Procedural sedation and analgesia in children

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Procedural sedation and analgesia for children—the use of sedative, analgesic, or dissociative drugs to relieve anxiety and pain associated with diagnostic and therapeutic procedures—is now widely practised by a diverse group of specialists outside the operating theatre. We review the principles underlying safe and effective procedural sedation and analgesia and the spectrum of procedures for which it is currently done. We discuss the decision-making process used to determine appropriate drug selection, dosing, and sedation endpoint. We detail the pharmacopoeia for procedural sedation and analgesia, reviewing the pharmacology and adverse effects of these drugs. International differences in practice are described along with current areas of controversy and future directions.

Procedural sedation and analgesia is the use of sedative, analgesic, and dissociative drugs to provide anxiolysis, analgesia, sedation, and motor control during painful or unpleasant diagnostic and therapeutic procedures. During the past 20 years, this procedure has evolved into a distinct skill set with a growing number of indications and practice settings. Given the logistical and economic advantages of not requiring the operating theatre, procedures once restricted to the theatre are now done by many different practitioners (cardiologists, dentists, emergency physicians, gastroenterologists, intensive care doctors, oncologists, plastic surgeons, and radiologists) in inpatient and outpatient settings. The rapid growth of procedural sedation and analgesia has been fuelled by new drug and monitoring technology, expanded practitioner skills, the need to shift procedural work to outpatient settings, and widespread acceptance of the ethical imperative to treat pain and anxiety in children. We review the state of international paediatric procedural sedation and analgesia, highlighting the relevant principles, indications, and pharmacopoeia, as well as current controversies and future directions.

Underlying principles

The principles of the procedure, including presedation assessment, continuous monitoring during the procedure, and recovery scoring systems, mirror longstanding anaesthesia practices.

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and relevant specialty journals (all from 1980 to June, 2005). We used the search terms "procedural sedation and analgesia" or "conscious sedation" or "sedation and analgesia for procedures". We largely selected publications in the past 15 years with an emphasis on the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We only searched articles in the English language or those translated into English. We also searched the reference lists of articles identified by this strategy and selected those we judged relevant. We included four types of studies: randomised controlled trials, observational studies, retrospective studies, and meta-analyses. Abstracts and case reports were excluded and, when cited, small preliminary studies were noted as such. However, we searched the entire published work, including abstracts and case reports, when attempting to determine whether a specific adverse event or complication had been reported. Some small studies from under-represented countries were included to give an international perspective. Several review articles, editorials, and book chapters were included because they provided comprehensive overviews that were beyond the scope of this Review.

Sedation continuum

Progression from minimum sedation to general anaesthesia does not lend itself to arbitrary division. Low doses of opioids or sedative-hypnotics induce mild analgesia or sedation respectively, with little danger of adverse events. Higher doses provide progressively deeper sedation, increasing the risk of respiratory and airway compromise. Almost all non-dissociative drugs for procedural sedation and analgesia in common use, including opioids, benzodiazepines, barbiturates, etomidate, and propofol, can induce a state of general anaesthesia with loss of protective airway reflexes. Additionally, sedation depth will drift during any given procedure. Noxious stimuli can lighten sedation, and the withdrawal of external stimuli at the end of a procedure can deepen it. Accordingly, continuous monitoring is essential and clinicians must be prepared to rescue patients from levels of sedation deeper than intended.

Initial guidelines and terminology

In 1985, the National Institutes of Health and the American Academy of Pediatrics issued guidelines for procedural sedation and analgesia in response to several sedation-related deaths.[1,2] These documents defined three levels of sedation: conscious sedation, deep sedation, and general anaesthesia. The language has evolved and the misleading term conscious sedation[3–5] has been replaced by moderate sedation.[3,6,7] Unfortunately, responsiveness is a crude surrogate marker for respiratory drive and retention of protective airway reflexes.[8,9] Despite better terminology, there is still no objective way to describe sedation depth, and titration to a precise endpoint can be difficult.

Current guidelines and standards

Many specialty societies and regulatory bodies have published guidelines for procedural sedation and analgesia, each designed to address their specific perspectives (panel 1).[1,3,5–7,10–33] The most widely disseminated were published by the American Academy of Pediatrics,[2,5] the American Society of Anesthesiologists (ASA),[3] and the American College of Emergency

Physicians.[6] Guidelines are intended to standardise the procedure and enhance patients' safety, but they are non-binding. By contrast, standards such as those issued by the US Joint Commission on Accreditation of Healthcare Organization (JCAHO) are mandatory for subject hospitals. In 2001, JCAHO released standards for pain management, sedation, and anaesthesia care.[7] Hospitals outside the USA are not bound by these standards, but they are a benchmark of interest. The JCAHO standards dictate that procedural sedation and analgesia care should be similar throughout an institution: it should not vary between the operating theatre, emergency department, or endoscopy suite. Accordingly, US hospitals must develop and enforce institution-wide protocols for this procedure, although there is some flexibility based upon specific needs and available expertise. Among other things, JCAHO standards require that practitioners can manage a compromised airway, that those who administer deep sedation can rescue patients from inadvertent general anaesthesia, and that those administering moderate sedation can rescue patients from inadvertent deep sedation (panel 2).[6,7,34,35]

Presedation assessment

The practice of procedural sedation and analgesia has three components done in sequence: presedation assessment, sedation for the procedure, and post-procedure recovery and discharge. A directed history and physical examination should precede the process, and if additional risk is discovered, the advisability of sedation should be reconsidered. High-risk cases might be better postponed or managed in theatre.

Presedation assessments are a JCAHO requirement in the USA, and hospitals have developed specific forms to facilitate consistent documentation. The risks, benefits, and limitations of the procedure should be discussed with the patient (or their parent or guardian) and verbal agreement obtained. Written consent is not required unless it is a local institutional requirement.

General

Physicians should assess the type and severity of underlying medical problems. These can be quantified with the ASA physical status classification, used for preoperative risk stratification (table 1). Although most procedural sedation and analgesia will be of healthy patients (ASA class I and II), data suggest that it could be safe for patients with comorbidity (ASA class III).[36–38] Current medications and allergies should be verified and inquiry made about previous adverse experiences with procedural sedation and analgesia or anaesthesia.

Airway

The airway should be inspected for abnormalities that might impair airway management or limit neck mobility (eg, severe obesity, short neck, small mandible, obstructive tonsils, large tongue, trismus).

***Panel 1:* Guidelines and standards for procedural sedation and analgesia**

Australia and New Zealand
- Australasian College for Emergency Medicine, Australian and New Zealand College of Anaesthetists[10]
- New Zealand College of Anaesthetists, Royal Australian College of Dental Surgeons, New Zealand Dental Association[11]

Canada
- Canadian Association of Emergency Physicians[12]

Italy
- Società Italiana di Anestesia Analgesia[13]

South Africa
- Medical Association of South Africa[14]

UK
- British Society of Gastroenterology[15]
- General Dental Council[16]
- Scottish Intercollegiate Guidelines Network[17]
- Standing Dental Advisory Committee[18]
- United Kingdom National Clinical Guidelines in Paediatric Dentistry[19]

Netherlands
- National Organisation for Quality Assurance in Hospitals[20]

USA
- American Academy of Pediatrics[2,21]
- American Academy of Pediatric Dentistry[22]
- American Academy of Periodontology[23]
- American Association of Critical-Care Nurses[24]
- American College of Critical Care Medicine[25]
- American College of Emergency Physicians[6]
- American Nurses Association[26]
- American Society for Gastrointestinal Endoscopy[27,28]
- American Society of Anesthesiologists[3]
- American Society of Plastic and Reconstructive Surgeons[29]
- Association of Operating Room Nurses[30]
- Emergency Nurses Association[31]
- Joint Commission on Accreditation of Healthcare Organizations[7]
- National Institutes of Health[1]
- Society of Gastroenterology Nurses and Associates[32]
- Society of Nuclear Medicine[33]

Cardiovascular

Cardiac auscultation should be done to assess for abnormalities. For patients with known cardiovascular disease, their degree of reserve should be noted, as most drugs for procedural sedation and analgesia can cause vasodilatation and hypotension.

Respiratory

Lung auscultation should be done to assess for active pulmonary disease, especially obstructive lung disease

Panel 2: **Terminology and definition for procedural sedation and analgesia**

Minimal sedation (anxiolysis):[7] a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination might be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate sedation (formerly conscious sedation):[7] a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. Reflex withdrawal from a painful stimulus is not considered a purposeful response. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Dissociative sedation:[6,34,35] a trance-like cataleptic state induced by the dissociative drug ketamine characterised by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability.

Deep sedation:[7] a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function could be impaired. Patients might require assistance in maintaining a patent airway and spontaneous ventilation might be inadequate. Cardiovascular function is usually maintained.

General anaesthesia:[7] a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation might be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function can be impaired.

and active upper respiratory infections.[39] In a series of 136 929 patients undergoing inhalational anaesthesia, the risk of developing laryngospasm was 5·5 times higher for children with an upper respiratory infection and 3·7 times higher for those with active asthma than that for patients without intercurrent respiratory illness at the time of the surgery.[40] Although it remains unproven whether these same increased risks extrapolate to procedural sedation and analgesia, a careful risk-benefit assessment should be made for such children.

Gastrointestinal

The time and nature of last oral intake should be assessed. For elective procedures, the ASA recommends an age-stratified fasting requirement of 2–3 h for clear liquids and 4–8 h for solids and non-clear liquids.[41] Despite this recommendation, they acknowledge that "the literature provides insufficient data to test the hypothesis that preprocedure fasting results in a decreased incidence of adverse outcomes".[3,41] For urgent or emergent procedures, when the ASA guidelines are difficult to achieve, the potential for pulmonary aspiration must be balanced with the timing of the procedure and the required depth of sedation.[6,8,9] Large, prospective studies of procedural sedation and analgesia have failed to show any association between fasting and adverse effects.[41–45]

		Examples	Suitability for sedation
1	Healthy patient	Unremarkable past medical history	Excellent
2	Patient with mild systemic disease—no functional limitation	Mild asthma, controlled seizure disorder, anaemia, controlled diabetes mellitus	Generally good
3	Patient with severe systemic disease—definite functional limitation	Moderate to severe asthma, poorly controlled seizure disorder, pneumonia, poorly controlled diabetes mellitus, moderate obesity	Intermediate to poor: consider benefits relative to risks
4	Patient with severe systemic disease that is constant threat to life	Severe bronchopulmonary dysplasia, sepsis, advanced degrees of pulmonary, cardiac, hepatic, renal, or endocrine insufficiency	Poor: benefits rarely outweigh risks
5	Moribund patient who is not expected to survive without the operation	Septic shock, severe trauma	Extremely poor

Table 1: **American Society of Anesthesiologist's physical status classification by class**

Hepatic and renal

The implications of delayed metabolism or excretion of procedural sedation and analgesia drugs in infants younger than age 6 months and in the presence of hepatic or renal abnormality should be carefully assessed.

Personnel and interactive monitoring

Continuous observation of patients by a health-care provider capable of recognising adverse sedation events is essential. This person must be able to continuously observe the patient's face, mouth, and chest-wall motion, allowing rapid detection of respiratory depression, apnoea, partial or complete airway obstruction, laryngospasm, emesis, and hypersalivation. Procedural sedation and analgesia personnel should be proficient at maintaining airway patency and assisting ventilation if needed.

Procedural sedation needs at least two experienced providers, usually one physician plus one nurse or respiratory therapist. Although the physician oversees drug administration and undertakes the procedure, the nurse or respiratory therapist continuously monitors the patient. During deep sedation, the individual dedicated to monitoring should be experienced with this depth of sedation and the advanced level of monitoring and

documentation required.[21] An individual with advanced life-support skills, if not already present, should be readily available.

For intramuscular, oral, nasal, inhalational, or rectal administration, intravenous access is not mandatory although it might be preferable depending upon anticipated depth of sedation or comorbidity, or for the convenience of additional drug titration. When sedation is done without intravenous access, an individual skilled in initiating such access should be readily available.

Panel 3: Indications and procedures for procedural sedation and analgesia

Minor trauma

Wound care or laceration repair

Incisions and drainage

Reductions
- *Fracture*
- *Dislocation*
- *Hernia*
- *Paraphimosis*

Burn debridement

Cast placement or removal

Instrumentation

Lumbar puncture

Voiding cystourethography

Renal biopsy

Intravenous access
- *Central*
- *Indwelling*
- *Peripheral*

Gastroenterology procedures
- *Flexible sigmoidoscopy*
- *Oesophagoduodenoscopy*
- *Polypectomy*
- *Dilatation (rectal, oesophageal)*
- *Colonoscopy*
- *Anorectal manometry*

Cardiothoracic procedures
- *Chest tube placement or removal*
- *Thoracentesis*
- *Cardiac catheterisation*
- *Angiography*
- *Cardioversion*

Dental procedures

Electroencephalography

Electromyography

Bone marrow aspiration or biopsy

Brainstem audio evoked response

Botulinum toxin injection

Arthrocentesis

Foreign body removal

Foley catheter placement

Slit lamp examination

Equipment and mechanical monitoring

The use of mechanical monitoring has greatly enhanced the safety of procedural sedation and analgesia. Continuous oxygenation (pulse oximetry with an audible signal), ventilation (capnography), and haemodynamics—blood pressure and ECG—can all be monitored non-invasively in spontaneously breathing patients. Pulse oximetry is not a substitute for monitoring ventilation, as there is a variable lag time (depending on age, physical status, and use of supplemental oxygen) between the onset of hypoventilation or apnoea and a change in oxygen saturation.

Capnography allows continuous assessment of ventilatory status and is the earliest indicator of airway or respiratory compromise.[46,47] It is an accurate and direct (ie, non-impedance) measure of respiratory rate, and is more sensitive than clinical assessment in detecting respiratory compromise.[48,49] Early detection of respiratory compromise is especially important in young children who desaturate more rapidly than older children or adults because of their proportionally smaller functional residual capacity and greater relative oxygen consumption. Further, capnography allows the use of supplemental oxygen without concern about blunting the response of the pulse oximeter.

Continuous ECG monitoring is not required in the absence of cardiovascular disease since it has not been shown to improve outcomes during procedural sedation and analgesia. Newer monitoring modalities that measure the brain's response to anaesthetic drugs

Panel 3 (continued)

Diagnostic imaging

Ultrasonography
- *Echocardiogram*
- *Transthoracic echocardiography*

Neuroimaging
- *MRI*
- *CT*
- *Single photon emission computed tomography*
- *PET*

Cisternography

Myelography

Antegrade pyelogram

Barium enema

List of indicated procedures may vary by country. Many procedures for special populations (mentally challenged, syndromic, and psychiatric patients) may also require procedural sedation and analgesia.

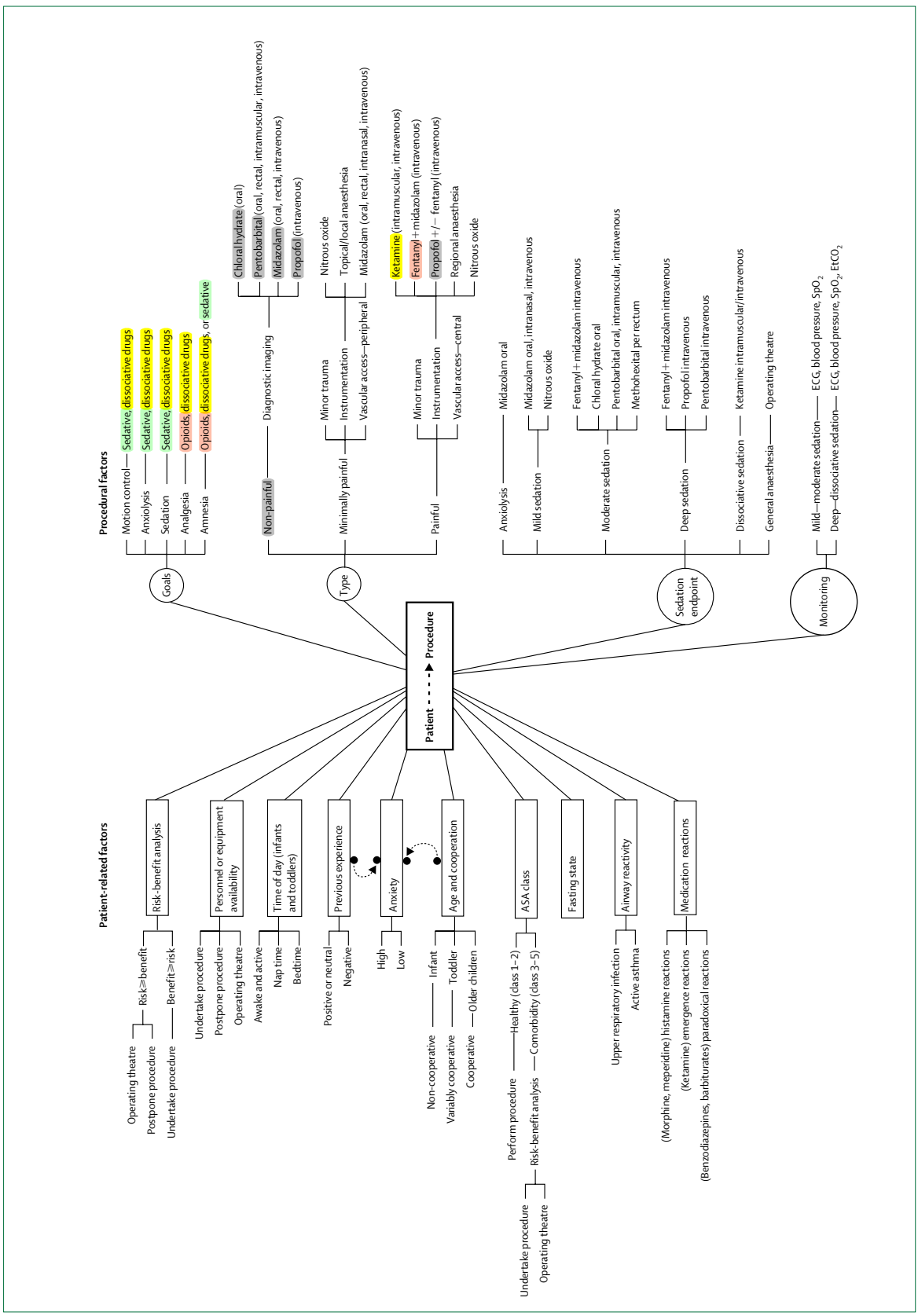

Figure: **Factors determining medication choices and sedation endpoint**
SpO_2=oxygen saturation. $EtCO_2$=end-tidal carbon dioxide.

(eg, processed electroencephalogram and auditory evoked potential monitoring) are undergoing investigation for use in procedural sedation and analgesia. These technologies have been validated as a method for monitoring depth of anaesthesia in the operating theatre; however, their predictive value for the remainder of the sedation continuum remains unclear.[50–52]

The sedation area should include all necessary age-appropriate equipment for airway management and resuscitation, including oxygen, a bag-valve mask, suction, and drug reversal agents. A defibrillator should be available for patients with cardiovascular disease.

Procedural sedation and analgesia is widely practised both with and without supplemental oxygen, and whether this intervention enhances safety remains unstudied. Although it will decrease the incidence and severity of hypoxaemia, it will also delay the detection of apnoea with pulse oximetry.[3] If oxygen is given and capnography is not available, visual inspection of chest-wall motion and air movement is especially important.

Vital signs should be measured at intervals including at baseline, after drug administration, on completion of the procedure, during early recovery, and at completion of recovery. During deep sedation, vitals signs should be assessed every 5 min. Patients are at highest risk of complications 5–10 min after intravenous medications and during the immediate post-procedure period when external stimuli are discontinued.

Post-procedure assessment

Children should be monitored until they are no longer at risk for cardiorespiratory depression, their vital signs are stable, they are alert and at age-appropriate baseline level of consciousness, and they can talk and sit unaided, according to age. It is not a requirement that young children be able to walk unaided.[21] Many hospitals use standardised recovery-scoring systems similar to those used in surgical post-anaesthesia recovery.[53] A reliable adult should be given discharge instructions about appropriate diet, medications, and activity level in the 24 h after sedation.

Indications

Indications for procedural sedation and analgesia can be divided into three categories: minor trauma, instrumentation, and diagnostic imaging (panel 3). Many such procedures do not require procedural sedation and analgesia and can be accomplished with psychological techniques that can also reduce adverse responses to painful or frightening procedures.[54–57] A multifactorial decision-making process is used to determine the appropriate drugs, dosing, and sedation endpoint.[53,58] Selection of drug and depth of sedation depend on individual needs (some children need only anxiolysis; others extensive analgesia; and others only motor control; figure).

Sedation endpoint

The ideal sedation endpoint would be one at which the procedure can be successfully accomplished with as little distress to the patient as possible and with cardiopulmonary stability and retention of protective airway reflexes.

Time of day

A young child near nap time or bedtime will need less medication than one who is well rested, alert, and active. Young children also tend to become irritable and uncooperative when hungry. Some children are deliberately deprived of sleep for electroencephalography and non-urgent diagnostic imaging. These children might need little or no procedural sedation and analgesia.

Age, cooperation, anxiety level, and previous experience

A child's anxiety and cooperation are affected by age, anxiety of the parent, and previous medical experiences. Cooperation could be absent (infants), variable (toddlers), or often good (older children). Toddlers are especially distractible and directed storytelling or guided imagery can be very effective.[54]

Previous experience in hospital can greatly affect response to an upcoming procedure.[57,59] Direct experience as well as images from television or films, accounts from peers, or having watched a sibling be forcefully immobilised for a procedure can leave a powerful and lasting impression. This type of influence should be considered especially for children whose anxiety seems out of proportion to the present situation. Eliciting a history of a previous negative medical experience can be a decisive factor in determining the level of sedation necessary.

Medication reactions

True type I immunoglobulin-E-mediated allergic reactions to procedural sedation and analgesia drugs are unusual. More common are reactions associated with histamine release (morphine, meperidine), nasal pruritus (fentanyl), and paradoxical reactions (benzodiazepines, barbiturates).[53] Emergence reactions to ketamine are uncommon.[34,60,61]

Pharmacopoeia

Classes of drugs

The five classes of procedural sedation and analgesia drugs are sedative-hypnotics, analgesics, dissociative sedatives, inhalational agents, and antagonists (table 2). The most widely used are sedative-hypnotics, including benzodiazepines (eg, midazolam, diazepam), barbiturates (eg, pentobarbital, methohexital, thiopental), and several drugs in their own pharmacological class (eg, chloral hydrate, etomidate, propofol). Propofol, etomidate, methohexital, and thiopental are referred to as ultra-short acting agents because of their extremely rapid onset and brief duration of action that can increase when additional doses are given. Sedative-hypnotics lack specific analgesic properties and are frequently supplemented with opioids

	Paediatric dosing	Onset (min)	Duration (min)	Comments
Sedative-hypnotics				
Choral hydrate	Oral: 25–100 mg/kg, after 30 min can repeat 25–50 mg/kg. Maximum total dose: 2 g or 100 mg/kg (whichever is less) Single use only in neonates	Oral: 15–30	Oral: 60–120	Effects unreliable if age >3 years
Diazepam	Intravenous: initial 0·05–0·1 mg/kg, then titrate slowly to maximum 0·25 mg/kg	Intravenous: 4–5	Intravenous: 60–120	Reduce dose when used in combination with opioids
Etomidate	0·1 mg/kg intravenous; repeat if inadequate response	Intravenous: <1	Intravenous: 5–15	Adverse effects include respiratory depression, myoclonus, nausea, and vomiting
Midazolam	Intravenous (0·5–5 years): initial 0·05–0·1 mg/kg, then titrated to maximum 0·6 mg/kg Intravenous (6–12 years): initial 0·025–0·05 mg/kg, then titrated to maximum 0·4 mg/kg	Intravenous: 2–3	Intravenous: 45–60	
	Intramuscular: 0·1–0·15 mg/kg	Intramuscular: 10–20	Intramuscular: 60–120	Reduce dose when used in combination with opioids. May produce paradoxical excitement
	Oral: 0·5–0·75 mg/kg	Oral: 15–30	Oral: 60–90	
	Intranasal: 0·2–0·5 mg/kg	Intranasal: 10–15	Intranasal: 60	
	Rectal: 0·25–0·5 mg/kg	Rectal: 10–30	Rectal: 60–90	
Methohexital	Rectal: 25 mg/kg Intravenous: 0·5–1·0 mg/kg	Rectal: 10–15	Rectal: 60	Avoid if temporal lobe epilepsy or porphyria
Pentobarbital	Intravenous: 1–6 mg/kg, titrated in 1–2-mg/kg increments every 3–5 min to desired effect	Intravenous: 3–5	Intravenous: 15–45	May produce paradoxical excitement Avoid in patients with porphyria
	Intramuscular 2–6 mg/kg, maximum 100 mg	Intramuscular: 10–15	Intramuscular: 60–120	
	Oral or rectal (<4 years): 3–6 mg/kg, maximum 100 mg Oral/rectal >4 years): 1·5–3 mg/kg, maximum 100 mg	Oral or rectal: 15–60	Oral or rectal: 60–240	
Propofol	Intravenous: 1·0 mg/kg, followed by 0·5 mg/kg repeat doses as needed	Intravenous: <1	Intravenous: 5–15	Frequent hypotension and respiratory depression. Avoid with egg or soy allergies
Thiopental	Rectal: 25 mg/kg	Rectal: 10–15	Rectal: 60–120	Avoid in patients with porphyria
Analgesics				
Fentanyl	Intravenous: initial 1·0 µg/kg up to 50 µg/dose, may repeat every 3 min, titrate to effect	Intravenous: 3–5	Intravenous: 30–60	Reduce dosing when combined with benzodiazepines
Morphine	Intravenous: initial 0·05–0·15 mg/kg up to 3 mg/dose, may repeat every 5 min, titrate to effect	Intravenous: 5–10	Intravenous: 120–180	Reduce dosing when combined with benzodiazepines
Dissociative drug				
Ketamine	Intravenous: 1–1·5 mg/kg slowly over 1 min, may repeat dose every 10 min as needed	Intravenous: 1	Intravenous: dissociation 15; recovery 60	Multiple contraindications.* Unpleasant dreams or hallucinations rare in children
	Intramuscular: 4–5 mg/kg, may repeat (2–4 mg/kg) after 10 min	Intramuscular: 3–5	Intramuscular: dissociation 15–30; recovery 90–150	Often given with concurrent atropine or glycopyrrolate to counter hypersalivation
Inhalational drug				
Nitrous oxide	Preset mixture with minimum 30% oxygen self-administered by demand valve mask (requires cooperative child). Continuous flow nasal mask in uncooperative child with close monitoring	<5	<5 following discontinuation	Requires specialised apparatus and gas scavenger capability. Several contraindications
Reversal drugs (antagonists)				
Naloxone	Intravenous or intramuscular: 0·1 mg/kg/dose up to maximum of 2 mg/dose, may repeat every 2 min as needed	Intravenous: 2	Intravenous: 20–40 Intramuscular: 60–90	If shorter acting than the reversed drug, serial doses may be required
Flumazenil	Intravenous: 0·02 mg/kg/dose, may repeat every 1 min up to 1 mg	Intravenous: 1–2	Intravenous: 30–60	If shorter acting than the reversed drug, serial doses may be required

Alterations in dosing may be indicated depending on the clinical situation and the practitioner's experience with these drugs. Individual dosages may vary when used in combination with other drugs, especially when benzodiazepines are combined with opioids. *Ketamine is absolutely contraindicated in children younger than 3 months (higher risk of airway complications) and in setting of known or suspected psychosis (can exacerbate condition). Relative contraindications include age younger than 12 months, procedures involving stimulation of posterior pharynx, history of tracheal surgery or stenosis, active pulmonary infection or disease (including upper respiratory infection), known or suspected cardiovascular disease, head injury associated with loss of consciousness, altered mental status, or emesis; central nervous system masses, abnormalities, or hydrocephalus; glaucoma or acute globe injury; porphyria; thyroid disorder or thyroid medication.

Table 2: **Drugs for procedural sedation and analgesia**

(eg, fentanyl, morphine) for painful procedures. Two other popular techniques are dissociative sedation (ketamine) and inhalational sedation (nitrous oxide alone or in combination with regional nerve blocks or opioids).

Routes of administration

For non-dissociative drugs, intravenous titration to a patient's response is the best method of obtaining rapid and safe analgesia and sedation. With opioids, initial endpoints can be ascertained by observing for drug effects such as miosis, somnolence, decreased responsiveness to verbal stimuli, altered respiratory pattern, very slightly impaired speech, and diminished pain on questioning. Sedative-hypnotics have similar signs, such as ptosis, somnolence, slurred speech, and gaze alteration.

Oral, transmucosal (ie, nasal, rectal), and intramuscular routes are more convenient, less invasive, and especially useful for children for whom intravenous access is difficult or for non-painful procedures (eg, diagnostic imaging). However, they are less reliable for timely dose titration. With the exception of ketamine, intramuscular administration results in erratic absorption and a variable

onset of action and prolonged observation might be necessary. Another route of administration is via nitrous oxide inhalation delivered by a demand flow system (controlling the concentration of nitrous oxide and oxygen) by use of a hand-held mask, or by a continuous flow system under close physician supervision with a nose mask.

Because individual needs can vary widely, application of arbitrary ceiling doses (whether as an absolute dose in mg or by bodyweight in mg/kg) of analgesic and sedative regimens is unwarranted. The true ceiling dose of a drug is that dose that provides adequate pain relief or sedation without major cardiopulmonary adverse effects.

First generation agents

Painful and anxiety-provoking procedures in children not judged severe enough for the operating theatre typically used to be done without drugs but with forcible immobilisation. Procedural sedation and analgesia developed as clinicians attempted to provide analgesia, anxiolysis, and sedation at levels below general anaesthesia by using the drugs already available to them. These first-generation drugs included: chloral hydrate, pentobarbital, methohexital, thiopental, diazepam, morphine, and pethidine (meperidine).

Chloral hydrate

Chloral hydrate is a pure sedative-hypnotic drug without analgesic properties. When administered orally, the average time to peak sedation is about 30 min, with a recovery time of an additional 1–2 h.[62] Residual motor imbalance and agitation can persist for several hours beyond. Rectal administration is erratically absorbed and therefore not recommended.

Chloral hydrate is widely used as a sedative to facilitate non-painful diagnostic procedures such as EEG[62] and CT or MRI scanning,[63–66] and is most reliable in children younger than 3 years old. Intravenous pentobarbital seems to be more effective for diagnostic imaging than chloral hydrate,[66] although many prefer chloral hydrate in younger children (eg, <18 months) to avoid intravenous catheterisation.[63–66] Despite a wide margin of safety, chloral hydrate can cause airway obstruction and respiratory depression,[62–65] especially at higher doses (75–100 mg/kg) with an incidence of 0·6% in one large series.[62] There is no known dosage threshold below which these potential complications can be consistently avoided,[64,65] and accordingly standard monitoring precautions apply to chloral hydrate as they do to other drugs for procedural sedation and analgesia. Despite being restricted in some countries (eg, France) as a result of potential carcinogenicity, in the USA the American Academy of Pediatrics has judged the evidence insufficient to avoid single doses of chloral hydrate for this reason alone.[67]

Pentobarbital

Pentobarbital is a barbiturate with no inherent analgesic properties that produces profound sedation, hypnosis, amnesia, and anticonvulsant activity in a dose-dependent fashion. With intravenous titration, sedation is evident in 3–5 min with a duration of roughly 30–40 min.[68] Like other barbiturates, pentobarbital can lead to respiratory depression and hypotension.[66,68] In many centres, pentobarbital is the intravenous sedative of choice for diagnostic imaging in children,[66,68–70] and is regarded as better than midazolam[66,68] or chloral hydrate[66] for this indication.

Methohexital and thiopental

When given intravenously, both methohexital and thiopental produce effective sedation within 1 min and induce potent respiratory depression in the same manner as propofol and etomidate.[71,72] Clinical recovery is rapid (about 15 min). The depth of sedation achieved in existing small series is not well described, but seems to be at or beyond levels consistent with deep sedation.

Barbiturates are rapidly absorbed rectally and methohexital or thiopental given by this route can reliably produce anxiolysis and sedation suitable for CT or MRI scanning.[73–76] Although respiratory depression is unusual with typical doses, it can occur.[73–76] When transporting patients who have received pentobarbital, methohexital, or thiopental from a more controlled location such as the emergency department to a radiology suite, vigilance is required to maintain adequate monitoring and to ensure that skilled personnel remain available to manage airway complications.

Diazepam

Although diazepam was the first benzodiazepine used for procedural sedation and analgesia, midazolam is now preferred because of its shorter duration of action and multiple routes of administration.

Morphine and meperidine

Although morphine and meperidine have been used extensively for procedural sedation and analgesia, fentanyl is preferred pharmacologically to other opioids because of its faster onset, shorter recovery, and lack of histamine release.

Second generation agents

Although diazepam and morphine were effective in the early period of procedural sedation and analgesia, their extended duration of action meant lengthy recoveries and made their use resource-inefficient. The availability of a short-acting opioid (fentanyl) and benzodiazepine (midazolam) greatly lowered the logistical barriers to providing procedural sedation and analgesia. Renewed interest in the procedure prompted clinicians to re-examine ketamine and nitrous oxide—drugs previously

limited to the operating theatre—and investigate ways in which they could be safely used for procedural sedation and analgesia.

Midazolam

Benzodiazepines are a group of highly lipophilic agents with anxiolytic, amnestic, sedative, hypnotic, muscle relaxant, and anticonvulsant properties. They do not have direct analgesic properties, and are commonly given with opioids. Their effects can be reversed with the antagonist flumazenil. Caution must be exercised when giving benzodiazepines and opioids together, since the risks of hypoxia and apnoea are much greater than when either is used alone because the effects are not just additive but synergistic.[53,58] Benzodiazepines induce mild cardiovascular depression and although hypotension can arise it is rarely of clinical importance when the agents are carefully titrated.

Midazolam is the most common benzodiazepine used for procedural sedation and analgesia, and is preferred over the longer-acting diazepam unless unavailable. Time to peak effect for midazolam is brief with intravenous administration (2–3 min) and duration is short (45–60 min). To avoid the need for intravenous access in frightened or uncooperative children, midazolam (unlike diazepam) can be administered via the intramuscular, oral,[77–79] intranasal,[79–81] and rectal[82] routes. Respiratory depression can also arise via these routes. Both the oral and the intranasal routes have limitations. The oral route can lead to unreliable concentrations in serum and clinical effect due to first pass hepatic metabolism. The intranasal route typically has a mucosal irritating effect, which can be painful and produce anxiety in the child. Mucosal irritation is a result of the low pH and the presence of the preservative benzyl alcohol. Buffering the solution does not decrease the irritation.[79–81]

Midazolam can be effectively used for moderate and deep sedation through careful intravenous titration. However, some children need larger doses than would be typical for adults on an mg/kg basis, and paradoxical responses (ie, unexpected agitation and hyperexcitability) are not uncommon.[77,83] Paradoxical reactions, characterised by inconsolable crying, combativeness, disorientation, agitation, and restlessness, have been reported in 1–15% of children receiving midazolam. They have also been reported with intramuscular, intranasal, and rectal administration of benzodiazepines.[84]

When given by skilled practitioners using standard precautions, the safety profile for midazolam is excellent.[6,58,85–87] However, when giving benzodiazepines, one must maintain continuous vigilance for respiratory depression.[64,65,85–87] Such respiratory depression is dose-dependent and greatly increased in the presence of ethanol or other depressive drugs, especially opioids. A series of widely publicised deaths from undetected apnoea were reported shortly after this drug's release in the mid-1980s and before widespread use of continuous interactive and mechanical monitoring,[64,65] highlighting the critical importance of these latter interventions.

Fentanyl

Fentanyl is a potent opioid with no intrinsic anxiolytic or amnestic properties. A single intravenous dose has rapid onset (<30 s) with a peak at 2–3 min and brief clinical duration (20–40 min). Its effects can be reversed with opioid antagonists (ie, naloxone, nalmefene).

Intravenous fentanyl can be easily and rapidly titrated for painful procedures.[86–88] As sedation does not occur at low doses (1–2 μg/kg) the concurrent administration of a pure sedative—most commonly midazolam—is advisable. The combination of fentanyl and midazolam is a popular procedural sedation and analgesia regimen in children, with a strong safety profile when both drugs are carefully titrated to effect.[85–87] For patients who present in pain (eg, with a fracture) and must wait for a procedure, morphine can be given for extended pain relief during the waiting period before the procedure. Fentanyl can then be given for analgesia during the procedure for shorter duration and faster recovery.

The oral transmucosal preparation of fentanyl has never become popular for procedural sedation and analgesia because titration is difficult, effectiveness is variable, and the incidence of emesis is high (31–45%).[89] Like all opioids, fentanyl can cause respiratory depression. Because of the lack of histamine release with fentanyl, nausea and vomiting are less common than with morphine or meperidine. In the absence of substantial ethanol intoxication, hypovolaemia, or concomitant drug ingestion, hypotension is rare, even with very large doses of fentanyl (doses of 50 μg/kg are common in adult and paediatric cardiac surgery). A common reaction to fentanyl is isolated nasal pruritus.

A widely-described but rare adverse effect of fentanyl with potential for respiratory compromise is chest-wall rigidity. This complication is associated with much higher doses (>5 μg/kg as a bolus dose) than those used for procedural sedation and analgesia;[85–88] indeed, this adverse event has not been reported in this setting.

Ketamine

Ketamine produces a unique state of cortical dissociation that allows painful procedures to be done more consistently and effectively than with other procedural sedation and analgesia drugs. This state of "dissociative sedation"[69,35] is characterised by profound analgesia, sedation, amnesia, and immobilisation, and can be rapidly and reliably produced with intravenous or intramuscular administration. Ketamine has been widely used worldwide since its introduction in 1970 and its safety profile has proven excellent in various settings.[34,85,87,90–93]

Clinicians giving ketamine must be especially knowledgeable about the unique actions of this drug and the numerous contraindications to its use (table 2).[59] Ketamine differs from other procedural sedation and

analgesia drugs in several important ways. First, it uniquely preserves cardiopulmonary stability. Upper-airway muscular tone and protective airway reflexes are maintained. Spontaneous respiration is preserved,[94] although when administered intravenously ketamine must be given slowly (over 1 min) to prevent transient respiratory depression. Second, it does not have the characteristic dose-response continuum to progressive titration. At doses below a certain threshold, ketamine produces analgesia and sedation. However, once a critical dosage threshold is reached (roughly 1–1·5 mg/kg intravenously or 3–4 mg/kg intramuscularly), the characteristic dissociative state abruptly appears. This dissociation has no observable levels of depth, and thus the only value of ketamine titration is to maintain the presence of the state over time. Finally, the dissociative state is not consistent with JCAHO definitions of moderate sedation, deep sedation, or general anaesthesia, and therefore must be considered from a different perspective than drugs with the classical sedation continuum.[34,35]

Ketamine is most effective and reliable when given intravenously or intramuscularly. Ketamine has a one-arm brain circulation time (ie, the drug takes effect in 30–45s, the time it takes from injection into the arm until the drug reaches the brain) when given intravenously with onset of dissociation noted within 1 min and effective procedural conditions lasting for about 5–10 min. When given intramuscularly, the same effect is achieved within 3–5 min, with effective procedural conditions lasting 20–30 min. The typical duration from dosing until dischargeable recovery is 50–110 min when given intravenously, and 60–140 min when given intramuscularly.[34,90,93] Ketamine can induce salivation, and anticholinergics (eg, atropine or glycopyrrolate) have traditionally been coadministered to counter this effect. Oral and rectal administration are not commonly used for ketamine procedural sedation and analgesia, as substantial first pass hepatic metabolism results in less predictable effectiveness and delayed onset and recovery.[82,95]

Unpleasant recovery reactions (so-called emergence reactions) are uncommon in children and teenagers, and are typically mild.[34,60,61] There is no evidence of any benefit from the prophylactic administration of concurrent benzodiazepines in children,[34,60] and their role should be confined to treating unpleasant reactions if they arise. Horizontal nystagmus is a characteristic effect of ketamine, and to avoid undue anxiety parents should be told that this is a normal effect of ketamine.

In an emergency department series of 1022 patients, the following adverse airway events were noted: airway malalignment (0·7%), transient laryngospasm (0·4%), and transient apnoea or respiratory depression (0·3%). All were quickly identified and treated with no sequelae.[90]

In 30 years of regular use, there have been no documented reports of clinically significant ketamine-associated aspiration in patients without established contraindications. Because of its unique preservation of protective airway reflexes, ketamine might be preferred over other agents for urgent or emergent procedures when fasting is not assured.[34,90]

Nitrous oxide

Inhaled nitrous oxide provides anxiolysis and mild analgesia and sedation. It is commonly dispensed at concentrations between 30% and 70% with oxygen composing the remainder of the mixture. Nitrous oxide has rapid onset (30–60 s), maximum effect after about 5 min, and rapid recovery upon discontinuation. At typical procedural sedation and analgesia concentrations there is preservation of haemodynamic status, spontaneous respirations, and protective airway reflexes.[96–98]

Nitrous oxide has an excellent safety profile; however as a sole agent it does not reliably produce adequate procedural conditions, and in many cases is supplemented with an opioid or local or regional anaesthesia. Administration can also be useful for intravenous access or venipuncture in frightened children.

The safest method of nitrous oxide administration is via a self-administered demand-valve mask, which needs negative inspiratory pressure to activate gas flow.[96–98] If the patient becomes somnolent, the mask will fall from their face and gas delivery will cease. The main limitation of self-administration is that it is ineffective in uncooperative patients, including most frightened young children. Continuous-flow nitrous oxide has been used in this population with a mask strapped over the nose, or over the nose and mouth producing moderate or deep sedation and necessitating an additional physician dedicated to continuous gas titration.[99] This technique is associated with more frequent emesis than self-administration (0% *vs* 4%), posing a potential hazard when a mask is strapped over the child's mouth.

Several minor adverse effects can be evident, including nausea, dizziness, voice change, euphoria, and laughter.[96–99] Because of its high diffusibility, nitrous oxide should be avoided in patients with potential closed-space diseases such as bowel obstruction, middle ear disease, pneumothorax, or pneumocephaly. A scavenging system must be in place to ensure compliance with occupational safety regulations as occupational exposure to nitrous oxide has been associated with increased rates of spontaneous abortions.[100]

Third generation agents

Although propofol and etomidate became available in the 1980s, their application for procedural sedation and analgesia outside the operating theatre has only been recent.[101–104] These ultra-short-acting drugs are extremely potent and have rapid onset and recovery and can be used for general anaesthesia or for procedural sedation and analgesia depending on the dose given. The role for ultra-

short-acting agents in non-theatre settings remains controversial.[101]

Propofol

Propofol has many desirable characteristics for procedural sedation and analgesia: extremely rapid onset, substantial potency that reliably produces effective conditions for procedural sedation and analgesia, extremely short recovery (5–15 min), and high satisfaction to patients as a result of its antiemetic and euphoric properties. Large emergency department,[101] gastroenterology,[103] and critical care series[104] show that propofol can be given to children in these settings with good efficacy, apparent safety, and rapid recovery. The depth of sedation achieved is not well described in these reports, but usually seems to be at or beyond levels consistent with deep sedation.

The most serious adverse effect of propofol is potent respiratory depression, and apnoea can arise suddenly. Rates of respiratory depression range widely by study (8–30%)[101] since the technique for administration seems more dependent on the operator than does sedation with longer-acting drugs. Propofol can also produce hypotension (by direct negative inotropy as well as by arterial dilatation and venodilatation), although this adverse effect is typically transient and of little clinical importance in healthy patients.[101] The addition of lidocaine has been shown to decrease the incidence of pain during injection.[105]

Etomidate

Etomidate produces sedation, anxiolysis, and amnesia equivalent to that of barbiturates, but with substantially fewer adverse haemodynamic effects. Its intravenous onset of action and recovery are similar to other ultra-short-acting drugs, and preliminary reports describe rapid recovery and a high level of efficacy when used for procedural sedation and analgesia.[106–108] Similarly, the depth of sedation is not well documented in these reports, but seems to often be at or beyond levels consistent with deep sedation.

Like propofol, etomidate can cause respiratory depression.[106–108] Unlike propofol, however, etomidate can also induce myoclonus (sometimes pronounced), nausea, and vomiting,[106–108] and as such seems to be a less desirable choice for procedural sedation and analgesia than propofol. Transient adrenal suppression occurs with etomidate, but does not seem to have clinical significance in a single dose.[109]

Other short-acting analgesics

The opioid diamorphine has a similar onset and duration of action to morphine; however its higher water solubility allows dosing in the small (0·1 mL) volumes necessary for comfortable intranasal administration. In two studies of children with fractures,[110,111] 0·1 mg/kg of diamorphine provided a similar level of analgesia with faster onset than 0·2 mg/kg of intramuscular morphine. Intranasal spray administration via atomiser was better tolerated than the injection, and no adverse events were noted. Diamorphine might also prove a useful initial analgesic for children and teenagers with acute pain.

Sufentanil, alfentanil, and remifentanil are short-acting opioids that currently do not seem to have any advantage over fentanyl for procedural sedation and analgesia.[112–114] Dexmedetomidine is a selective alpha-2 agonist with both analgesic and sedative properties and minimum effect on respiratory drive or cardiac function, making it a potentially useful drug for procedural sedation and analgesia. In a small preliminary study,[115] dexmedetomidine was safe and efficacious as a rescue drug for failed sedations for diagnostic imaging in children. Recent studies on the use of oral sucrose (24% solution) have shown it to be an effective procedural analgesic in neonates, for venipuncture, heel lance, lumbar puncture, nasogastric tube placement, and intravenous catheterisation.[116]

Antagonists

Reversal drugs should not be routinely administered, but rather should be reserved for oversedation or respiratory depression that is more than transient and when the patient does not respond to verbal or tactile stimulation. Resedation after discharge can be avoided by continuing to monitor patients until the effects of the procedural sedation and analgesia drugs (which could last longer than the antagonist) wear off.

Naloxone

This opioid antagonist can be given intravenously, intramuscularly, subcutaneously, or even sublingually if needed,[117] and dosing has been standardised for infants and children.[118] Reversal can be associated with nausea, anxiety, and sympathetic stimulation, and patients with persistent pain after their procedure will be uncomfortable. Careful titration of small amounts of naloxone can allow partial rather than complete reversal.

Nalmefene

Nalmefene is a long-acting opioid antagonist that has been used to accelerate recovery from fentanyl procedural sedation and analgesia.[119] Unlike naloxone, its half-life (4–8 h) is sufficiently long to ensure that it outlasts fentanyl. A disadvantage of this strategy is that post-procedure pain cannot be effectively treated with opioids for several hours.

Flumazenil

This antagonist promptly reverses benzodiazepine-induced sedation and respiratory depression.[120] Flumazenil lowers the seizure threshold and should be used with extreme caution in settings of benzodiazepine dependence, seizure disorder, cyclic antidepressant overdose, elevated intracranial pressure in patients, and in patients taking medications known to lower the seizure

threshold (eg, ciclosporin, cyclic antidepressants, propoxyphene, theophylline, isoniazid, lithium).[120] Rapid reversal can lead to sympathetic stimulation and careful titration can allow partial rather than complete reversal.

Ancillary drugs

Topical anaesthetic technologies (eg, cream or gel emulsions, electricity, laser, ultrasound, heat) are an important new option for instrumentation-related procedures (eg, laceration repair, venipuncture, intravenous placement, lumbar puncture). They can be used on both intact and non-intact skin, achieving anaesthesia penetration to a depth of 3–12 mm in roughly 10–90 min (depending on the drug and delivery system).[121]

International differences in practice

The practice of procedural sedation and analgesia internationally can be divided into three categories: (1) anaesthetists are the sole practitioners, with most procedures happening in the operating theatre or day surgery units (eg, most of Europe, Africa, Latin America, and Asia); (2) a few trained practitioners outside of anaesthesia undertake procedural sedation and analgesia in well-defined circumstances and locations (eg, UK, Singapore, Hong Kong, South Korea, Taiwan, Philippines); (3) multiple specialists outside of anaesthesia routinely do procedural sedation and analgesia in various settings (eg, USA, Canada, Australia, New Zealand).

Within the pharmacopoeia, drugs of choice (table 3) vary by country and practitioner. Differing preferences exist for specific opioid and sedative-hypnotic drugs as well as for systemic drugs, inhalational drugs, and regional nerve blocks.[85,122,123] In many settings not all options are available or sanctioned for procedural sedation and analgesia, the most common restricted drugs being fentanyl, ketamine, propofol, and etomidate.[17,35,101] By contrast, monitoring standards do not seem to vary much internationally with routine use of pulse oximetry, cardiac monitoring, and observation by trained personnel.[3,5–7,10–33] Capnography is not widely used at the moment.

Existing guidelines for procedural sedation and analgesia are formulated in general terms, leaving the specific implementation to local institutions. Some settings use hospital-based credentialling for all providers of the procedure (consisting of didactic or web-based learning modules, testing before and after learning, and minimum life support training requirements), whereas others use residency training and specialty board certification as a sufficient standard. Some residency training programmes (eg, critical care and emergency medicine in the USA, Canada, Australia, and New Zealand) have adopted procedural sedation and analgesia as a core element of their curricula.

Existing guidelines also lack uniformity. Although some have argued the merits of a single universally-binding set of guidelines for children,[124] the reality is various specialty-specific and often conflicting recommendations. Rather than polarising the field, these variations have catalysed evidence-based debate and spurred research in the areas of controversy.

Areas of controversy

There are two general areas of controversy in the practice of procedural sedation and analgesia: practitioner skills (who is qualified to undertake the procedure) and practise standards (what are they qualified to practise).

Practitioner skills

Given the diversity in training for practitioners of procedural sedation and analgesia, defining what specific practices are appropriate for what types of clinicians is difficult. The ASA has divided clinicians into two groups: anaesthetists or non-anaesthetists.[3] However, this categorisation does not account for the substantial heterogeneity in skills within non-anaesthetists—although some practitioners receive little or no formal training in key practice elements for procedural sedation and analgesia (airway management, resuscitation, vascular access, pharmacology), others routinely receive this training as part of their postgraduate curricula. It is therefore reasonable to expect differences in complication rates between practitioners, a factor overlooked in studies grouping all non-anaesthetists together.[124]

The safety profiles of procedural sedation and analgesia as practised by various specialists outside of anaesthesia have been documented.[42,43,69,85,87,101,103,125] In a compilation of sedation adverse events and associated complications from various settings, Cote[124] noted that adverse events happen irrespective of physician type but complications are related to the skill set of the practitioner. Studies are needed to stratify the risk of complications by skill level and competency to determine the appropriate qualifications for safe and effective procedural sedation and analgesia.

Practice standards

In many settings, practitioners of procedural sedation and analgesia have restrictions on the depth of sedation they may induce or the specific drugs they may give. Many clinicians—especially those with more advanced skills in this area—have fought contentious battles to lessen such limitations. The resolution of this controversy awaits a sufficient body of published research showing the safety and effectiveness of drugs for procedural sedation and analgesia in the hands of the different practitioners. Although individual hospital protocols for the procedure are common, there is wide variation in the mechanisms of qualification and in the minimum skills required to do procedural sedation and analgesia. Is a two-day lecture and manikin-based course (eg, Advanced Cardiac Life Support, Pediatric Advanced Life Support) sufficient? If not, what does constitute appropriate training?

The future

The future of procedural sedation and analgesia will focus on enhancing training, safety, and effectiveness. Training issues include establishment of uniform minimum skill requirements, investigation of the effectiveness of simulation-based training in teaching and improving procedural sedation and analgesia skills, and development of curricula for training in countries where the practice is not well established. Safety issues involve defining the most appropriate monitoring for the different levels of sedation, and establishing adverse event registries to monitor safety and standards of practice. Efficacy studies will determine which drugs are most effective for a specific procedure and age of patient, and will operationally define what constitutes a successful sedation for the patient, the family, and the practitioners.[126]

Conflict of interest statement

B Krauss is a consultant for Oridion Medical (a capnography manufacturer), and holds two patents in the area of capnography. S M Green declares that he has no conflict of interest.

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