



ED sedation

Queen Mary University London MSc in Emergency and Resuscitation Medicine

Module 3: Lecture 7

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Lecture goals and cases to guide discussion

The discussion goals are to outline salient points regarding provision of sedation in the ED. With some notable exceptions (*e.g.* calming for CT), sedation is virtually always provided in conjunction with local, regional, or systemic analgesia, but the overarching topic of procedural sedation and analgesia (PSA) is not covered comprehensively here. Use of potent opioids for their sedative side effects is common, but not endorsed here. The information in this Sedation lecture is provided with the understanding that clinicians appropriately and judiciously utilize analgesia along with sedative agents.

Sedation is critical because it can facilitate patient comfort and improve the overall ED experience of patients, families, and even clinicians. It is nonetheless true that sedation is inherently associated with real (although manageable) risk. Provision of sedation must be approached with the same attention to caution and detail as any other procedure with potential adverse effects. Furthermore, while proper EM training includes emphasis on myriad PSA-relevant facets (*e.g.* airway management, sedation pharmacology, patient monitoring), EM should never be hesitant to look to those who administer these drugs daily – Anesthesia – for advice and guidance on sedation issues.

The following cases are typical of those in which EM clinicians may choose to administer sedation. As with other types of clinical problem-solving, there are often multiple acceptable approaches. The aim of this handout is to provide information which can be of aid to clinicians formulating a rational approach to provision of sedation. Of course, any hospital-specific guidelines or protocols carry more weight than the information in this monograph; we can always work with Anesthesia to try and modify anything we think may be incorrect but we violate hospital protocol at our own (significant) peril.

Cases for discussion basis (Patients to be considered hemodynamically stable and lacking clinical issues other than as noted)

- 1) 8 year-old male requiring a head CT to assess for possible sinusitis
- 2) 6 year-old female with severe developmental delay and VP shunt, needs head CT to rule out hydrocephalus
- 3) 35 year-old male undergoing incision/drainage of a large thigh abscess
- 4) 3 year-old female requiring a painful packing change of a deep wound
- 5) 3 year-old female in Case #4, returns for repeat (still painful) packing change but now with a URI
- 6) 22 year-old male, very anxious, who requires lumbar puncture to rule out subarachnoid hemorrhage
- 7) 7 year-old male with congenital cardiac disease, requiring incision and drainage of a buttocks abscess
- 8) 58 year-old male requiring electrical cardioversion for an atrial tachycardia
- 9) 42 year-old male, psychotic and dangerous to E.D. personnel, requiring sedation for M.D. evaluation
- 10) 17 year-old male, to undergo shoulder reduction for anterior dislocation sustained 6 hours before
- 11) 5 year-old female with impending respiratory failure from status asthmaticus
- 12) 5 year-old female with post-pericardiotomy syndrome and hemodynamically significant pericardial effusion

General considerations regarding ED sedation

References for this and most subsequent sections given in a group at each section's commencement¹⁻⁴⁷

Definitions and terminology relevant to sedation, conscious sedation, procedural sedation, etc.

Tend to differ between various organizations (*e.g.* ACEP, AAP, ASA)

Review articles (such as that by Flood and Krauss) give details but to some degree this is semantics

A typical policy (disseminated by anesthesiologists to providers at the MGH) uses the following definitions:

Conscious sedation – minimally depressed level of consciousness

Patient retains ability to maintain a patent airway independently and continuously

Conscious sedation may be administered during therapeutic, diagnostic or surgical procedures

Patients do not respond appropriately to physical stimulation and verbal commands

Conscious sedation is not intended to produce loss of consciousness

Deep sedation – controlled state of depressed consciousness

Deep sedation may also involve unconsciousness from which the patient is not easily aroused

Other characteristics of deep sedation are:

Partial or complete loss of protective reflexes

Loss of the ability to maintain a patent airway independently
Inability to respond purposefully to physical stimulation or verbal command
General anesthesia – controlled state of unconsciousness with a loss of protective reflexes
There is loss of ability to maintain a patent airway independently
Patients cannot respond purposefully to physical stimulation or verbal command
Not surprisingly, when general anesthesia occurs in ED sedation, complication rates rise
Most EM-relevant sources (*e.g.* ACEP Clinical Policy) prefer the term “PSA” (*Procedural Sedation & Analgesia*)

Importance of learning sedation techniques

Sedation and associated analgesia are important goals for good clinical care in both adults and children
Poor procedural sedation/analgesia are associated with long-term poor procedural tolerance in children
Even minor procedures in the ED cause significant pain and distress to patients

Anxiolysis is an important part of PSA

Pediatric EM researchers have clearly demonstrated association between anxiety and sedation failure
Strong inverse correlation between anxiety level and sedation success, independent of pain levels and other factors
Anxiety should be ameliorated as much as possible before sedation begins, in order to maximize success chances

Nonpharmacologic adjuncts to PSA

Many nonpharmacologic adjuncts to procedural sedation/analgesia have been proven at least somewhat effective
Some of the non-drug approaches of potential utility:

- Distraction
- Deep breathing or blowing
- Suggestion
- Superhero imagery
- Spot pressure or counterirritation

Non-drug therapies may be appropriate for some “minor” procedures such as blood draws, immunizations
This lecture concentrates on pharmacologic sedation while acknowledging utility of non-pharm approaches

Sedation risk: The most important subject to consider

As with any procedure, consider “if there is a problem, was the procedure needed in the first place?”
Non-pharmacology techniques should be adequate for many minor procedures (*e.g.* IV placement)
Imaging technology may obviate need for sedation now, where it used to be needed
CT scanning is a major indication for sedation in children historically (and currently)
Image acquisition speed can translate into less need for PSA (8.6% sedation rate in one series)
The issue: Regardless of training, sedation entails risk and proper training and preparation are required

Overall adverse reaction rate with multiple agents varies in different ED settings: Most important message is there is risk

In one large study ($n = 1180$) the adverse event rate was 2.3% for serious events (no deaths or long-term issues)
In a prospective ED sedation study ($n = 1341$) “serious” adverse effects occurred in 11.9%
Most (84%) of the adverse events were limited-duration hypoxia episodes
No patient required intubation or hospital admission for sedation-related problems
Another prospective study identified hypoxemia in about 3% of cases (no ETIs)
Investigators focusing on post-ED discharge adverse effects have found no dangerous cardiorespiratory issues
Typical study: 468 children receiving a variety of agents, with ketamine most frequently used (62% of cases)
At least one adverse event occurred in 42% of patients post-discharge (no serious events)
Adverse events included: lethargy, nausea/vomiting, headache, behavioral changes, nightmares
Rates of each individual adverse event were low (lethargy 12%; others 4-7%)
The bottom line: We need to *always* discuss risks with patients/family
The evidence gives different risk assessment numbers depending on how “risk” is defined
Make sure and include post-discharge issues (*e.g.* vomiting) in risk conversation
Risk is, of course, specific to the circumstances both of the patient and the drug used

Keys to managing risk:

1: Thorough familiarity with basics of patient monitoring and emergency care (e.g. airway management)

Have properly trained staff present

Assure the right equipment is there (e.g. no excuse for lack of at-hand airway equipment in elective PSA)

Don't try and be a contrarian based upon inherently limited (due to rarity of problems) ED evidence

2: Solid understanding of sedation agents and their pharmacology

Drug understanding is critical to successful provision of safe sedation

Specific drugs have specific effects: Know them and discuss them with patients/families

It's important to talking about drug-specific effects *before* drug administration

Forewarning patients can in and of itself be reassuring to patients

- If you tell patients they may vomit when they get home, it's far less problematic if it does occur; you've warned them of a side effect.
- If you don't tell patients they may vomit, they may call you and you're now in a position of potentially having to explain away something you should've told them about before.

Knowing drug-specific effects is (appropriately) reassuring

Fentanyl makes the nose itch

Ketamine often causes hypersalivation/secretions (even if give antisialogogues)

Midazolam (like other agents) risks paradoxical reactions

3: Don't let the pressures of the ED patient load translate into your rushing things

Don't give sedation if you're not ready and appropriately prepared (including staffing)

If you have any doubt about risk/benefit of sedation, stop and think (and consult with others)

- Example: Cardiac monitoring should be selectively used (ACEP Clinical Policy notes there are no data that support an absolute requirement for cardiac monitoring during ED PSA). Cardiac monitoring often isn't needed. However, it should be used in patients with prolonged QT who receive ED PSA. On the other hand, those with prolonged QT are at increased risk with just about any PSA regimen – these may not be good candidates for ED sedation in the first place.⁴⁸
- Anesthesiology residents have phones and are amenable to conversations about sedation use, drug selection, etc. Work with them to do right by our patients.

Notes on supplemental oxygen and monitoring of respiratory gases

Supplemental O₂ has risks of artificially propping up S_pO₂ until a major crash from respiratory depression

As noted by Miner & Burton⁴⁹: "Supplemental oxygen negates oximetry as an early warning device."

End-tidal carbon dioxide monitoring has been effectively used to detect respiratory compromise

Especially when O₂ is given, hypoxemia may not occur despite respiratory depression

Expert commentators now regularly and strongly recommended adding ETCO₂ to S_pO₂ monitoring

Addition of ETCO₂ monitoring (e.g. with nasal cannula devices) may be important step for EDs

Lines between "deep sedation" and general anesthesia can be somewhat blurred

If ED specialists cross these lines, the higher monitoring standard should be met

One *caveat*: Clinical relevance of early detection of respiratory depression

Those tracking ETCO₂ (& S_pO₂) question clinical implications of occult respiratory depression

ACEP Clinical Policy: ETCO₂ may detect hypoventilation earlier than S_pO₂, but ? clinical impact

Bottom line: If we can get ETCO₂ we should use it but not necessarily act drastically on it

Nearly a decade ago, the EM evidence became weighted toward use of ETCO₂

2007 editorial by Green in *Annals EM*: capnography is earliest warning of potential for airway compromise

2007 review by Krauss & Hess in *Annals EM*: capnography earliest mechanism to detect variety of problems

Capnography detects, in addition to respiratory depression and apnea:

Airway obstruction

Laryngospasm

Bronchospasm

Of course EM folks using ETCO₂ monitoring must understand waveforms and this is another lecture

More recent studies in ED confirm ability of capnography to detect otherwise-occult hypoventilation^{44,50}

ETCO₂ appears to detect hypoventilation approximately a minute prior to development of hypoxemia

Use of capnography provided warning for all hypoxia in these cases, and reduced incidence of hypoxia

Notes on adverse event timing

Clinicians must of course know pharmacology of agents they use in PSA

As a general rule, though, one item to keep in mind is the risk of *post-procedure* complications including apnea

In a large, prospective study, 92% of adverse events occurred during (not after) procedure

Serious adverse events (AEs) tended to occur within minutes of final medication administration

When hypoxemia occurred, initial episode always within minutes of medication administration

However: when AEs occurred *during* procedure, they were likely to *recur* post-procedure

After the procedure, there can be less attention to monitoring and less stimulation to patients

Take-home message from this review (not yet validated by other studies, but appears reasonable):

Consider half-life of drug administered when considering discharge timing

If no complications during the procedure, observe patient for 30 minutes before consider discharge

Discharge is likely safe if no problems at all during procedure or for half-hour afterwards

Notes on reversal agents (see later information on specific drugs)

Reversal agents have a definite place in ED PSA, but they have downside

Perhaps the most important downside: their presence may cause inappropriate risk-taking by inexperienced clinicians

Reversal agents may take time to work, may not quickly/reliably reverse respiratory depression (*e.g.* flumazenil)

Bottom line: Pharmacologic reversal agents (*e.g.*, naloxone) do not replace any of the above requirements

Patient selection and initial evaluation

The basic history and physical examination for sedation are consistent with those for any patient

Thorough medical history, with respect to pertinent findings relating to various medications, is important

American Society of Anesthesiologists (ASA) Physical Status Classification is often mentioned in ED sedation setting

Patients ASA Class IV-V are not considered appropriate for elective ED sedation

Patients with ASA Class III *may* be appropriate for ED sedation but added caution is indicated

ASA classes are:

- Class I – No organic, physiological, biochemical or psychiatric disturbance. The pathologic process for which the operation is to be performed is localized and is not a systemic disturbance. [usually a candidate for ED sedation]
- Class II – Mild to moderate systemic disturbance caused either by the condition to be treated or by other pathophysiologic processes. [usually a candidate for ED sedation]
- Class III – Severe systemic disturbance or disease from whatever cause, even though it may not be possible to define degree of disability with finality. [often not candidate for ED sedation]
- Class IV – Indicative of the patient with a severe systemic disorder already life-threatening, not always correctable by the operative procedure. [usually not candidate for ED sedation]
- ASA Class V – The moribund patient who has little chance of survival but is submitted to operation in desperation. [usually not candidate for ED sedation]

Beware performance of truly elective procedures (with PSA) in “sick” patients

One study (Miner, 2005) reported that side effect rates no higher for Class III/IV than lower classes

However, another study (Caperell, 2009) finds the opposite in a pediatric ED

Remember the rule: Be conservative and balance risks and benefits

Notes on paperwork and documentation

Use of documentation such as history/physical exam and vital signs tracking sheets is universal

It's required (by Joint Commission) so no point in trying to avoid it

Work with Anesthesia to adjust paperwork and reduce the burden: It may be good for patients

Increase in paperwork/time has “chilling effect” on PSA use

In one study (LSU), sedation dropped by 33% for shoulders after JCAHO papers put in place

If you don't do the paperwork, you aren't protected – don't try and skip it

Aspiration risks with sedation

Section references^{27,40,43,51}

The importance of aspiration in ED PSA is indicated by

- Virtually all sedatives entail risk of depressed airway reflexes and aspiration

- Beware aspiration risk also in obese, pregnant, or intoxicated patients

- Literature suggests that aspiration is not be a common problem in ED sedation

 - One large analysis of studies concluded aspiration risk about 1 in 1000-14,000 cases

 - Caveat* to interpreting literature: beware being too reassured by a retrospective grouping of studies

 - Aspiration may not even be detected at the time of ED PSA

 - Low numbers could be due to low assessment rates (everyone's not getting CXRs post-PSA)

- Bottom line: aspiration is an issue, but probably occurs quite rarely when proper technique is used

Aspiration risk and *NPO* status – an area of controversy

- Management of aspiration risk is controversial in ED PSA, since *NPO* is not easy to achieve

- Low overall aspiration risks with proper patient selection mean aspiration risk is likely low

- Furthermore, *NPO* itself *may* be associated with some risk

 - Procedures are delayed, patients have ongoing pain, and patients/families get upset

 - ED operations are hindered

 - If *NPO* makes children irritable, higher doses of sedation agents may be needed (suggested in one study)

 - One study suggests irritability secondary to hunger, makes fasted children difficult to sedate

 - The author (Keidan)²⁷ suggested that higher doses of sedatives translated into higher risk

- Extrapolation of *NPO* guidelines to the ED is based upon questionable generalization

 - The guidelines have not been rigidly studied in the ED, and perhaps shouldn't even apply to ED patients

 - General *NPO* guidelines are primarily intended for planned sedation

- Why is there controversy? Because the ED often (about half the time) does *not* meet the *NPO* guidelines

 - If the *NPO* guidelines must be met, then we are often providing unsafe PSA in the ED

 - On the other hand, withholding of PSA is also associated with untoward patient outcomes

 - So it's worth assessing the overall risks and evidence base for *NPO* guidelines for ED PSA

- Some data are present that address *NPO* status for ED PSA

 - Complications in one large ($n = 905$) series were rare and unrelated to *NPO* status

 - Overall, emesis occurred in 1.5% of patients

 - Emesis was no more likely in patients meeting *NPO* guidelines, than in those who didn't

 - Aspiration occurrence in this study was 0% (one-sided 97.5% CI 0.0-0.4%)

 - Another ED study (Roback) also found preprocedural fasting "compliance" unrelated to risk

- Since 2005 ACEP policies have provided some direction:

 - Recent food intake doesn't contraindicate, but *does* guide sedation timing/target level

 - 2008 ACEP policy: "No evidence supporting requirement for preprocedural fasting"⁴³

- NPO* guidelines must be extended situationally (*e.g.* patients with gastroesophageal reflux)

- Ann Emerg Med* Clinical Practice Advisory⁴⁰ provides some guidance for EM specialists and fasting (see Appendix)

Example: *NPO* guidelines for *elective* sedation (per MGH policy) follow:

- Adult guidelines (patients at least 16 years of age)

 - No milk, solids, or other opaque liquids within 6 hours

 - No clear liquids within 3 hours

- Pediatric guidelines

 - No milk or solids within 6 hours

 - No breast milk within 5 hours [*N.B.* some anesthesia sources give 4 hours for this cutoff]

 - No clear liquids within 2 hours

- Keep in mind that Anesthesiology *NPO* guidelines appropriately reflect a very conservative approach

 - ASA position: preprocedural sedation *NPO* guidelines should equal those for general anesthesia

 - Position of some ED experts (*e.g.* Krauss, Green): these rigid guidelines should not apply in ED

Specific note on CT oral contrast

2013 study⁵¹ in pediatric patients assessed PO contrast and aspiration risk

Oral contrast (in violation of NPO guidelines) before sedation-facilitated CT was found to be safe

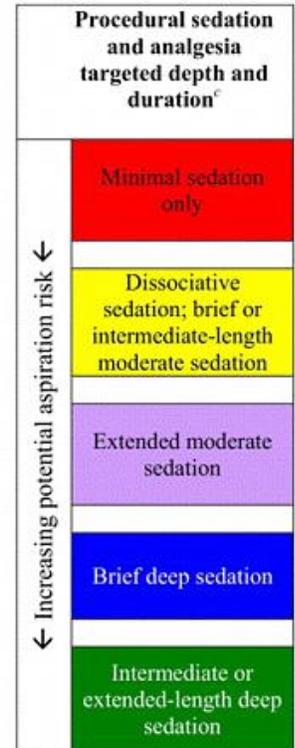
American College of Emergency Physicians clinical practice advisory below can inform and support decision-making:

Standard-risk patient^a

Oral intake in the prior 3 hours	Procedural Urgency ^b			
	<i>Emergent Procedure</i>	<i>Urgent Procedure</i>	<i>Semi-Urgent</i>	<i>Non-Urgent</i>
<i>Nothing</i>	All levels of sedation	All levels of sedation	All levels of sedation	All levels of sedation
<i>Clear liquids only</i>	All levels of sedation	All levels of sedation	Up to and including brief deep sedation	Up to and including extended moderate sedation
<i>Light snack</i>	All levels of sedation	Up to and including brief deep sedation	Up to and including dissociative sedation; non-extended moderate sedation	Minimal sedation only
<i>Heavier snack or meal</i>	All levels of sedation	Up to and including extended moderate sedation	Minimal sedation only	Minimal sedation only

Higher-risk patient^a

Oral intake in the prior 3 hours	Procedural Urgency ^b			
	<i>Emergent Procedure</i>	<i>Urgent Procedure</i>	<i>Semi-Urgent</i>	<i>Non-Urgent</i>
<i>Nothing</i>	All levels of sedation	All levels of sedation	All levels of sedation	All levels of sedation
<i>Clear liquids only</i>	All levels of sedation	Up to and including brief deep sedation	Up to and including extended moderate sedation	Minimal sedation only
<i>Light snack</i>	All levels of sedation	Up to and including dissociative sedation; non-extended moderate sedation	Minimal sedation only	Minimal sedation only
<i>Heavier snack or meal</i>	All levels of sedation	Up to and including dissociative sedation; non-extended moderate sedation	Minimal sedation only	Minimal sedation only



Brief: <10 minutes
Intermediate: 10-20 minutes
Extended: >20 minutes

From Green *et al*⁴⁰

^aHigher-risk patients: those with at least one of the following, present to a degree individually or cumulatively judged clinically important by treating MD:

- Potential difficult/prolonged assisted ventilation (eg, short neck, small mandible/micrognathia, large tongue, OSA)
- Conditions predisposing to esophageal reflux (eg, elevated ICP, esophageal disease, hiatal hernia, PUD, gastritis, bowel obstruction, ileus, tracheo-esophageal fistula)
- Extremes of age (eg, >70 years or <6 months)
- Severe systemic disease with definite functional limitation (ie, ASA physical status 3 or greater)
- Other clinical findings leading EP to judge higher than standard risk (eg, altered level of consciousness, frail appearance)

^bProcedural urgency:

- Emergent (eg, cardioversion for life-threatening dysrhythmia, reduction of markedly angulated fracture or dislocation with soft tissue or vascular compromise, intractable pain or suffering).
- Urgent (eg, care of dirty wounds and lacerations, animal and human bites, abscess incision and drainage, fracture reduction, hip reduction, lumbar puncture for suspected meningitis, arthrocentesis, neuroimaging for trauma)
- Semi-urgent (eg, care of clean wounds and lacerations, shoulder reduction, neuroimaging for new-onset seizure, foreign body removal, sexual assault examination)
- Non-urgent or elective (eg, non-vegetable foreign body in external auditory canal, chronic embedded soft tissue foreign body, ingrown toenail)

Sedation and respiratory depression

Primary safety issue in ED sedation is respiratory depression: it's detection isn't always easy

Desaturation ($S_pO_2 < 90\%$) may occur in up to 30% of ED-sedated patients

Risk is of course agent-specific and situational

With some agents respiratory depression risk can exceed 50% (depending on definitions)

Wide risk variability among different agents (across-the-board average: approx. 2%)

Hypoxemia is usually undetected by treating clinicians (in the absence of pulse oximetry monitoring)

Pulse oximetry is therefore recommended in nearly all cases

Pulse oximetry placement can often be delayed until the patient's eyes close (to avoid irritating them)

Level of evidence supporting end-tidal CO_2 monitoring for all sedation is mounting

ET CO_2 is easy to apply, and easy to interpret

ET CO_2 can detect hypoventilation/respiratory depression some minutes before clinical/ S_pO_2 clues appear

Patients with mild respiratory depression usually respond to verbal or tactile stimulation: try these first

Ask patient to take deep breaths

If necessary, provide painful stimulus

Available evidence is suboptimal, but suggests that supplemental oxygen isn't necessary

In analysis of 80 patients randomized to supplemental O_2 or sham, no difference in hypoxemia

Expert editorialists have contended that supplemental O_2 can mask respiratory depression

This is especially a concern if not monitoring end-tidal CO_2

Green³⁸ contends: "If not using capnography, supplemental O_2 may hurt more than it helps"

2008 editorial in *Annals EM*: "reasonable case for either adding or withholding O_2 with propofol"⁵²

Bispectral index (BIS) monitoring and respiratory depression

BIS is a processed EEG parameter (0-100) which correlates with patients' levels of awareness

Some information in the ED setting suggests utility of BIS in adults and children

BIS correlates with levels of sedation (*N.B.* ET CO_2 level *doesn't* correlate with sedation level)

BIS can be used to "titrate" sedation so patients remain responsive, but are amnesic

BIS may help clinicians aim for efficacious sedation with minimal respiratory depression risk

At least one ED study: less hypoventilation with multiple sedative doses, in BIS patients

Goal: BIS 70-85 to achieve sedation (as efficacious as with lower BIS, with less respiratory depression risk)

BIS score 70-85 associated with less respiratory depression risk than lower BIS

N.B. Some ED studies have employed a "target range" for sedation of BIS = 60-90

ACEP Clinical Policy: still premature to advocate routine BIS use

2007 *Annals of EM* editorial by Green³⁸: "BIS does not appear useful for PSA"

Most literature tends to count "respiratory depression" now in one of two categories

Data-driven diagnosis of respiratory depression (*e.g.* elevated ET CO_2 levels)

Intervention-requiring respiratory depression – this is the emphasized endpoint in most recent papers⁵³

Interpreting the ED sedation literature

Over 600 articles on ED sedation were published during one sampling of 6 years

But typical study is <50 nonconsecutive patients

Conclusions are often overextended or inappropriate

Not uncommon for "successful" regimen to have apnea rate exceeding 10%

Patient numbers are almost always too small for definitive safety conclusions

Certain adverse events are so rare that meaningful statistical (prospective) study is all but impossible

Balancing sedation's risks are risks (other than patient comfort/recall) associated with undersedation

Problems with undersedation have been well-characterized in the critical care literature

Undersedation's problems relevant to EM include tachycardia, hypertension, increased O_2 consumption

It is unclear whether all ICU benefits of sedation (*e.g.* prevention of PTSD) are applicable in the ED

Just as titration is important to reduce oversedation, it is important to reduce undersedation

Recently, good sedation evidence reviews, focusing on best papers, have become available (*e.g.* EMSC panel)²⁵

New directions in sedation research include

Patient-administered sedation (preliminary work suggests safety)⁵⁴

Newer agents and combinations (“don’t be the first or the last to use a new agent”)

Administration of procedural sedation for historically “tough it out” procedures (*e.g.* incision/drainage)⁴⁶

Overview of ED sedation approach for optimizing safety and efficacy

Bottom line of body of sedation literature: there are numerous safe agents available

It’s best to choose a few pharmacologic approaches to sedation; use consensus guidelines/reviews

Learn your chosen agents’ characteristics, risks, and benefits well so you know your agents thoroughly

Have appropriate conversations with patients/parents, and obtain consent as for other procedures

The conversation about consent is as important as – in fact, more important than – the paperwork

Don’t try and talk patients/families into sedation; if they want to grit their teeth and get it done without PSA that’s OK

Remember: one cannot simultaneously perform procedure, administer medications, and monitor the patient

MGH sedation policy requires two individuals (three if “high risk”) be present during any sedation

MGH policy: individuals must be healthcare providers (*i.e.* family members don’t count)

The requirement for additional personnel should be considered situationally

It *may* be rational for a single physician to provide sedation for cardioversion

It’s unlikely to the point of impossibility for a single physician to safely manage sedation for hip reduction

Post-procedure monitoring should not be left to parents, regardless of the temptation

Lower-grade physicians or even medical students *may* be appropriate depending on the situation

Leaving lower-grade personnel to monitor sedation can only occur with:

Clear instructions

Immediate availability of senior

Always assume worst-case scenario in planning and executing sedation

Recall that even experienced anesthesiologists can run into problems with procedural sedation

Recall also, that even experienced anesthesiologists can be surprised by difficulties with oxygenation/ventilation

Getting into the habit of having everything at hand in case of problems, will (one day) pay off when there is trouble

If equipment isn’t available (*e.g.* being used elsewhere) consider delaying procedure (or at least documenting issue)

Resist temptation to try newest agents based on preliminary data

Also resist temptation to be “sold” on new agents when the evidence shouldn’t be convincing

“Never be the first nor the last to use a new sedative” may be wise advice especially for junior physicians

All sedation in the ED should occur under the auspices of the EM (or anesthesia) specialist

Problems are predictably rare, but equally predictably going to happen sooner or later

Unlike much ED care, sedation complications represent potential for preventable iatrogenesis

Specific agents used in ED sedation

DPT/MPC

Section references^{11,55-58}

Mixture of: meperidine (Demerol), promethazine (Phenergan), chlorpromazine (Thorazine)

Few good papers; one well-conducted ED study of MPC from 1991

Dose: meperidine/promethazine/chlorpromazine 2/1/1 mg/kg IM

Efficacy: moderate to well-sedated states occurred in 71%

Time parameters

To sleep 27 ± 24 minutes

Sit upright 103 ± 87 minutes

ED d/c 4.7 ± 2.4 hours

Act normal 19 ± 15 hours

The MPC “lytic cocktail” has problems noted in the ED study mentioned above

Ineffective sedation occurred too frequently (29% of patients)

Timing was unpredictable, with large variation in ED turnaround times

IM injection is painful and untitratable (30' before effects can be assessed)

The paper cites an earlier study with 4% rate of respiratory depression (and an arrest)

Presence of promethazine and chlorpromazine is pharmacologically problematic

Promethazine has antianalgesic properties and can cause hypotension

Promethazine counters opioid analgesia

Goldfrank, anesthesia texts recommend avoiding combination of phenothiazines, opioids

Both promethazine and chlorpromazine may cause significant hypotension

MPC arguably fell out of standard of care years ago

1992 *Yearbook of Emergency Medicine*: never use MPC in the ED

Risks are too great and failure rate is unacceptably high

Rescue agents are rendered less safe after MPC has been given

Many are unfamiliar with exact constituents/dosages

Agency for Health Care Policy and Research (AHCPR) discouraged use of MPC long ago

Recommendation: little indication for MPC use in current ED practice

Sucrose

Section references^{43,59}

Oral sucrose has a “Level A” recommendation from an EM/Pediatrics panel for minor painful procedures in neonates

Recommendation is for term or preterm neonates, up to 28 days of age

Sucrose is safe for low-birthweight infants

Effective dose ranges from 0.1 mL 24% sucrose, to 2 mL 50% sucrose (most commonly studied: 2 mL 24% sucrose)

Concomitant use of pacifier appears to improve efficacy

Oral sucrose should be administered 2 minutes before procedure

Chloral hydrate

Section references^{11,27,43,60-62}

This decades-old PO agent (PR route has been used, but absorption is erratic) primarily studied for imaging sedation

Dose: optimal success with 60-100 mg/kg (max recommended dose 2 g or 100 mg/kg, whichever is less)

Single-dose only in neonates

After 30 minutes, repeat dose 25-50 mg/kg *if* max total dose (2 g or 100 mg/kg) is not exceeded

Success rate for patients receiving 60-75 mg/kg: 93-100%

Success rate usually defined as “able to complete neuroimaging study”

Chloral hydrate significantly outperformed PO midazolam in one head-to-head study

Time parameters (for 60-75 mg/kg single oral dose)

Patients achieving sedation were asleep within 30 minutes

Recovery occurred within 90-120 minutes

Recommendation: safe, dependable for sleep induction (*e.g.*, for CT scan); not good for anything painful

Chloral hydrate tends to be less effective in:⁴³

Older children

Patients with chronic neurological conditions

Possibly, patients who have been fasted (they may be too irritable)

Few interactions about which to be concerned

Avoid use of chloral hydrate in the (hopefully rare) child who has EtOH on board

Due to potential for hepatitis, chloral hydrate should be avoided in patients with liver disease

Synergistic CNS depression is common when co-administered with other agents

Chloral hydrate may cause arrhythmias (*e.g.* with stimulants/pressors) by shortening refractory period

Methohexital

Section references^{11,25,63-67}

Ultrashort acting barbiturate demonstrated as effective at inducing reliable sedation in some procedural settings

Dose regimens

One approach: 1 mg/kg, followed by repeat boluses of 0.5 mg/kg every 2-5 minutes until adequate sedation

PR route suggested by some (limited study)

Time parameters

Less than 1 minute to significant sedation

Usual duration about 7.5 minutes (from a single dose)

One 2009 CT sedation paper finds total sedation time (50 minutes) significantly shorter than for pentobarbital

Problems

Respiratory depression (17% in one study, 48% in another) or transient apnea (5-10%) are significant risks

No patients in ED studies required intubation, but apnea duration was 10 to 180 seconds

Degree of respiratory depression was not necessarily dose-related and therefore not easily predictable

One study (2009) of MTX use for CT: 1 desaturation (no intervention required) in 21 patients

3% incidence of hypotension

Like other barbiturates, not recommended for use in patients with porphyria (increased porphyrin synthesis)

Recommendation: effective and fast-acting but with reputation of a bit too-high risk of respiratory depression

Pentobarbital

Section references^{11,18,67-75}

Short-acting barbiturate primarily useful for facilitation of nonpainful diagnostic studies

Particularly popular at specialized pediatric emergency care centers

Has outperformed other agents in head-to-head trials

Versus etomidate (for CT sedation)

One study assessed pentobarbital (up to 5 mg/kg) *vs.* etomidate (up to 0.4 mg/kg)

Pentobarbital was far more effective than etomidate (97% *vs.* 76%) but had more side effects

Versus midazolam (for CT sedation): pentobarbital regimen (as below) unsuccessful in only 1/29 cases

Versus etomidate

Studies not ideal (*e.g.* unblinded) but results provide argument for pentobarbital use

Also can be used for agitation control in cases where fentanyl/midazolam fails

Suggested regimen: 2.5 mg/kg IV is given initially (more may be needed in patients on barbiturates for seizure disorder)

Some authors prefer a slightly lower initial dose of 2.0 mg/kg (for use for CT sedation in a 2009 study)

After initial dose wait 60-90 secs, then administer 1.25 mg/kg q60-90 secs

Another approach: 2 mg/kg q5' to max 6 mg/kg

Maximum total dose: 5-6 mg/kg

Continuous infusion 1-4 mg/kg/hr reported effective in critical care literature but possibly risky in the ED setting

Time parameters

Sleepiness produced within 30-60 seconds, sedation appropriate for CT achieved within 5 minutes

Duration variable; most children awaken within 30-60 minutes

A 2009 CT sedation paper finds total sedation time (77 minutes) significantly longer than for methohexital

Problems

Primary issue is respiratory depression

Rate depends on study: in some series occurs in 3-8% (no intubations in ED series)

A pediatric ED study identified oxygen desaturation to 90% in only 1 of 33 patients

One study of 400 pediatric cases receiving pentobarbital (titrated to an average 4 mg/kg): 1% desaturation

Cardiovascular depression may also occur

This is especially likely with rapid IV administration

One large prospective series: hypotension occurred in 3 children (2.5% of total) receiving pentobarbital

1 case resolved spontaneously

2 others resolved with a single bolus each, of 20 mL/kg normal saline

Tends to be associated with longer recovery times (*e.g.* to “normal behavior”) than other agents

Like other barbiturates, not recommended for use in patients with porphyria (increased porphyrin synthesis)

Recommendation: Pentobarbital is a good choice for imaging-related sedation when chloral hydrate fails/not indicated

One expert review ranked pentobarbital as first choice for failed midazolam sedation for CT

Pentobarbital is arguably an agent of choice for head CT in hemodynamically stable head trauma patient

Thiopental

Section references^{11,76,77}

This RSI drug can be given rectally for procedural sedation with good results

Dose (PR): 25 mg/kg

Time parameters from one ED study (comparing PR thiopental to IM MPC)

From suppository to suturing in 30 minutes (compared to 60 mins. for MPC control group)

Recovery times for thiopental group were within 90 mins. (much faster than MPC)

Problems

Respiratory risks for IV thiopental are significant

These risks historically preclude its non-RSI use

More recent data⁷⁷ suggests 3 mg/kg IV followed by an additional 1 mg/kg doses outperformed ketofol

Risks of IV thiopental (hypotension, airway spasm) not borne out in studies of PR route

Like other barbiturates, not recommended for use in patients with porphyria (increased porphyrin synthesis)

Recommendation: PR thiopental appears maybe safe and effective for use in the ED, although there are relatively few data

Ketamine

Section references^{9,11,25,29,38,56,78-119}

Phencyclidine analog producing dissociative analgesia and sedation (cortex doesn't perceive pain)

Produces dissociative state; patient has blank, glassy-eyed stare with nystagmus

Even in subdissociative state there is some (varying) analgesic benefit¹¹⁵

Primary advantage: preservation of airway reflexes, coughing, sneezing, swallowing

Respiratory & hemodynamic safety profile unmatched (for equipotent sedation)

Preservation of some reflexes translates into decreased chances for aspiration

JCAHO (Joint Commission) has relaxed ketamine *NPO* guidelines compared to other agents

“No full meal within 3 hours” is *NPO*-compliant for ketamine sedation

Ketamine may be best agent when sedation is necessary and patient may lack empty stomach

Ketamine appears safe (no increase in side effects) even when opioids have been previously administered

Most data addressing ketamine's use in for ED procedural sedation come from pediatric studies

Ketamine's risk profile is similar for adults, at least younger adults (*e.g.* with no major cardiac risk)

There are series^{106,110} demonstrating ketamine's safety/efficacy in adults (basically same conclusions as pediatrics)

IM route safe/effective in ED (no IV access required)

Dosing: 4 mg/kg IM (with atropine 0.01 mg/kg max 0.3mg)

Ketamine, atropine, and midazolam can be admixed and given in the same syringe

Glycopyrrolate (5 mcg/kg, max 250 mcg) can replace atropine if non-central antisialagogue is preferred

Evidence¹⁰⁹ indicates atropine is likely just as good, if not better, in terms of side effects (less vomiting)

Neither atropine nor glycopyrrolate appear to reduce airway/laryngospasm side effects

May repeat ketamine dose after 10 minutes

In 1022 children, IM doses between 4 and 5 mg/kg produced adequate sedation in 93-100%

Time parameters

Onset and peak: 3-4 minutes (peaks within a few minutes of onset)

Duration: 15-30 minutes

Recovery: 30-180 minutes

ED safety and efficacy are extremely well-established even in austere settings¹²⁰

Typical study findings include:

Up to 98% adequate sedation, analgesia, and immobilization with a single dose

In nearly all cases procedure can be done within 5 minutes of ketamine administration

Usually, no change in oxygen saturation noted in patients receiving ketamine

Only a few patients (nearly always those with long procedures) required repeat dose

In pediatric use, 96% parents satisfied with ketamine in one study (1% had negative comments)

Potential indications reported in difficult/unusual circumstances in limited case series

Genital exam in abuse cases

Sedation for mentally disabled adults

Ketamine used in 17 mentally disabled adults: no emergence reactions

Avoid ketamine if disability related to VP shunt or hydrocephalus

IV route provides effective sedation with shorter time parameters than IM

Dose (initial) – pediatrics: 1.5-2 mg/kg over one minute (1 mg/kg doesn't reliably work in children)

In one study, 1.5 mg/kg dosing resulted in need for just a single dose in 94% patients

In another ED series with mean initial dose of 1.5 mg/kg, 60% got at least one repeat dose

Total mean dose in the largest ED study of IV use: 2.5 mg/kg

Often combined with midazolam: One study of 350 cases, ketamine 1-2 mg/kg with midazolam .05-.1 mg/kg IV

Dose (initial) – adults: few large-scale data; one study reports success with IV dose of 1.5 mg/kg¹¹⁰

Pharmacokinetic study¹⁰⁷ suggests advantages (equal sedation, earlier d/c) to a "top-up" regimen:

Give initial IV dose: 1.25 mg/kg

Top-up dose 8 minutes after initial dose: 0.625 mg/kg

Time parameters

Onset and peak: 30-60 seconds (peak 1-2 minutes)

Duration: 5-10 minutes

Patients dischargeable in one study in a median 25 mins (recovery time much shorter than for IM ketamine)

In series of 156 patients, median discharge time was 84 minutes

Patients requiring multi-doses had similar time parameters to IM

Time-to-discharge data do not include time to initiate IV access

Other ED studies: similar discharge times (67-180' in one study)

In pts receiving 1 mg/kg ketamine + .1 mg/kg midazolam:

Pre-sedation regimen impacted recovery times

Those who received morphine within a few hrs pre-sedation: recovery median 31 minutes

Those who received no pre-sedation analgesia: recovery median 27 minutes

Those receiving meperidine within a few hrs pre-sedation: recovery median 50 minutes

PO ketamine has been studied in the anesthesia setting and is occasionally used in EDs

Dose: varies between studies; 6 mg/kg recommended

100% sedation achieved with 6 mg/kg

Only 73% sedation rate with 3 mg/kg

Time parameters

Onset: 11 minutes

Peak: 20 minutes

Duration: not fully characterized, but likely 30-60 minutes

There are few problems with oral dosing

17% of patients complained of the taste but none refused to drink ketamine

No delirium, vomiting, or prolonged emergence noted in one anesthesia study

Relatively less ED experience with other routes of administration

Rectal ketamine: dose of 5-10 mg/kg has been suggested

IN ketamine 0.5-0.75 mg/kg was useful (non-dissociative analgesia) in one study¹¹⁶

Potential problems with ketamine lie in both physiologic and psychological side effects

Side effects of ketamine can be unpredictable as they are largely non-related to dose (once dissociation is achieved)

Data from (observational) meta-analysis of over 8000 cases finds:^{111,121}

- Risk factors that predict ketamine-associated airway and respiratory adverse events were the following:
 - High intravenous doses (more than 1.5 mg/kg)
 - Administration to children younger than 2 years or aged 13 years or older
 - Use of co-administered anticholinergics or benzodiazepines (but recall this was observational data)
- Risk factors associated with emesis and recovery agitation in the 8000-case meta-analysis included:
 - Early adolescence is the peak age associated with emesis
 - IM administration or high IV dose (initial dose >2.5 mg/kg or total >5.0 mg/kg) linked to emesis
- Recovery agitation not age-associated to a clinically important degree
- Overall, no benefit or harm of co-administering anticholinergics or benzodiazepines
- Overall, no increase in adverse events found with oropharyngeal procedures or underlying illness (ASA 3)

Muscle hypertonicity and random movements may occur (thus ketamine is not ideal for CT sedation)

Sympathomimetic stimulation: if possible, avoid ketamine where ICP, IOP, or cardiovascular disease are issues

Decision's situational: sometimes ketamine's the best agent for the job at hand even with relative contraindications

IOP issues with ketamine are particularly subject to debate, even in recent expert panel reviews

- In one scenario with periorbital lac and hyphema:
 - One expert specifically recommended ketamine
 - This person noted that evidence for ketamine and IOP adverse effects was very thin
 - The reviewer also noted that ophthalmology at his institution preferred ketamine
 - Two other experts on the same panel specifically stated ketamine was contraindicated

Emerging literature and discussion seems to heavily weighted towards acceptance of ketamine for TBI, IOP, ICP

- There is a single case report of ED VTach post-ketamine
 - No treatment needed
 - Case was a pediatric patient with normal heart, no risk factors¹¹⁷

Apnea has been reported rarely; occurred in 2 of 1022 patients in one series

Laryngospasm risk historically contraindicates ketamine use in patients <6-12 months or with URIs

- This risk factor may potentially be modified by interpretation of Green's meta-analysis (see previous page)
 - Green: laryngospasm in 4 of 1,022 uses
 - Chudnofsky: laryngospasm in 1 of 70 adults (patient had history of URI) but
 - Larger adult ketamine trial: no laryngospasm¹¹⁰
- Shavit: ketamine (with propofol) safe and effective in performance of intraoral procedures in children¹¹⁸

Treatment: oxygen, suction, bagging, IV lidocaine

- Succinylcholine if needed for extreme cases
- Delayed laryngospasm has been reported in patients (lacking risk factors) up to half-hour post-procedure

Hypersalivation occurs in up to 30% patients despite atropine, and this is clinically a nuisance or worse

- Atropine is almost always indicated with ketamine use for ED PSA (even if it doesn't work ideally)
- Hypersalivation is an airway issue
- Hypersalivation is also distracting (e.g. to parents to watch, to caregivers to need to be suctioning)
- Prospective controlled double-blind trial¹¹⁴: Atropine does work to reduce hypersalivation
 - Ketamine-associated hypersalivation 28% with placebo)
 - With atropine administration the ketamine-associated hypersalivation dropped to 12%

Harmless hyperemic flushing occurs in up to a fifth of patients receiving ketamine

Vomiting (in 3-7% of patients) is often delayed until hours after the procedure (make sure and warn patients/families)

- It's not an issue during the procedure
 - Ketamine's actually used by Anesthesia (in some cases) for esophageal endoscopy
 - Intraprocedural vomiting (with obvious aspiration risk) is not reported as an ED ketamine issue
- Evidence suggests that midazolam⁴³ or ondansetron¹⁰⁵ co-administration reduces incidence of vomiting
- Pediatric evidence (Green's observational meta-analysis – see previous page) contradicts this
- Observational meta-analysis is limited by likely administration of anti-emetics to those most likely to vomit

ACEP Clinical Practice Guideline suggests that NNT for ondansetron prophylaxis is about 9

Ondansetron's harmless and cheap (the ODT is off-patent), and nausea is unpleasant, so many lean towards Rx
Emergence reactions, which may last up to 24 hours, are a primary concern with ketamine for PSA

Emergence is a major reason why Anesthesia doesn't use more ketamine in their practice

But Anesthesia practice parameters are different from those of the ED

Ketamine's overall safety and side effect profile may be more acceptable in the ED than elsewhere

Emergence reactions are not rare and they must be discussed with patients and families

However, discussion should include the fact that emergence isn't frequent and may not be "bad"

One ED study analyzed ketamine-related emergence reactions' risk/severity

91.3% normal recovery; 7.8% mild, 0.9% moderate to severe agitation

Emergence reactions were often reported to be quite pleasant by patients/families

Reactions are more likely to be described as not "bad" if clinicians provide forewarning

Prophylaxis against emergence: which agent and who needs it?

Overall, the older the patient, the less likely co-administration of anti-emergence drug is required

Emergence reactions are uncommon in patients <10 yrs old and they're more likely if >15 years Green's
meta-analysis (observational) suggests no reason for prophylaxis if age < about 10

Data suggest mild post-recovery agitation is more common than severe "emergence" in children

Two double-blind studies suggest midazolam didn't help with emergence in patients less than 15

Data show that emergence wasn't improved with the midazolam group

However, same data suggest that midazolam *does* reduce post-procedure vomiting

Adult ketamine study¹¹⁰ reports benzo reduces unpleasant emergence in adults – NNT about 6

Patient-specific parameters (*e.g.* age, history of psychiatric issues) should inform prophylaxis decisions

Which agent to use if prophylaxis is to be given for emergence?

Benzo seems best choice for prophylaxis if a prophylactic is to be given

One midazolam/ketamine (adult) co-administration study: zero emergence reactions

Optimal benzo regimen unknown; ACEP Clinical Practice Guideline:¹¹³ midazolam 0.03 mg/kg IV

Overall: Choose patients wisely, give a benzo (*e.g.* lorazepam PO if using IM ketamine), and recover in quiet place
If emergence occurs:

Reduce stimulation

Administer a benzodiazepine (dose/route depending in situation)

If above don't work, situationally consider haloperidol or pentobarbital

Contraindications listing (as generally applicable to elective ketamine use for ED PSA, where there are alternatives):

Patient younger than 3 months (absolute contraindication as per 2011 *Annals EM Clinical Practice Guidelines*)¹¹³

Psychosis such as schizophrenia (absolute contraindication as per 2011 *Annals EM Clinical Practice Guidelines*)¹¹³

History of airway instability or tracheal surgery/stenosis

Procedures involving posterior pharyngeal stimulation

Active pulmonary or upper airway infection or disease

Ischemic cardiac disease, CHF, or hypertension

Head injury or CNS mass or hydrocephalus

Glaucoma or acute globe injury

History of seizures

Porphyria or thyroid disease

Combination of ketamine with propofol^{77,104,108,112,119,122-124}

Many studies note ketamine's complementary properties with those of propofol (which lacks analgesic effect)

"Ketofol" has been coined as term for combination approach, done slightly differently in varying ED studies

Administered in boluses with median dose about 0.75 to 0.8 mg/kg of each agent

Example administration method (arguably the easiest method):

Mix propofol 10 mg/mL concentration, with ketamine 10 mg/mL concentration, in same syringe

Administer aliquots of 0.5 mg/kg (of either component) over 30-60 seconds

Second approach: 0.5 mg/kg ketamine bolus followed by 30-second infusion of 1 mg/kg propofol

Second doses of ketamine (0.25 mg/kg) and/or propofol (0.5 mg/kg) allowed at MD discretion

This approach seems to avoid risks attendant to getting ketamine/propofol mixture correct

A third approach:¹²⁵

Mix propofol 10 mg/mL concentration, with ketamine 10 mg/mL concentration, in same syringe
Administer aliquots of 0.025 to 0.05 mL/kg of solution, over 30 seconds, titrated to sedation
Above equals 0.125-0.25 mg/kg of ketamine/propofol
Example: 80 kg adult receives 2 to 4 mL aliquots, each aliquot representing 10 to 20 mg ketamine/propofol
This approach validated in 728 patients with good ED results

98% efficacy

Need for BVM in 2.1% [1-3.1%]

Recovery agitation in 3.6% [2.2-4.9%]

Idea is for hemodynamic boost from ketamine to counter propofol's cardiovascular depression

Hypotension or serious adverse effects are rare

Overall risk of need for positive pressure ventilation in one large study: 1 in 219 cases (95% CI 0-1.2%)

Median recovery time in one study was only 14 minutes

Ketofol's recovery time is usually reported to be about 40 minutes for time to discharge

One head-to-head trial found IV thiopental significantly outperformed ketofol in recovery time⁷⁷

Compared to fentanyl-propofol, 0.3 mg/kg ketamine-facilitated propofol PSA 5x fewer serious adverse effects

Data on ketofol vs. either propofol or ketamine have been sometimes reported as showing ketofol superiority

Some data: higher overall satisfaction with ketofol as compared with ketamine alone

Possible propofol-sparing effects and improved provider satisfaction

One of largest data sets (in mid-2012)¹²⁶ finds no benefit to ketofol as compared to propofol

No reduction in respiratory or other adverse events

No difference in induction time, efficacy, or sedation time

Another large (nearly 600) RCT found little difference between propofol and ketofol¹¹⁹

Recommendation for ketofol: May be reasonable but not clearly superior to ketamine alone¹²⁷

Mixing two drugs nearly always complicates things as compared to single-sedative therapy

Propofol is a superb drug (see below) but it's doubtless more dangerous in hands of EM than ketamine

In selected cases there may be utility to ketofol, when subdissociative ketamine regimen is desired

Recommendation for ketamine:

Appropriately utilized ketamine is safe/effective for ED use in children

Fewer data exist for adults but there are sufficient data to support ketamine is safe/effective in this group

One multispecialty evidence-based medicine review found ketamine both safe (Level A) and effective (Level A)

In some reviews ketamine is the *only* PSA drug with sufficient evidence for Level A ED recommendations

Consider co-administering a benzodiazepine when ketamine used in adults¹¹⁰ (but this is not absolutely required)¹¹¹

Midazolam

Section references^{6,11,20,25,29,72,85,128-149}

Oral midazolam

Dose: 0.45-0.75 mg/kg max dose 7.5-10 mg (including adults)

Time parameters

onset: 20-30 minutes

peak effects range from 15-50 minutes in various reports

duration 30-120 minutes (all study pts in one report were d/c'd within 15 minutes of suturing)

PO route is as effective, and easier to give, than nasal route in ED studies

Oral midazolam has compared very favorably to oral diazepam in at least one head-to-head ED trial

Intranasal (IN) midazolam has been recommended for infants

Dose: 0.1-0.3 mg/kg

Time parameters

Onset ranges from 5-15 minutes

Peak effects reported at 10 minutes

Duration 30-120 minutes

Demonstrated efficacy when mixed with IN sufentanil in ED setting (one study)

In general, the IN route is less well-tolerated than the PO route; this relegates IN use to (primarily) infants

IN tends to have faster onset than PO or aerosolized midazolam

IN tends to have worse tolerance than PO or aerosolized midazolam

Atomized intranasal midazolam (using commercially available atomizer that delivers the midazolam in fine mist)

Dose: 0.3-0.8 mg/kg (mean and median doses were both 0.4 mg/kg)

Time parameters similar to those reported for IN midazolam (see above)

Efficacy was good in one study ($n = 205$), with only 5% of children (1.5-60 months' age) requiring additional sedation

Overall, a viable option if one has access to atomizer; more tolerable to children than dripped-in midazolam

Rectal midazolam

Dose: 0.4 mg/kg (in 5cc NS) has some demonstrated safety/efficacy in anesthesia, ED studies

Other doses used include 0.5mg/kg and 1 mg/kg (so-called "high dose" rectal midazolam)

Head-to-head trial of 0.5 mg/kg *vs.* 1 mg/kg has shed important light on PR midazolam's role in sedation

Time parameters

Onset within 10-15 minutes

Peak effects expected by 15-30 minutes

Duration 30-120 minutes

Good news and bad news on PR midazolam can be summarized as follows:

Good news: PR route is easy to use, and has some demonstrated efficacy, for many patients, in ED setting

Bad news: relatively high failure rates and agitation

"Standard dose" (0.5 mg/kg) had high failure rate of 56% in one study

"High dose" (1 mg/kg) had lower, but still concerning, failure rate of 30%

Agitation occurred infrequently (6%) in standard-dose group

Agitation occurred frequently (27%) in high-dose group

IV/IM midazolam (IV is far preferable in terms of titration)

Midazolam is water-miscible, allowing for co-injection and decreased injection pain

Dose: 0.1 mg/kg either route (IM or IV)

Time parameters

Inject 1 mg per minute, with a 2-minute lag time after each 1 mg

Onset: 1-2 minutes after either IM/IV

Peak: 3-5 minutes after either IM/IV

Duration 30-120 minutes

Many studies have demonstrated ED safety/efficacy of IV midazolam

Average dose 3.9 mg; range is wide (0.5-20 mg in one study)

Most patients also received opioids or sedative/hypnotics

Overall complication rate 1% in most ED studies but of course the results vary

0.5% developed clinically significant respiratory depression in one large series

Both of these patients constituting the 0.5%, had also received fentanyl

Both cases of respiratory depression responded to naloxone

About 1% (again, depending on situation) develop hypotension that tends to respond to fluids

One study reports (unsurprisingly that midazolam/ketamine has less respiratory depression risk than midazolam/opioid

Advantages of midazolam over diazepam and lorazepam

Profound amnesia produced by midazolam appears better than that with other agents

Midazolam: Less mucosal irritation, well-absorbed IM, combinable in same syringe with other agents

Problems with midazolam

Primary problem has been respiratory depression

Scores of fatalities reported; opioids were simultaneously administered in most cases

Experts recommend reducing midazolam dose by 50% when co-administering opioid

Respiratory depression has been rare (nearly never) when PR route is used (even at 1 mg/kg)

Respiratory depression may be avoided by patient selection with appropriate use guides including:

Avoidance (if at all possible) in elderly patients or those with underlying lung disease

Close monitoring: slow injection and constant monitoring for clinical effect and side effects

No analgesia is provided by midazolam; it is sometimes inappropriately used alone

Most studies assessing midazolam *vs.* newer agents (*e.g.* propofol) find midazolam inferior

Both induction and recovery times are more favorable for etomidate and propofol

Adequate level of sedation also appears more favorable for other newer agents

Midazolam inferiority isn't due to dosing: one trial *vs.* etomidate used 0.1 mg/kg midazolam over 90 sec

Paradoxical emergence-type reaction may be seen with midazolam

This reaction is not uncommon, and has even occurred with PO administration

Flumazenil effectively treats this dysphoria in most cases

Haloperidol is also suggested as effective treatment for these reactions

Recommendation: midazolam is a good-to-excellent first-line sedative for single or combination therapy use in ED

Many routes have been specifically demonstrated effective in the ED

Large body of literature supports (proper) use of midazolam in the ED setting

2005 ACEP Clinical Policy: Midazolam (+ fentanyl) got Level B recommendation (ketamine was only Level A)

As recently as 2008, large-scale reviews find midazolam equally safe and effective as newer agents such as propofol

Diazepam

Section reference¹⁴³

Prototype benzodiazepine gaining “new” following in ED and critical care settings

Critical care literature has illustrated that benzodiazepines often perform similarly in the ICU setting

Diazepam has primary advantages of cost and (probably, though with some controversy) good muscle relaxation

Dose: 0.1 mg/kg IV (max 3-5 mg initial dose) with repeat dosing up to 10 mg

Time parameters (IV): Administer 1-2 minutes prior to procedure

Onset: 1-2 minutes

Peak effects: 2-5 minutes

Duration: may last up to 4-6 hours

Demonstrated safety/efficacy for joint reductions in ED setting although there is some ongoing debate on this

Historically, diazepam was felt to have “best muscle relaxation”

More recent data have suggested that at ED doses, there is little clinically useful muscle relaxation

Beware giving high doses of diazepam trying to obtain muscle relaxation (especially with opioid analgesia)

Potential problems

Primary problem (like that for other benzos) is respiratory depression – particularly with co-administered agents

May be irritating to veins or when given IM (not recommended for IM use in ED)

Recommendation: Reasonable first-line agent for major joint reductions when a benzodiazepine is to be used

Fentanyl, alfentanil, sufentanil, remifentanil

Section references^{8,11,25,29,121,150-157}

These synthetic opioids have rapid onset, short duration of action, and easy titratability

Fentanyl has roughly 100 times the potency of morphine

Compared to fentanyl, alfentanil: 20% potency, 33% duration, 38% half-life

Rapid onset is due to lipophilicity (fentanyl 7000x that of morphine) and rapid CNS uptake

Alfentanil less lipid soluble (less prone to accumulation with repeat dosing) than fentanyl

Sufentanil has also been studied in the ED but not enough to recommend its general use

7x potency of fentanyl

Frequently recommended as useful for IN administration

Primarily studied as a combination agent with midazolam (see above)

Remifentanil: ultra-short, ultra-potent analog remifentanil highly efficacious with very limited ED data¹⁵⁶

Essentially 100% effective in a series of a dozen cases 0.5-3 mcg/kg initially, 0.25-1 mcg/kg repeat as needed

Most patients had recall of procedure

LMA and/or BVM required in 17%

Wakefulness achieved 4 minutes post-last dose remifentanil

Fentanyl is the recommended agent for ED use

Much more studied, and therefore currently preferable, in ED setting

Other agents efficacious and safe in Anesthesia hands but at this point not clearly superior to fentanyl for ED

Dose

Fentanyl

1-3 µg/kg fentanyl IV over 3 minutes

10-15 µg/kg oral transmucosal fentanyl (not used much at TCH due to vomiting)

1.5 µg/kg IN has been administered with nitrous oxide; effective but high rates of vomiting (about 20%)¹⁵⁷
Alfentanil: 8-15 µg/kg IV over 3 minutes
Sufentanil: 0.7-1.0 µg/kg IN (limited data to support or characterize isolated use of this agent)

Time parameters

IV fentanyl

Onset: within 30-60 seconds
Duration: 20-30 minutes of clinical usefulness

IV alfentanil

Onset: within 1-2 minutes
Duration: less than fentanyl due to shorter half-life

Oral transmucosal (lollipop) fentanyl

Onset: within 15 minutes
Duration: 1-2 hours

Advantages of IV fentanyl are related to its rapid onset, potency, and short half-life

Easily titrated in the ED, without problems of long-term sedation

Maximal respiratory depression occurs early (within 5 minutes)

Minimal cardiovascular effects (little or no histamine release)

Oral transmucosal fentanyl route provides non-stressful, generally effective delivery for pediatric patients

Well-documented in ED for sedation, anxiolysis, analgesia

Oral fentanyl doesn't require IV but has side effects

Pruritis occurs in many cases

The rate of vomiting is high (31-45%) and has been termed "unacceptable"

Alfentanil

Advantage is short terminal half-life and lack of accumulation with repeat dosing

One ED study¹²¹ finds effectiveness, suggests 39% rate of airway/respiratory events; 3% BVM (no major sequelae)

Potential problems – fentanyl

"Significant" respiratory depression is uncommon: <1% respiratory depression in 3,000 patients

However, a healthy volunteer study shows potential for respiratory depression

Boluses of only 2 µg/kg caused hypoxemia ($S_pO_2 < 90\%$) as monitored (no interventions)

Fentanyl + midazolam (.05mg/kg): nearly all hypoxemic, ~50% transient apnea

Respiratory depression incidence reduced with judicious administration of titrated doses

Muscular and glottic rigidity impairing respirations may occur

Rigidity also may occur with morphine and meperidine

Rigidity is historically thought to be risked if use >5 µg/kg fentanyl or >20 µg/kg alfentanil

There are about a dozen reports in the pediatric literature¹⁵⁸ of chest wall rigidity at far lower doses

Low-dose chest wall rigidity seems a risk consideration in the very young (newborn to months old)

Doses of fentanyl in reported cases of rigidity are above 5 µg/kg and up to 17 µg/kg

Chest wall rigidity exceedingly unlikely with ED doses (<3-5 µg/kg)

Slow administration of frequent smaller doses decreases chances of rigidity

Rigidity is treated with naloxone (this may not work) or succinylcholine

Many patients receiving fentanyl get harmless nasal pruritis (inform patient/parent before administer)

Recommendation: IV fentanyl represents well-tested first-line ED agent

ACEP Clinical Policy: Fentanyl (+ midazolam) got Level B recommendation (ketamine was only Level A)

Oral transmucosal fentanyl appeared promising but emesis limits this route to second-line use at best

Alfentanil/sufentanil may arguably have better pharmacology but are second line due to fewer ED studies

Propofol

Section references^{11,20,21,25,29,30,33,49,53,63,77,89,146,147,159-186}

Ultra-short acting alkylphenol (2,6-di-isopropylphenol) sedative-hypnotic

Proven utility in many non-ED settings

Characteristics: rapid-onset, short duration rapid-offset

Dose regimens vary depending on the study

Many tend to use infusions due to the medication's short half-life

Dosages used in outpatient elective series tend to be a little higher than those used for ED patients
One common, easy-to-remember ED regimen: 1 mg/kg bolus followed by 0.5 mg/kg every 5 minutes as needed
A large ED series in children:

1 mg/kg (maximum 40 mg per dose) administered over 1-2 minutes (opioids also administered)

0.5 mg/kg (maximum 20 mg per dose) repeat doses at the discretion of the treating physician

Repeat doses were administered over 1-2 minutes

Minimum of 60 seconds was required between repeat doses

Total dose required was about 3 mg/kg for study patients

A relatively recent (2014)¹⁸⁶ series from a Pediatric ED reported success and safety with a higher dose of propofol
886 cases

Median initial dose: 2 mg/kg

Median total dose: 3.6 mg/kg

Problems were rare: desaturation to less than 90% occurred in 7.2% of cases (no intubations were needed)

Success was very high even when propofol was given alone (*remember*: propofol is not an analgesic)

The only thing most physicians reported they'd change: giving a higher initial dose of propofol in the future

One infusion method: 25-125 µg/kg/min (many protocols start at 50 µg/kg/min)

Another approach uses propofol in combination with fentanyl; in one series of 33 patients in a PICU study

Step 1: fentanyl (1 µg/kg) then wait three minutes before propofol

Step 2: propofol 1.5-2.0 mg/kg gradual loading dose

Step 3: propofol infusion 150 µg/kg/min

One ED group recommends infusion as a safer alternative to bolus dosing (pretreated all patients with 2 mcg/kg fentanyl)

Initial dosing is 0.21 mg/kg/min until patient sedated

Then procedure started, and 3-6 mg/kg/hour propofol administered

Findings of dosage in 3-center trial showed variable dosing was used

Adults: initial dose ranged from 0.3 to 3.8 mg/kg with mean total propofol dose was 1.7 ± 0.9 mg/kg

Children (<12 yrs): mean total dose 3.6 ± 3.2 mg/kg

Another regimen incorporates fentanyl (1 mcg/kg) then propofol 20mg administered over 20-30 secs, repeated q2-minutes

Pediatric study⁵³: median of 3 doses used, with total average dose 2.1 mg/kg

Initial and subsequent mean doses: 1 mg/kg, 0.5 mg/kg, 0.4 mg/kg

Doses tend to be slightly higher for younger patients

Doses required tend not to be related to any other parameters (including co-administered opioids)

Recent work clearly demonstrates that side effects are more likely with the higher doses, older age

Side effects also reported more likely with co-administrations (particularly opioids)

Miner¹⁸¹ finds no benefit from addition of alfentanil in morphine-pretreated patients receiving propofol

Time parameters

some effect is seen within 30 seconds

Onset of sedation always occurs within 5-10 minutes; can be as fast as 1-2 minutes

High first-pass metabolism results in half-life of 5-10 minutes

Clinical half-life in a recent cardioversion study was about 20 mins

Fentanyl/propofol combination: time to dismissal is much shorter than for other sedation protocols

This is a major advantage of propofol use (even with opioids)

Propofol wears off within 5-15 minutes when given alone

Opioid (usually fentanyl) + propofol: range 10 to 50 minutes but in general about 20-30 minutes

Advantages of propofol

Reliable, dose-dependent sedation ranging from light to general anesthesia

Anesthesiologist-rated "general anesthesia" state occurred in 25% of ED propofol patients in 1 series

Recent editorials dispute the significance of "inadvertent general anesthesia"¹⁸⁰

Very effective, easily controlled sedation

Oversedation is potentially less likely to occur since the drug is titratable

Based upon a double-blind trial: if oversedation occurs, shorter duration than occurs with midazolam

May have future uses as co-administered agent with potent short-acting analgesics

Rapid offset is useful for busy ED setting

Mean recovery time is much faster than even midazolam (overall nursing time reduced by nearly half)

Cost-effectiveness analyses: shorter offset time of propofol is financial advantage over midazolam

In one prospective, blinded study, propofol performed better than midazolam/fentanyl with respect to:

Time to first awakening (propofol offset about 5 minutes faster; 3 minutes vs. 8 minutes)

Time to full consciousness (propofol offset about 22 minutes faster; 7 minutes vs. 29 minutes)

About $\frac{3}{4}$ of patients will have some amnesia for details of the procedure (some amnesia in 80-90% of ED cases)

Patient satisfaction high: All 20 patients asked (in an ED study) would agree to propofol/fentanyl for future cases

Propofol has antiemetic properties (unusual for a sedative agent)

Propofol has antiepileptic properties (useful for head-injured patients)

Propofol does not interfere with cerebral autoregulation or adversely affect ICP

Multispecialty support: SCCM expert committee recommends propofol (or midazolam) for short-term ICU sedation

Combination studies

Most ED series include at least some opioid as a co-administered agent (for analgesia)

Fentanyl/propofol combination: no respiratory depression, hypotension, or nausea in 33 patients

Morphine/propofol combination: no significant respiratory depression or hypotension in 43 pts.

May be useful for fast-onset sedation and some analgesia (preliminary favorable data for pediatric migraine)¹⁸⁵

Potential problems (other than respiratory depression)

Except during deep anesthesia, propofol lacks analgesic properties

Propofol's 100% efficacy comes at a cost due to its potency: vigilant monitoring is always required with propofol

Propofol and etomidate may be considered "high-potency" PSA approaches

Overall incidence of need for airway intervention of some type is about 15%

Propofol indicated only when deep sedation is needed (*e.g.* fracture/dislocation reduction, cardioversion)

Hypotension is a major issue as well

3.5% in multicenter ED study of 792 patients

5% in another study, when given with fentanyl 2 $\mu\text{g}/\text{kg}$ IV

another study using propofol infusion (also with 2 mcg/kg fentanyl)

SBP<100 in 12%

No pressors required in this series

Hypotension is potentially an issue when propofol is given by rapid bolus

Beware hypotension in patients on calcium channel or beta-blockers

Hypotension is also more likely in older patients

Cardiovascular collapse is a risk in pediatric patients as well (at least one pediatric death in ED)

Pressors are not generally required in pediatric propofol series

Evidence varies with respect to hypotension in children receiving propofol

One pediatric study: 84% of children had SBP drop with propofol (no pressors)

Another pediatric study: no hypotension in 48 propofol cases

In most studies, some systolic BP drop occurs in nearly all patients (median drop of about 20 mmHg)

It appears that relatively frequent use of IV fluid boluses (in about a quarter of patients) may be useful

Pressors

MGH Cardiac Anesthesia: "Propofol combo therapy means Propofol and Levophed"

Fluids alone may be best maneuver

Burning on injection: Add 30 mg lidocaine (without epi) to the propofol bolus injection to reduce this problem

Unusual problems and considerations

Avoid propofol use in patients with allergy to eggs or soybean products

Odd effects have been reported with use in ICU and OR settings (likely less risk in ED use)

Urine, hair, liver discoloration

Pulmonary lipid deposition

Postoperative pancreatitis

Respiratory depression

Dose-related, serious respiratory depression is a problem

Respiratory depression rates vary but some degree occurs in about 5-22% of patients in various studies

Incidence depends somewhat on definition: most precise estimate is probably around 10-15%

Apnea is seen in up to 10% of ED study patients in adults, and about 1% in pediatric ED studies

"Serious" respiratory depression in one large pediatric ED study occurred in 5% of children

Another series: 0% apnea, but transient S_pO_2 drops (addressed with manual vent.) in 31% of cases
In one ED study of 48 propofol patients, 12.5% had decrease in respiratory rate
Another ED study of propofol infusion: 16% respiratory depression no intubations (2 pts: BVM 7, 9 minutes)
A large ($n = 792$) multicenter series: 7.7% desaturation, manual ventilation required in 3.9%
Prospective study of propofol for cardioversion: apnea rate 9%; desaturation rate nearly 20% if age >65

Median respiratory parameter changes in one methodologically rigorous analysis:

Respiratory rate dropped about 7 per minute (with very wide range)

Median S_pO_2 drop was 3 (range 0 to 20)

Respiratory depression short of hypoxemia may be an issue

ED propofol studies have usually not addressed $ETCO_2$ (e.g. monitoring via nasal cannulae)

In one center assessing $ETCO_2$ with propofol, hypoventilation occurred in 19-49% cases

At least one ED propofol study notes their propofol protocol now requires $ETCO_2$ monitoring

Respiratory depression more frequent (26% in one study) when patients sedated to “general anesthesia”

Miner (2005): pts ASA Classes III/IV, respiratory depression “equally common” than with lower classes

Respiratory depression defined as: loss of $ETCO_2$ waveform, $ETCO_2$ increase >10, S_pO_2 <90%

Respiratory depression occurred in 19 of 31 patients (61.3%) receiving propofol

No adverse events were reported

Newer reports with low incidence of respiratory depression included O_2 in propofol sedation protocol

Early reports were up to 30% respiratory depression (in absence of supplemental O_2)

The new practice of providing O_2 probably “hides” (per Green and Krauss) some depression

Miner & Burton note providing O_2 negates “early warning” use of S_pO_2 but recommend O_2 anyway

2011 study¹⁸⁴ demonstrates significantly lower incidence of hypoxemia with O_2 administration

Significant interpatient variability in effects requires vigilance for cardiorespiratory depression

EM experts have noted that “general anesthesia training” is required by drug labeling

Reviews have concluded that even with proper use, some cardiorespiratory depression will occur

Some hospitals require anesthesiologist for propofol procedural sedation

One study found that 1 mg/kg dosing (with 0.5 mg/kg q2mins) had 50% respiratory depression rate

Deep sedation is expected to occur, necessitating compliance with JCAHO *npo* guidelines

If deep sedation is possible, the guidelines for general anesthesia are in force

These guidelines: no solids within 6-8 hours, no liquids within 2-3 hours

Difficult for ED to comply with these guidelines, yet deep sedation is possible

One large study (n of 25433) of ED physicians and propofol focuses largely on propofol use by a “sedation service”¹⁸³

Serious adverse events occurred in 2.3% (95% CI 2.1-2.5%)

Only one unplanned intubation in the entire series (also 2 aspirations and 1 cardiac arrest)

Risk factors for more serious events:

Weight less than 5kg

ASA classification 3 or higher

Adjunctive medications (e.g. benzos, ketamine, opioids, anticholinergics)

Nonpainful procedures (i.e. lack of ongoing respiratory stimulus)

Primary diagnoses of prematurity or URI

Study in ED setting is growing and EM expert reviews argue potently for incorporation of propofol into ED use¹⁸⁰

2008 large-scale reviews: propofol equally safe and effective as (and possibly less expensive than) midazolam^{146,147}

Multicenter trial with 792 patients¹⁷⁵ adds significantly to available data and demonstrates safety/efficacy

Another trial (propofol *v.* etomidate)¹⁷⁸ with n for propofol = 109, also suggested safety/efficacy

Side effects tend to be common, however:

A comparison with methohexital concluded both were safe – but 50% had respiratory depression

Trial of propofol (1.5 mg/kg) use for ED cardioversion found it was better than midazolam or etomidate but risky

This trial was limited by very low numbers (n for propofol group = 9)

Study findings:

Repeat dosing was only required for one patient

Efficacy was 100% and overall sedation characteristics were best for propofol

No hypotension occurred although the authors specifically assessed for this

4 patients (of 9) had desaturation and 2 had apnea

Expert reviewers/commentators continue to evolve with respect to use of propofol use in ED

Older reviews are negative

Flood (2003): “further studies are needed to evaluate the safety and efficacy of propofol...”

Green and Krauss (December 2003): “few questions are as controversial”

Cumulative supporting evidence has driven change in direction in favor of propofol

In other words, no one was “too quick” to jump on propofol train in the ED

One recent evidence-based review: propofol is safe (Level B) and effective (Level B)

A 2007 editorial by Green³⁸: propofol (and etomidate) “ready for prime time in ED practice”

2008 editorial by Green/Krauss: Propofol should be used in emergency medicine¹⁸⁰

Annals of EM practice guideline in 2007 (Miner/Burton) is an excellent overall resource supporting propofol

Compared to alternatives, propofol’s managed risks appear to be able to be mitigated

Perhaps because of (appropriate) caution, the risks are managed and problems are prevented

Overall, efficacy and side effects of ED PSA improve after propofol is added to ED formulary¹⁸²

Recommendation: excellent sedative with growing ED experience but clear risks that must be predicted/managed

Propofol is a first-line agent for some circumstances if clinicians remain aware of risks and monitoring needs

Particularly likely procedures for propofol include short, intensely painful ones: cardioversion, fx reduction

2005 ACEP Clinical Policy: Propofol got Level B recommendation (ketamine was only Level A)

Nitrous oxide

Section references^{11,43,56,157,187-193}

Inhaled analgesia possessing light sedative effects, with varying ratios of N₂O:O₂ (at least 40% O₂)

Numerous advantages and overall excellent safety profile in less-monitored settings (*e.g.* dentistry)

Ease of use and solid evidence base for safety in a variety of settings

Noninvasive self-administration by patient allows titration to effect

Utility demonstrated in both adult and pediatric patients

Useful for short procedures where local anesthesia is ineffective (*e.g.*, I & D)

Demonstrated utility in aiding with emergency procedures (*e.g.* laceration repair in pediatric patients)

May obviate or reduce need for opioids for fracture reduction

Excreted unchanged by lungs and not affected by renal/hepatic dysfunction

Overall advantages as noted in a head-to-head randomized comparison against IV ketamine included:¹⁹³

Lighter sedation

Much faster recovery (median 0 minutes for nitrous oxide as compared to 21 minutes for ketamine)

Similar satisfaction to ketamine for both patients/families and nurses

Similar intra-procedure (laceration repair) pain scores for patients

Usual dose/administration: oxygen/N₂O mixture is self-administered

Patient will drop mask when sufficiently dosed

Children may not be able to generate sufficient negative inspiratory pressures for self-admin.

Continuous-flow N₂O device has been tested (see below) but not standard of care

At this time, self-administration is only route widely accepted as appropriate for ED use

“Non-self-administration” is used but appears to result in higher rates of emesis (20% or so)¹⁵⁷

Time parameters

Onset: within 2-5 minutes

Duration: effects usually subside within 5 minutes of cessation

Observe for up to 45 minutes post-procedure depending on recovery

In one study: offset was noted to occur within 4 minutes¹⁹³

Potential problems

Safety comes at some efficacy cost: in ED concentrations, N₂O not as potent as sedative/analgesic as other agents

Nitrous oxide is highly diffusible

May accumulate in enclosed body cavities (*e.g.*, middle ear or bowel)

ED use contraindicated in patients with lung disease (*e.g.*, COPD)

Use of nitrous oxide with other agents may increase risk of respiratory compromise

Ambient nitrous oxide may be dangerous to health-care workers (equipment issues are significant)

Attention must be paid to potential for emesis (up to 10% in some regimens) and aspiration

At least one report suggests that for toddlers (aged 2-6) continuously-administered N₂O may be safe and effective

The gas was easily administered through a special nasal mask

Sedation was very effective with the mask, and more effective than oral midazolam

Addition of midazolam to the N₂O regimen accrued no additional sedative benefit

Emesis was a concern – in about 1 in 10 cases – and thus mask positioning must be watched carefully

Recommendation: Good safety with good efficacy, especially for short procedures (often best used with local anesthetics)

Etomidate

Section references^{11,20,25,29,30,75,145,178,194-203}

Ultrashort acting (within 15-30 seconds) imidazole sedative-hypnotic with primary ED use as intubation aid

Activity probably mediated through GABA neurotransmission

Many advantages: hemodynamic stability, favorable cerebral blood flow and ICP considerations

Dose: 0.1-0.2 mg/kg as bolus

If lower doses are used then the dose may be repeated if necessary

One study in adults used bolus of 0.1 mg/kg with 0.05 mg/kg every 3-5 minutes as needed

Pediatrics dosing

One pediatric study finds an average dose of 0.33 mg/kg (titrated) is required

In a pediatric series 0.3 mg/kg was associated with high failure rate so max dose was increased to 0.4 mg/kg

A 2012 pedi study (including fentanyl 1 mcg/kg) recommends 0.2 mg/kg with option to add 0.1 mg/kg²⁰²

Time parameters

Onset within 30 seconds

Duration approximately 10 minutes

Full recovery occurs as soon as 30 minutes for nearly all patients; time to “discharge-ready” is median 21 minutes²⁰²

Advantages

Hemodynamic stability is very good – this may be a useful agent when BP is a concern

Familiarity with etomidate in the ED as a result of widespread use in intubation

Favorable cerebral perfusion profile (less likely a factor in procedural sedation than in intubation)

Overall procedural amnesia rate 96% for some degree of amnesia (total amnesia in 69%, partial in 27%)

As compared to midazolam

More rapid recovery (when used in combination with analgesics)

More rapid induction even when tested against relatively high-dose (0.1 mg/kg) midazolam

Many studies show safety and efficacy in ED

Prospective study in 51 adults and children: adequate sedation in 50 of 51 patients

Mean number of doses 1.6

Desaturation <90% was noted in 5 patients; no apnea and no assisted ventilation

There were four cases of myoclonus with no post-procedure myalgia noted

0.1-0.2 mg/kg bolus for fracture reduction in retrospective series of 53 children

One repeat dose was given as needed (9 of 53 patients)

All patients in the pediatric study received opioids as well

Median initial dose 0.17 mg/kg in patients of all ages

2 doses were necessary in 9% of cases; 3 doses in 0.2%

Amnesia rate was 93% and overall effectiveness was similarly high

Comparison versus midazolam for combination therapy with fentanyl for shoulder reduction

Primary advantage: shorter recovery times post-procedure as compared with midazolam

Myoclonus noted in 21% of patients receiving etomidate

One elderly woman (of etomidate *n* = 19) required 2 minutes of BVM ventilation

Comparison versus pentobarbital for CT sedation: study #1

Initial regimen, allowing for dosings of 0.1 mg/kg repeated to 0.3 mg/kg, failed in 43%

Study protocol then changed to allow for 0.4 mg/kg maximum: 76% efficacy

Though pentobarbital worked more frequently (97%) patients/families happier with etomidate

Comparison versus pentobarbital for CT sedation: study #2

Large numbers (*n* = 396 pentobarbital, *n* = 446 etomidate)

Very low incidence of concerning side effects with either regimen

Overall, etomidate preferable (0.9% *vs.* 4.5% incidence of inadequate sedation or side effects)

Assessment in ED (as well as other outpatient areas) for procedural sedation in head-to-head trial *vs.* midazolam

0.2 mg/kg etomidate *vs.* 0.1 mg/kg midazolam in randomized double-blind trial design

50 patients received each therapy

Sedation far better for etomidate group, and both induction and recovery were faster

About 1 in 5 patients in both study groups had desaturation

Comparison versus propofol in 2007 study: both agents performed well, both with 10-15% respiratory depression

Potential problems have been identified

ED evidence base continues to demonstrate safety but also identify unusual problems (*e.g.* recovery agitation)

Flood (2003): larger studies needed before reliable conclusions can be drawn about etomidate in children

Increasing data from pediatric ED/CT sedation literature makes strong case for etomidate's safety/efficacy

Arguably, insufficient data to support use in very young (under approximate 10 years of age)

One study of relevance assessed propofol *vs.* etomidate (0.2 mg/kg) *vs.* midazolam for cardioversion – its findings:

Repeat dosing was only required for one patient

Efficacy was very high and overall sedation characteristics were good

No hypotension occurred but 4 cases of myoclonus (responded to benzos), 1 bronchospasm, 1 “cough”

1 patient (of 9) had desaturation and 2 had apnea

Respiratory depression

Etomidate may be similar to other potent agents – about 10-15% respiratory depression

In particular, adverse event rate for older patients (up to 10% for age >55) is problematic

An outpatient study of 0.2 mg/kg etomidate found desaturation in 1 in 5 subjects

Hypoxemia and/or hypotension are risked with repeat dosing, with or without opioids

When co-administered with fentanyl, respiratory depression in 16.4% and desaturation in 39%²⁰²

36.2% experienced respiratory adverse event requiring brief intervention

Positive-pressure ventilation was not required in any of the 60 patients studied

Miner (2005): pts ASA Classes III/IV, respiratory depression “no more common” than with lower classes

Respiratory depression defined as: loss of ET_{CO₂} waveform, ET_{CO₂} increase >10, S_pO₂ <90%

Respiratory depression occurred in 18 of 31 patients (58.1%) receiving etomidate

In pediatric patients respiratory depression seems very uncommon (0 cases in 446 administrations, 2007 study)

Burning on injection has been reported (consider lidocaine co-injection in same vein)

Myoclonus

Likely due to interruption of GABA pathways

May be common but usually doesn't render etomidate suboptimal for PSA

Myoclonus rates for PSA range to up to 20-25% as best ED/outpatient estimate

One series reported 3 cases of myoclonus (facial twitching or more severe) with duration 30-120 seconds

2013 report²⁰³: myoclonus is common (72% of cases) but only rarely (3%) interfered with procedure

Myoclonus can be prevented with small doses of benzodiazepine (prevents subcortical disinhibition)

Green in *Annals EM* recommends propofol over etomidate in part due to myoclonus

Recommendation: Not quite as effective as propofol, but very good and probably a bit less likely to cause major side effects

2005 ACEP Clinical Policy: Etomidate got Level C recommendation (ketamine was only Level A)

most recent (2007) editorial by Green³⁸:

etomidate (and propofol) ready for prime time in ED practice

myoclonus renders etomidate less desirable than propofol

clinicians with access to both should use propofol

Other PSA agents

Methoxyflurane²⁰⁴

Inhalational anesthetic frequently used for prehospital analgesia in Australia

Seems well-suited (based upon preliminary data) for sedation for some pediatric patients (who can be coached)

More data needed before endorsement for broader ED use

Dexmedetomidine²⁰⁵

First licensed 1999 for OR use, with few data addressing use in ED setting

Central alpha-2 agonist, which mediates side effects of bradycardia and hypotension

Side effects (hemodynamic depression) are a concern although overall the agent is relatively safe/effective

Side effects are to be adjudicated against procedure at hand

Dexmedetomidine seems particularly useful in the ICU setting (but less so in the ED setting)²⁰⁶

Time parameters seem less desirable than those of other options (*e.g.* propofol)

Further study may identify ED role but for now there is little such role supported in the evidence

Widespread use seems premature given extant data and availability of alternative agents

Special topics of relevance to ED sedation

Sedation for combative patients ²⁰⁷⁻²²¹

Butyrophenones (*note: droperidol is often unavailable in some hospitals, particularly in the U.S., due to issues with cardiac arrhythmia*)

Historically, both haloperidol and droperidol are effective and very stable to cardiovascular system

Dose (for either agent): 0.1 mg/kg either IV or IM

There is more experience with higher-dose haloperidol given IM and this is usually preferred

The dose can be repeated to max 0.5 mg/kg

Note that the use of haloperidol IV is “off-label”

Regimen from MGH Psychiatry: double initial IV dose q10-20', IM dose q10-30' until calming begins

Adding benzodiazepines helps reduce total required haloperidol/droperidol dose

Time parameters

Effects of haloperidol/droperidol noticeable within 3-5 minutes with good clinical effect in 30'

ED study suggests IM droperidol has onset as fast as IV haloperidol

Another study suggests that if agents are given IM, droperidol works better at 10, 15, and 30'

Addition of droperidol to midazolam speeds sedation by 4-5 minutes and has no additional safety cost²²⁰

Potential problems

Dysphoria may occur (up to 40% in one study of oral haloperidol) and exacerbate “psychotic behavior”

Dystonia

Intravenous route may minimize risk of dystonia

Dystonia occurs in up to 20% of patients receiving IM haloperidol

Dystonia may be exhibited in form of akathisia, which can appear as “worsening in psychosis”

Studies suggest that up to 42% of episodes of dystonia go undiagnosed in the clinical setting

Masking of dystonia by benzodiazepines

Dystonia may be initially masked by co-administered benzodiazepines

Due to half-lives of butyrophenones/benzos, dystonia can emerge after benzos wear off

Respiratory depression is usually not a problem in this setting, even with lorazepam

Cardiac dysrhythmia

Rapid administration of either haloperidol or droperidol may risk arrhythmia and death

Patients should be on cardiac monitoring (if safe/possible) before butyrophenone is administered

Head-to-head trial, droperidol *vs.* midazolam: droperidol equally efficacious with fewer side effects²²²

ACEP Clinical Policy (2006) and butyrophenones

Droperidol or haloperidol are acceptable as monotherapy; droperidol may be preferable if need faster onset

Combination of haloperidol and a benzodiazepine may produce more rapid sedation than monotherapy

Benzodiazepines are often useful given with butyrophenones, but this class has also been investigated for single-agent Rx

Midazolam performed at least as well as droperidol in one clinical trial with a few more side effects

Compared to droperidol, midazolam-alone sedation is more likely to be associated with need for airway support

ACEP Clinical Policy (2006):

Lorazepam or midazolam is appropriate single-agent therapy for initial treatment

Oral benzodiazepine (lorazepam) and risperidone are recommended for agitated/cooperative patients

Pediatric review article (2014)²²¹ lists lorazepam (.05-.1 mg/kg/dose, usually 1-2 mg) as fastest-onset single-agent

Ketamine has some reports of utility for combative patients

Reported use of ketamine (5 mg/kg IM) for very rapid tranquilization of violent patient

Emergence risks renders ketamine 2nd-line

Ketamine can conceivably be used in cases where there is true danger to care providers

Atypical antipsychotics: Risperidone, Olanzapine, Ziprasidone

All are at least potentially more useful than historically used agents

All are newer, with less clinical experience

The newer agents may be more expensive with unclear cost/benefit support

Risperidone (Risperdol[®])

An early study suggests it is as effective as older regimens

Oral agent (2mg) combined with PO lorazepam (2mg) was tested

Test regimen was as effective as IM haloperidol (5mg) + IM lorazepam (2mg)

One regimen: 2mg orally (with 2mg lorazepam), repeated once in two hours (no more than 4mg/24 h)

Bioavailability of various risperidone forms appears equal (so doesn't matter which formulation is used)

Narrow therapeutic index before extrapyramidal sx are problematic

Clinicians should check medication lists and beware pharmacokinetic interactions

Lower dose (1mg) should be considered in elderly patients or those with liver/kidney disease

If oral agent is to be used for emergent antipsychotic therapy in ED, risperidone is probably best (fastest)

Olanzapine (Zyprexa[®])

Can be given orally, but primary utilization in ED is IM

IM olanzapine vs. haloperidol: olanzapine less dystonia/extrapyramidal, less amblyopia, less dyspepsia

One IM administration regimen:

10mg first dose – 10mg second dose 2 hours after first dose – 10mg third dose 4 hours after second dose

Olanzapine and benzodiazepines: combination potentially risks oversedation, cardiorespiratory depression

Old recs: “co-administered” benzodiazepines should be given at least 1 hour after olanzapine

Newer data: olanzapine/midazolam co-administration is effective and decreases time to sedation²²⁰

Adding *either* olanzapine *or* droperidol to midazolam effected sedation 4-5 minutes faster

No additional complications with combination therapy as compared to benzo alone

Ziprasidone (Geodon[®])

Ziprasidone is generally given IM in the ED

Clinical effects are seen within 15-30 minutes after IM injection

Peak serum concentrations are achieved within an hour after IM dosing

Clinically effective half-life after IM dose is 2-5 hours

Ziprasidone worked well (possibly better than midazolam) in one ED study when given 20mg IM

Overall side effects and extrapyramidal sx both less common with ziprasidone than with haloperidol

Ziprasidone is primarily metabolized by aldehyde oxidase (no known inducers or inhibitors)

Though definitive evidence is lacking, caution should be exercised before administering IM ziprasidone to:

Patients with renal failure

Patients receiving other drugs known to prolong the QT_c interval

Two regimens both allow a 40mg total dose in 24 hours:

10mg IM with up to 3 repeat 10mg doses, administered every 2 hours

20mg IM with single repeat dose in 4 hours (this seems to be slightly preferred by some authors)

Either above regimen still entails risks:

QT_c prolongation

Extrapyramidal reactions

Potential for hypotension/hypoventilation

Pediatric considerations based upon 2014 review article in *Pediatric Emergency Care*²²¹

For general anxiety/agitation benzos as sole therapy are just as acceptable as newer agents

If there is mania/psychosis then haloperidol or risperidone or olanzapine or ziprasidone are preferred

All of the newer non-benzodiazepines (including haloperidol) incur some risk of QT prolongation

Olanzapine has anticholinergic properties so it's not recommended in patients where this is a problem

Bottom line expert panel recommendation for sedating the combative patient in ED:

- 1) If IM therapy isn't clearly indicated (by time or safety requirements), offer patient choice of PO or IM therapy
- 2) For PO therapy: risperidone 2mg (solution, oral tablet, or oral disintegrating tablet) *plus* lorazepam 2mg
- 3) For IM therapy: ziprasidone 20mg (with repeat doses 10-20mg, every 4 hours to total 40 mg/24 hours)
- 4) When above regimens fail, rescue regimen: IM lorazepam 2mg

Reversal agents ¹⁰⁰⁻¹¹⁰

Reversal agents (at least naloxone) should be at hand when providing ED PSA

However, reversal agents' presence should never be used to justify pushing PSA agent selection or dosing

Too-early reversal (*e.g.* to be able to discharge patients) has frequently resulted in suboptimal pain control

Naloxone

IV dose ranges from 0.1-2.0 mg depending on indication (same dose for children/adults)

Partial reversal (0.1-0.4 mg) is indicated for post-procedural oversedation

Maximum dose for opioid-induced respiratory depression: 10 mg
Half-life is 64 minutes but clinical effects (reversal) are shorter-lived (15-45) minutes
Patients should be observed for 60-90 minutes after naloxone for sedation recurrence
Remember: When you give naloxone for respiratory depression you also reverse analgesia

Nalmefene

Opioid reversal agent with half-life of 10.8 hours (10x that of naloxone)
Clinically useful half-life depends on opioid being treated but is approx. 8 hours
Recommended dose 1 mg but there isn't much reported ED experience with this agent
Pediatric series (15 patients) suggested utility in reversal of fentanyl/midazolam sedation
Dosed in 0.25 mcg/kg increments (max 10 mcg/dose) until sedation was reversed
Max dose in this study was 40 mcg
Beware precipitation of prolonged (6-8 hours) opioid withdrawal (has been reported once in ED literature)

Flumazenil

Competitively/reversibly binds GABA-benzodiazepine receptors
Reversal of sedation within 1-2 minutes with peak effect 6-10 minutes
Post-midazolam return to baseline alertness is hastened by about 10 minutes when flumazenil given
In one study, placebo patients required 25 minutes vs. 11 for flumazenil
In another study, no difference in proportion returning to baseline within 10 minutes
1.0 mg recommended dose for sedation reversal lasts 45-60 minutes
Less chance of seizures in patients receiving 1.0 mg flumazenil or less
Dose of 1.0 mg usually doesn't interfere with amnesia but such reversal may occur
Probably effective for reversal of paradoxical reactions to benzodiazepines
Reversal of benzodiazepine-induced respiratory depression occurs, but is inconsistent
Flumazenil and seizures
Flumazenil can cause seizures in patients on as few as two weeks of benzodiazepines
Flumazenil has been implicated as causing seizures in children receiving chloral hydrate

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