activating the limbic system
  – blocks perception of visual, auditory, and pain by higher centers of the brain
  – result is a cataleptic state

JOMS. 2007;19:454-47

Dissociative Anesthesia

➢ patient remains still during the surgery
➢ eyes may be open
  – vacant stare, glassy eyes, & horizontal nystagmus
➢ may see involuntary movements
  – at low doses: patients may be trying to reach out & touch imaginary objects

JOMS. 2006; 64:693
NMDA Receptor

- glutamate & NMDA are excitatory amino acids
- glutamate binds to NMDA receptors
  - opens ion channel to influx of Na, K, and Ca
  - depolarizes the post synaptic neuron
- ketamine binds to the NMDA receptor
  - it blocks the ion channel
  - get inhibition of the post synaptic neuron

Ketamine

- no GABA activity
- does bind to other sites
  - nicotinic
  - muscarinic
  - kappa opioid receptors

Pharmacokinetics

- rapid onset due to high lipid solubility
- peak plasma concentrations
  - IV: 60 seconds
  - IM: 5 minutes (range of 5 to 15)
  - PO: ~ 30 minutes
- Redistribution in 7 to 15 minutes with IV route
  - expect to see anesthetic effects wear off during that time if you only use a single IV bolus
- IM route: see effects start to wear off in 30 to 120 minutes after the IM injection
  - $t_{1/2}$ = 2 to 3 hours (elimination half life)
**Metabolism**

- Clinical effects wane not because of elimination
  - Due to redistribution
- Ketamine metabolism: Liver P450 enzymes
  - Metabolite is active drug: Norketamine
    - One third to one fifth as potent as ketamine
    - Responsible for some of analgesia seen

**Ketamine CVS Effects**

- Acts as a sympathomimetic agent
  - Expect to see an ↑ heart rate, blood pressure, & CO
  - Creates an imbalance in myocardial oxygen supply & demand
  - ↑ in myocardial oxygen consumption
  - Not a good drug to use in patients with long standing CAD, uncontrolled HTN, or CHF

**Ketamine & Respiratory**

- Preserves spontaneous respirations
- Laryngeal & pharyngeal reflexes are intact
- Respiratory depression is rare
- Functional residual capacity is increased
- Bronchodilator
  - Direct smooth muscle dilation, ↑ catecholamine levels in plasma, & inhibition of vagal conduction
- ↑ Airway secretions: ♦ possible but rare laryngospasm

**Ketamine: Other Effects**

- Myoclonus but no seizure focus
  - Ketamine has been used to terminate status epilepticus
- ↑ ICP secondary to ↑ in cerebral blood flow & cerebral perfusion pressures
- ↑ IOP
- Hypersalivation
**Emergence Reactions**

- emergence delirium
  - pleasant or unpleasant reactions
  - "body floating in air", vivid dreaming, nightmares, & hallucinations
  - may be crying but are still under control
  - may become violent
  - incidence with ketamine
  - adults: 0 to 50%
  - children: 0 to 10%

- contributing factors
  - age > 10, psychiatric disorders, female
  - high dose + rapid IV bolus

- agents that prevent or decrease incidence
  - benzodiazepines, propofol, & dexmedetomidine

- usually a short lived reaction
  - traumatic for parents of children & escorts for adults
  - may be traumatic for the staff

**Nausea & Vomiting**

- reported incidence 0 to 43%
- most likely after emergence during recovery
- antiemetics
  - intra operative propofol
  - high risk patients: use ondansetron
  - high doses of ketamine (especially if solo agent)
  - use ondansetron

**Ketamine Isomers**

- Racemic ketamine used in US
  - S + R isomer
- S isomer of ketamine (dextro isomer)
  - 2X as potent as racemic ketamine
  - 3X more potent than R isomer
  - faster elimination & less psychomimetic reactions
- R isomer is likely cause of emergence reactions

*Can J Anesth. 2003;50: 470-75*
Ketamine General Anesthesia

- IM injection adults
  - 4 to 6 mg/kg IM
  - onset ~ 5 minutes
- IV 1.0 to 2 mg/kg
  - onset ~ 1 minute
- maintenance dose
  - 0.1 to 0.3 mg/kg IV Q 10 to 15 minutes
  - 5 to 20 mg IV as needed
  - infusion 50 mcg/kg/min

Pediatric Patients

- IM dosing in children
  - 2 to 4 mg/kg
  - duration = 20 minutes of working time
  - consider starting an IV for maintenance by ketamine or another
    IV anesthetic agent
- Oral ketamine
  - can be used as a solo agent
  - most current studies combine ketamine + midazolam
    - decrease incidence of ketamine emergence delirium
    - deeper sedation than midazolam alone

Oral Ketamine

- oral ketamine has been used in children
  - more use in Europe than US
- extensive 1st pass metabolism in liver
  - bioavailability has been as low as 17%
  - reports of 59% bioavailability
    - ketamine + metabolite (norketamine)
- sedation onset range 17 to 25 mins
- no oral form so use parenteral drug and mix with a liquid carrier
  - 5 to 30 mL of carbonated drink, kool-aid, honey & water
- dose range: 4 to 10 mg/kg PO

Pediatric Dental Procedures

- 6 mg/kg PO
- onset of sedation: 20.5 minutes
- duration of sedation: 36.4 minutes
- all patients needed at least 1 hour of recovery prior to discharge
- $\text{SpO}_2 \geq 95$; no airway issues; no emergence delirium
- better sedation than meperidine 2mg/kg + promethazine
  - 0.5 mg/kg PO
  - Pediatr Dent. 1993
Pediatric Dental Procedure

- age 21 to 43 months
- ketamine 10 mg/kg PO
- onset 25 minutes
- procedure time 33 minutes
- no intraoperative complications
- after discharge: slept at home on average 3 hrs
  - range of 15 minutes to 6 hours

Anest Progress. 2002;49:14-18

Pediatric Dental Procedure

- age ≤ 36 months
- midazolam 0.5 mg/kg + ketamine 3 mg/kg PO
- onset: 20 minutes
- ketamine was S isomer of ketamine
  - study done in Brazil where isomer available
- no emergence delirium
- better sedation than midazolam 1.0 mg/kg
  - no maximum limit on midazolam: weight based only


Primary Teeth Excision

- 0.75 mg/kg midazolam + 5 mg/kg ketamine PO
- age group: 5.4 ± 1.6 years
- inject local anesthesia 30 min after ketamine
- if sedation insufficient for local
  - IM injection: 2 mg/kg ketamine + atropine 10 mcg/kg
  - in M + K group: 3 of 15 patients needed IM
  - in M (0.75 mg/kg): 13 of 15 patients needed IM
- M + K group tolerated excision better than M
- time to discharge: 108 ± 10.8 minutes
- no N/V or hallucinations

Eur J Paediatr Dent. 2010;11: 19

Intellectually Disabled Patients: Oral Agents (Adults)

- age group: 35 ± 2.06 years old
- ketamine 5 mg/kg + midazolam 0.3 mg/kg
- onset of sedation: 12 minutes
- maximum sedation: 25 minutes
- BP 123.6 ± 5.3 / 74.6 ± 3.2
- HR 94.2 ± 5.4
- SpO₂ 95.4 ± 0.07
- sedation produced cooperative patient for dental procedures

Other Oral Dosing

➢ combinations of ketamine + midazolam for pediatric dentistry ➔ oral route

<table>
<thead>
<tr>
<th>Midazolam (mg/kg)</th>
<th>Ketamine (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35</td>
<td>5</td>
</tr>
<tr>
<td>0.75</td>
<td>5</td>
</tr>
<tr>
<td>0.25</td>
<td>3</td>
</tr>
</tbody>
</table>

ER: Oral Dose for Lacerations

➢ midazolam 0.5 mg/kg + ketamine 5 mg/kg
➢ onset of sedation: 14.59 ± 6.3 minutes
➢ laceration repair time: 15.75 ± 6.53 mins
➢ time of discharge
  – administration of drug until discharge from ER
  – 186.79 ± 93.10 minutes
➢ more effective sedation than midazolam 0.5 mg/kg

Additional PO References

Pediat Anest. 2010;20:330
Emerg Med J. 2001;18:30
Anest Analg. 2000; 90:299
Br J Anest. 2000;84:335
Dent Res J. 2012;9:36

Clonidine

➢ highly selective α₂ adrenergic agonist
  – α₂ to α₁ ratio: 300 to 1
➢ produces sedation, anxiolysis, & analgesia
➢ improves separation anxiety in children
➢ ↓ anesthetic agent requirements by 40 to 60%
  – ↓ MAC of volatile agents & ↓ opioid doses
➢ attenuates reflex tachycardia & hypertension response to intubation
Clonidine

- oral dosing: peak plasma level 60 to 90 minutes
- oral bioavailability: 75 to 95%
- highly lipid soluble
- $t_{1/2}$ 6 to 23 hours
  - approximately 50% is metabolized in liver
  - excreted by kidney
    - ~ 50% is excreted unchanged
- IV form is available
  - mostly used outside of the United States

Alpha 1 Receptors

<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>SINAPTIC SITE</th>
<th>ANATOMIC SITE</th>
<th>ACTION</th>
<th>VENOUS VOLUME</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>Postsynaptic</td>
<td>Peripheral, visceral smooth muscle</td>
<td>Constriction</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Postsynaptic</td>
<td>Smooth muscle</td>
<td>Constriction</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Postsynaptic</td>
<td>Coronary arteries</td>
<td>Myocardial</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Postsynaptic</td>
<td>Kidney</td>
<td>Urodynamic</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

- $\alpha_1$ receptors have 2 subunits: $\alpha_{1A}$, $\alpha_{1B}$
- no presynaptic receptor identified
- post synaptic receptors only
- $\uparrow$ inotrope heart, $\uparrow$ vasoconstriction, $\downarrow$ urine output

Alpha 2 Receptors

- $\alpha_2$ receptors have at least 4 subtypes: $\alpha_2$ receptors
  - alpha 2A, 2B, 2C, & 2D

- presynaptic $\alpha_2$ receptor activity
  - inhibits the release of NEpi from presynaptic neuron into the synaptic cleft
    - acts as a negative feedback for further release of NEpi
      - together you get inhibition of the post synaptic neuron
    - reduction in sympathetic outflow
      - enhance parasympathetic outflow
  - result = $\downarrow$ SVR, $\downarrow$ cardiac output, $\downarrow$ myocardial inotropic effect, $\downarrow$ heart rate
- post synaptic $\alpha_2$ receptor activity
  - vasoconstriction
### Synaptic Cleft

**Clonidine**

### Alpha 2 Receptors

- **α2A receptors**
  - cause sedation, analgesia, and sympatholysis
  - brain & spinal cord
- **α2B receptors**
  - cause vasoconstriction by stimulating peripheral receptors
  - may be responsible for antishivering
- ↓ BP & HR during anesthesia
  - α2A receptors predominate over α2B receptors

### CNS Effects of Clonidine

- **Brainstem → pontine locus ceruleus**
  - clonidine binding to α2A receptor
  - produces sedation
- **Brainstem → medullary vasomotor center**
  - clonidine stimulates inhibitory neurons in medulla
  - α2A receptors
  - ↓ sympathetic outflow resulting in ↓ BP, HR, and CO
- **Spinal Cord** α2A receptor
  - inhibits the release of substance P
  - analgesia

### CVS & Respiratory Effects

- **CVS effects of clonidine**
  - ↓ heart rate, ↓ SVR, ↓ systolic blood pressure
  - dose dependent
- **Respiratory effects**
  - minimal respiratory depression at best
Other Effects

➢ post operative shivering
➢ dry mouth
➢ hypertensive patients using clonidine to control BP
  ➢ abrupt withdrawal will lead to acute, severe hypertension

Clonidine PO in children

➢ 4 mcg/kg PO: maximum 200 mcg PO
  ➢ took 1 mcg tablet crushed in fixed volume fluid
  ➢ administer 90 minutes pre op
  ➢ time from drug administration to induction of general anesthesia
    ➢ no episodes of hypotension, bradycardia, or $\text{SpO}_2 < 95$

Clonidine PO in children

➢ sedation describes as drowsy or asleep
➢ for venipuncture 33% were sedate
➢ for mask induction 26.6% were sedate
➢ better results than 0.5 mg/kg midazolam
  ➢ maximum dose 15 mg PO

Clonidine Premedication in Children

➢ superior to midazolam for pre induction sedation
➢ superior to midazolam post operatively
  ➢ less post operative pain reported
  ➢ lower incidence of emergence delirium


Acta Anaesthesiol Scand. 2010;54:397
Clonidine & Third Molars

- 150 mcg clonidine PO vs midazolam 7.5 mg PO
- age group: 18 to 40 yrs old
- anxiolytic dose of drug then local anesthesia only for surgery
- give 150 mcg clonidine PO 60 mins prior to Sx
- 1 patient fell asleep after 45 minutes
- no change in blood pressure reported
- equal anxiolytic effects for 2 drugs


Clonidine for Adults

- PO dose range: 100 to 200 mcg PO
  - 100 mcg dose: bradycardia & hypotension rare
  - 150 mcg dose: stable hemodynamics
  - 200 mcg: more episodes of bradycardia & hypotension
    - some case studies show stable hemodynamic
    - others show ↓ in heart rate & BP
      - especially in medically compromised patients
- 1.5 mcg/kg rare to see adverse hemodynamics


Clonidine for Adults

- optimal dose for 70 kg adult: 200 mcg PO
  - 60 to 90 minutes for peak
  - single dose will not cause rebound hypertension
  - rare to cause ↓ BP or heart rate
    - if it does occur usually responds to fluids
    - small decreases in BP & HR have no clinical consequences
- 200 mcg used pre operatively in Friedberg Technique
  - office plastic surgery: clonidine, ketamine, propofol

Anesth Prog. 2006;53:34-42

Use for Clonidine

- patient for local anesthesia but has “white coat” hypertension verified by PCP
  - documented normotensive outside healthcare office
- anxiolytic useful to try & calm patient
  - lorazepam, diazepam, triazolam
  - clonidine 100 mcg to 200 mcg PO
    - anxiolysis, sedation, analgesia
    - attenuate heart rate & BP response to stress
    - improves myocardial oxygenation status
Non Benzodiazepine Hypnotics

- chemical structure different from BZ
- are BZ receptor agonists
  - GABA<sub>A</sub> α 1 subunit
- reversible by flumazenil
- some selective binding to receptor
  - limits cognitive impairment & abuse
  - less anxiolysis but more hypnosis

Zolpidem (Ambien)

- approved in 1993 for insomnia
- sedative hypnotic at 5 to 10 mg
  - ↑ dose to get muscle relaxant & anticonvulsant effect
  - need ~ 20 mg to see antegrade amnesia
- onset 30 minutes  t<sub>1/2</sub> 1-3 hours
- no active metabolites
- side effects: headache & muscle pain
- do not use the controlled release compound

Zolpidem ⊢ Potential Problems

- FDA warning
  - drowsiness day after use for sleep aid
  - patients engaged in “activities while asleep”
    - walking, driving, eating, sex
    - all with no recall of events
  - patients with behavioral changes
    - ↑ depression, suicidal thoughts, hallucinations
  - patients engaging in at risk behavior without fear of danger
  - women at greater risk  lower the dose to 5 mg for sleep

Zaleplon (Sonata)

- non BZ agonist
- more hypnosis but less amnesia than BZ
- onset 15 to 20 minutes  t<sub>1/2</sub> 1 hour
- duration of action 4 hours
- 10 mg PO dose
- 1 study 3rd molars under local + Sonata
  - anxiolysis similar to triazolam
  - no amnesia  faster recovery

Anest Progress. 2005;52:128
Thank you