Ketamine for paediatric sedation/analgesia in the emergency department

M C Howes

This review investigates the use of ketamine for paediatric sedation and analgesia in the emergency department

The injured child presents a challenge to emergency department (ED) practitioners. The pain and distress can be upsetting for staff as well as parents. The child’s distress can be compounded by the fear of a painful procedure to follow, previous conditioning from unexpected “jabs” when receiving immunisations, or previous visits to an ED.

As doctors we strive to relieve pain and suffering, and swear to do no harm. Forced restraint, still performed in some departments in the country (personal communications), is no longer acceptable and may compound the hospital—and needle—phobia throughout life. Distraction techniques, play therapy, and adequate analgesia may be sufficient to produce a cooperative, relaxed child. When this fails the alternatives to enable a pain free treatment of the injury are general anaesthesia or sedation.

To compare these two approaches we must consider several factors; firstly, the ideal requirements of the agent to be used: rapid onset, adequate depth of sedation and analgesia, maintenance of spontaneous respiration, lack of response to the painful stimulus, rapid recovery, and minimal side effects. Secondly, the staffing, equipment, and facilities required. Thirdly, the preference of the parent, who acts as the child’s advocate; lastly, the procedure proposed.

The phencyclidine derivative ketamine has been described as the ideal agent for paediatric sedation in EDs, with departments in the UK, USA, Australia, Europe, Japan, Mexico, the Middle East (Green SM unpublished data), and Singapore using the technique regularly. The American College of Emergency Physicians and the Australasian College of Emergency Medicine both have formal guidelines for emergency physicians specifically for ketamine sedation, although the latest national guideline on paediatric sedation in the United Kingdom recommends “…the general anaesthetic agents […ketamine…]…are only used by those formally trained in paediatric or neonatal anaesthesia or intensive care.”

Ketamine is a unique drug giving complete anaesthesia and analgesia with preservation of vital brain stem functions. This “dissociative” state has been described as “a functional and neuro-physiological dissociation between the neocortical and limbic systems.” Ketamine dissociation results in a clinical state of lack of response to pain or other noxious stimuli, with relative preservation of respiratory and cardiovascular functions despite profound amnesia and analgesia, described as “cataleptic.” This trance-like state of sensory isolation provides a unique combination of amnesia, sedation, and analgesia. The eyes often remain open, though nystagmus is commonly seen. Heart rate and blood pressure remain stable, and are often stimulated, possibly through sympathetic actions. Functional residual capacity and tidal volume are preserved, with bronchial smooth muscle relaxation and maintenance of airway patency and respiration.

However, despite the enthusiasm of many authors and practitioners, ketamine may not be the ideal agent. Emergence reactions, subanaesthetic conditions, and airway problems do occur, and it is generally recommended that only physicians skilled in airway management and resuscitation are involved in the care of sedated children.

Is ketamine sedation the answer for the unconsolable injured child requiring a painful procedure in the emergency department? Such a child could require exploration of a wound, a strange adult with instruments invading the child’s personal space, and attention to functional and cosmetic outcome. Assuming distraction therapy has failed, a three part question can be formulated thus: “In [children with injuries requiring a painful procedure] is [ketamine sedation/analgesia] a [safe and acceptable technique in the A&E department]?”

LITERATURE SEARCH

Databases: Medline 1966 to present and Embase 1980 to present via the Ovid interface.

To specify trials involving the randomised comparison of ketamine with other sedative agents the following strategy was used:

“ketamine.mp. AND (children or child$ or paediatric or paediatric$ or pediatric or pediatric$).mp.” AND (maximally sensitive randomised control trial filter).

A further search for additional papers was performed with the following strategy: (ketamine or ketamin$).mp. AND (children or child$ or paediatric or paediatric$ or pediatric or pediatric$).mp. AND (emergency or emergenc$ or accident or accident$ or (accident and emergency$)).mp.

No limits were applied. The results were assessed for relevant articles by searching the abstracts. The references of review articles were also searched for any additional papers of...
relevance, and the following journals were hand searched for recent articles not yet included in the Medline or Embase databases that may be relevant: Annals of Emergency Medicine, Academic Emergency Medicine, Emergency Medicine Journal, Emergency Medicine, American Journal of Emergency Medicine, Pediatric Emergency Care.

Other sources include data from Lancaster Royal Infirmary and communications with authors in the field of ketamine sedation in children in A&E (Ray McGlone, Lancaster, UK, and Steven Green, California).

RESULTS

Randomised trials comparing ketamine with other agents

When comparing agents used for sedation the primary outcome measures must be the characteristics of our mythical “ideal agent.”

Only three trials were identified that directly compared ketamine alone with another sedative agent. Others used combinations of sedatives, were studying ketamine in the context of general anaesthesia for surgery in an operating environment, or studying the pharmacology of ketamine. Others studied ketamine for critical care procedures. One study was placebo controlled. Table 1 summarises these three trials. The trial published by Acworth et al is included to highlight UK experience and the attempts at blinding the investigators made. The trial was confounded as ketamine was given with midazolam.

It is difficult to perform a truly blinded comparison of sedative agents.

Acworth et al blinded the observers by bringing them into the sedation room to score the sedation level after drug administration and placing dummy intravenous cannulas on the patients. They also attempted to perform a quality control on their blinding by asking the observers to guess which sedation agent had been given; observers were right in 55%. However, these observers may introduce bias as the ketamine dissociated state can be recognised from other sedation levels. A study blinding the data analysis from the clinicians has yet to be reported, and so additional bias remains in the published work. Varying sedation scoring systems, and definitions of “agitation” and “satisfaction” complicate the analysis. The conclusion is that ketamine appears to provide better conditions of sedation, though a somewhat different level of sedation than other agents. Definitions of sedation levels will be dealt with later in this review.

Attempts to compare side effects of sedative agents would require statistical powering. Green et al calculated that 7216 subjects would be required for a study to detect a 50% relative difference in airway complications from a baseline incidence of 1.4%. Differences in defining and reporting adverse events may also invalidate reporting of such incidents. Without large, prospective, multicentre, randomised trials we have to assume that 1.4% of children undergoing general anaesthesia experience complications, so a study of 1.4% would be powered. Differences in defining and reporting adverse events might also invalidate reporting of such incidents.

Safety and side effect profile: observational studies and reviews

Green and Johnson published a comprehensive review of ketamine sedation in 1990, alongside a case series of 108 episodes of paediatric sedation in an ED. The authors pooled data from published reports including their own data on the use of ketamine sedation in the unintubated patient, and demonstrated an excellent safety profile in a wide range of procedures and settings, including burns ward dressing changes, cardiac catheterisation, dentistry or oral surgery, and minor surgery. Altogether 11 589 cases (97 case series) of

Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment arms</th>
<th>Number of patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGlone et al</td>
<td>IV midazolam 0.5 mg/kg</td>
<td>102</td>
<td>Behaviour, sedation</td>
<td></td>
</tr>
<tr>
<td>McGlone et al</td>
<td>IM midazolam 0.4 mg/kg</td>
<td>53</td>
<td>Physical status, sedation</td>
<td></td>
</tr>
<tr>
<td>Yonge and Kendall</td>
<td>Oral ketamine 10 mg/kg</td>
<td>87</td>
<td>Tolerance, time to sedation, parent satisfaction</td>
<td></td>
</tr>
<tr>
<td>Younge and Kendall</td>
<td>IV ketamine 1 mg/kg plus oral midazolam 0.1 mg/kg</td>
<td>59</td>
<td>Tolerance, time to sedation, parent satisfaction</td>
<td></td>
</tr>
</tbody>
</table>
paediatric sedation using ketamine are discussed and this is by far the most comprehensive review of the topic.

The authors quoted incidences of adverse events as follows (with referenced comments).

**Apnoea: “exceptionally rare”**
Spontaneous respiration is maintained with ketamine dissociation, although the review quoted incidences of transient apnoea after rapid intravenous administration or exceptionally high doses.

Apnoea has since been reported after intramuscular administration. Ketamine has been used successfully for many years as the sole agent to facilitate surgical and other procedures in remote third world locations without skilled anaesthetists present or supplemental oxygen, in battlefield and prehospital trauma victims, and in the ED during resuscitation of trauma victims for analgesia during manipulation and splinting of fractures (unpublished data). Green et al have reported the maintenance of spontaneous respiration in children receiving 5 (n = 3), 10 (n = 5), or 100 (n = 1) times the intended doses of ketamine. Two cases required brief periods of assisted ventilation, and two maintained spontaneous breathing but were intubated prophylactically to protect the airway. None of the recent case series have reported any episodes of apnoea requiring intervention other than supplemental oxygen or brief manual ventilation assistance (table 2).

**Laryngospasm: very rare—intrusion required in two cases (0.017%)**
The reported incidence in paediatric general anaesthesia is 0.87%, with children less than 10 years old more susceptible (1.74%) (Olsen and Hallen, 1984. Cited by Green et al as reference 158). Although Green et al highlight the safe use of ketamine sedation for dental surgery and tonsillectomy, they have subsequently reported an increased incidence (9.5%, all occurring during oesophagostroscopy) in procedures entailing stimulation of the oropharynx or hypopharynx. All of these episodes were transient with minimal clinical impact.

It is accepted that instrumentation of the hypopharynx including suctioning may precipitate an episode of laryngospasm. To help prevent the salivation associated with ketamine, most authors recommend concurrent administration of an antisialogogue. Salivation may still occur if atropine is given (59 of 501 cases, 12%). Green et al reported an incidence of hypersalivation of 1.7%. A randomised controlled trial may answer the question of whether antisialogogues prevent the salivation associated with ketamine.

**Emergence phenomena: 0%–10%—less common with IM administration. Rarely upsetting for children under 10 years old**
Emergence reactions (sensory misinterpretation—“trips”, vivid hallucinations, “floating feelings”, bizarre behaviour) were all reported. These are manifestations of ketamine’s unique effect of sensory isolation, recovering via sensory misinterpretation. It is felt that children find this effect less disturbing than adults because of their different perception of the world and their environment. The incidence of emergence reactions is said to increase with age, but can be reduced by positive psychology (“think of a nice dream”), and avoiding ketamine in patients prone to vivid dreaming or psychosis. Some authors advocate adjunctive midazolam to prevent emergence phenomena, but two randomised trials and a topic review have shown this to be ineffective, with oxygen desaturation occurring more frequently in the midazolam treated group. Green and

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**Table 2. Case series reporting incidence of side effects.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Dose</th>
<th>Number of cases</th>
<th>Analysis</th>
<th>Vomiting</th>
<th>Emergence dysphoria</th>
<th>Data collection</th>
<th>Follow up</th>
<th>Parent dissatisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green et al (1993)</td>
<td>1993</td>
<td>IM  4 mg/kg</td>
<td>108</td>
<td>Complete prospective</td>
<td>14</td>
<td>5 (6.5%)</td>
<td>Complete prospective</td>
<td>77 (71.3%)</td>
<td>5.2%</td>
</tr>
<tr>
<td>Dachs and Innes (1997)</td>
<td>1997</td>
<td>IV 1–2 mg/kg</td>
<td>30</td>
<td>Complete prospective</td>
<td>10</td>
<td>4 mild</td>
<td>Complete prospective</td>
<td>29 (96.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Green et al (1998)</td>
<td>1998</td>
<td>IM 4–10 mg/kg</td>
<td>52</td>
<td>Complete prospective</td>
<td>1</td>
<td>2 mild</td>
<td>Complete prospective</td>
<td>29 (96.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Green et al (1998)</td>
<td>1998</td>
<td>IM 4–10 mg/kg</td>
<td>156</td>
<td>Complete prospective</td>
<td>1</td>
<td>2</td>
<td>Complete prospective</td>
<td>29 (96.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Peña and Krauss (1999)</td>
<td>1999</td>
<td>IM 0.5–3.5 mg/kg</td>
<td>105</td>
<td>Complete prospective</td>
<td>1</td>
<td>12 nil</td>
<td>Complete prospective</td>
<td>29 (96.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Holloway et al (2000)</td>
<td>2000</td>
<td>IM 0.5–3.5 mg/kg</td>
<td>105</td>
<td>Complete prospective</td>
<td>1</td>
<td>12 nil</td>
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<td>105</td>
<td>Complete prospective</td>
<td>1</td>
<td>12 nil</td>
<td>Complete prospective</td>
<td>29 (96.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Ng and Ang (2002)</td>
<td>2002</td>
<td>IM 2–4 mg/kg</td>
<td>61</td>
<td>Complete prospective</td>
<td>1</td>
<td>6 mild</td>
<td>Complete prospective</td>
<td>29 (96.6%)</td>
<td>0</td>
</tr>
<tr>
<td>McGlone et al (2004)</td>
<td>2004</td>
<td>IM 0.5–3.5 mg/kg</td>
<td>21</td>
<td>Complete prospective</td>
<td>1</td>
<td>6 mild</td>
<td>Complete prospective</td>
<td>29 (96.6%)</td>
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</tr>
<tr>
<td>Holloway et al (2000)</td>
<td>2000</td>
<td>IM 0.5–3.5 mg/kg</td>
<td>105</td>
<td>Complete prospective</td>
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Johnson conclude “it is highly unlikely that ketamine causes permanent changes in personality or intellectual function.”

In a series of 501 cases at Lancaster, using a lower (often subdissociative) dose of 2.0 to 2.5 mg/kg, we found an incidence of emergence “euphoria” of 2%. None of these children had any recollection of the sedation, or feelings of anxiety or distress afterward, and parents reported a 98% level of satisfaction.

**Vomiting**: 8.5% from the pooled data (0%-43%), all but two cases during recovery

Postoperative vomiting from general anaesthesia in children is quoted as ranging from 0% to 70%. Vomiting after discharge from hospital may be influenced by early mobilisation or motion sickness during the car ride home. Despite variations in fasting recommendations including instances of sedation in unfasted patients, there were no episodes of aspiration reported. Green and Krauss have since argued that fasting recommendations for ED sedation may be unnecessary in view of the lack of evidence of pulmonary aspiration risk, particularly if ketamine is used.

Other reactions: nystagmus, ataxia, myoclonus, random limb movements, opisthotonus. Transient facial rash or flushing

Rarely clinically important and resolve with recovery. Ataxia may persist for up to four hours. It is recommended that children recovering from ketamine sedation be kept still, lying down, and quiet, until nystagmus and uncoordination have resolved.

Since this review was published, Green et al attempted to determine predictors of adverse events during intramuscular ketamine sedation, again using their data from 1022 cases. Multiple logistic regression analyses were used to determine the association of five variables (age, sex, ASA risk, ketamine dose, number of doses) with vomiting and recovery agitation. No variable was found to be associated with airway complications. Emesis was modestly associated with age over 5, with a difference in incidence of 8.6% (95% CI 4.9% to 12.1%). Age under 5 was associated with an increased incidence of recovery agitation (22.5% compared with 12.1% in the over 5 year age group); the reduction in incidence of vomiting in the children over 5 was −10.4% (95% CI −3% to −17.7%). The incidence of recovery agitation was 17.9% in ASA class 1 children and 33.3% in ASA class 2 or more, a difference of −15.4% (95% CI 0%–30.7%).

A dose of 2.0 to 2.5 mg/kg IM was given to 501 patients for sedation related issues. In Green’s series, 38 of the four dissatisfied parents only one had a complaint related to the sedation procedure.

**Doses of ketamine used**

In Green’s original review of 11,589 administrations, dose ranges from 0.5 to 16 mg/kg IM and 1 to 5 mg/kg IV were reported. Modern ED practitioners tend to use 2 to 5 mg/kg IM or 0.5 to 2 mg/kg IV. To further review, Green et al tried to determine the optimum dose of ketamine for paediatric sedation.

**Definitions of sedation and what does “ketamine sedation” mean?**

It is generally accepted that the term “conscious sedation” refers to a state of drug induced central nervous system depression, where the verbal contact is maintained with the patient, and airway and other reflexes are preserved. Sedation to a deeper level implies loss of verbal contact and response to gentle stimulation. This state of “deep sedation” risks the loss of protective reflexes, airway control, aspiration, and hypoxia. “Deep sedation” carries a requirement for a level of care consistent with general anaesthesia. The drugs used should have a wide margin of safety so that loss of consciousness is unlikely.

As described above, the state of ketamine dissociation does not follow this continuum of gradually increasing depth of sedation and concurrent cardiorespiratory depression, towards a state of general anaesthesia. Any sedative drug...
used in large enough quantities, or with a susceptible patient, will produce a state of general anaesthesia.5 6 10 (Midazolam, commonly used for sedation, was originally marketed and introduced as a general anaesthetic induction agent). Is the state of dissociation seen with ketamine actually general anaesthesia if no verbal, motor, or cardiovascular response to painful stimuli is observed?

It is commonly accepted that general anaesthesia, by definition, results in partial or total lack of airway reflexes, resulting in an inability to independently maintain an airway. From this topic review it seems ketamine dissociation occurs with maintenance of respiration and a patent airway in most situations probably because its primary site of action is the cerebral cortex and limbic systems and not the brain stem.30 31

There is no gradual slide from sedation to general anaesthesia with ketamine.17 No dose–response continuum is observed and patients are either dissociated or they are not, with no progressive “depth” of dissociation.6 17 EEG analysis of ketamine dissociated subjects fails to show the classic depression of the bispectral index seen in general anaesthesia17 70

Ketamine cannot therefore be classified by current guidelines on sedation. Green proposed a separate sedation category to describe the dissociative state demonstrated by ketamine.90 He later defined “dissociative sedation” thus:

“A trance-like cataleptic state characterised by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability.”11 17

CONCLUSIONS—WITH REFERENCE TO THE THREE PART QUESTION

In children with injuries requiring a painful procedure ketamine dissociative sedation is a safe and acceptable technique in the emergency department. Ketamine “dissociative sedation” is different from conscious sedation, deep sedation, and general anaesthesia. The rare instances of serious side effects necessitate the availability of experienced staff skilled in advanced airway maintenance, with adequate monitoring and resuscitation equipment. To provide a ketamine sedation service, EDs must be able to comply with the above; it may be that staffing levels, service commitments, and workload mean that children who could otherwise be managed in the emergency department and discharged home will have to be referred to another unit, or to an in-hospital team for general anaesthesia. This may mean an inter-hospital transfer if no paediatric anaesthetist is on site.32 Paediatric or general anaesthetists should not be required to assist emergency physicians sedating children with ketamine.74

As more EDs in the UK introduce a ketamine sedation protocol, our specialty must ensure, above all, the safety of our patients.4 65 Full and comprehensive prospective national audit is proposed and it is hoped that all departments around the country using ketamine for paediatric sedation will participate (personal communication).

REFERENCES


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LETTER

Monitoring junior doctors after a major incident

The major incident that occurred in the capital on July 7 2005 put many junior doctors on the front line, seeing badly injured and traumatised patients. Exposure to such horrific sights will make many health care workers vulnerable to post traumatic stress disorder (PTSD).1

Following the major incident, occupational health staff sent relevant line managers information alerting them to the symptoms of PTSD. In accordance with current recommendations, formal counselling was not routinely offered to staff immediately after the event.2 Evidence shows that it is not necessary for specific intervention until four to six weeks after the incident, when individuals have exhausted their normal coping mechanisms. It is difficult to achieve ‘watchful waiting’ in such a fluid environment as accident & emergency. In particular, four weeks after this major incident, the majority of the junior doctors moved on to other posts.

Four weeks after the event, we carried out a departmental survey based upon Chris Brewin’s Trauma Screening Questionnaire, in order to identify those more likely to be suffering from PTSD.3 The results showed that although no junior doctors were experiencing enough symptoms to suggest a greater risk of developing PTSD, only 50% knew where to access counselling despite detailed information available on the hospital’s intranet service.

We recommend that a senior staff member is responsible for informally following up junior doctors involved in a major incident. This should be for four to six weeks after the event, potentially by postal questionnaire and should identify any on going problems. Posters advertising counselling should be clearly visible in communal staff areas and ultimately, every accident & emergency department should have a follow up plan for remote monitoring of staff that were involved. This should be the final chapter of the major incident plan for any department.

J Blythe
Department of Accident & Emergency Medicine, Royal Free Hospital, London, UK

K Whitwell
Department of Accident & Emergency Medicine, Royal Free Hospital, London, UK

Reference

BOOK REVIEW

The high altitude medical handbook


If imitation is the best form of flattery, then the authors of The High Altitude Medicine Handbook should consider themselves flat-tered indeed. The “mini micro” bootleg version of the first edition of the handbook, published in India, and widely available in bookshops in Kathmandu, has perhaps sold more copies to those departing on high altitude treks than the original. This illicit version was my first copy of the handbook and it lived in my back pocket when I was working as a medical officer on expedition in remote parts of eastern Nepal. At high altitude, when cold, fatigue, and hypoxia muddied my brain, it was my constant reference text and bible.

I was therefore delighted to be asked to review the third edition, which was published in 2003 to coincide with the 50th anniversary of the first ascent of the summit of Mount Everest and the 25th anniversary of the first ascent without oxygen.

The handbook is not, nor does it set out to be, a definitive text on altitude medicine. There is therefore little on the physics of hypobaric hypoxia or the underlying pathophysiology of acute mountain sickness. Instead, it achieves exactly what it sets out to do: it is a clear, concise, commonsense guide to the management of all aspects of medical problems at high altitude. There are not only the expected chapters on high altitude illness, first aid and travel related illnesses, but also sections on children, ethics, culture, environmental and medicolegal concerns. All chapters are extensively referenced so readers can easily refer back to original literature. This third edition has been thoroughly revised to reflect the rapid increase in knowledge in the 5 years since the last edition.

The foreword by Sir Edmund Hilary reflects that both Andrew Pollard and David Murdoch are experienced mountaineers, Andrew Pollard having reached 8600 metres on the south col of Mount Everest in 1994. They are both experts in high altitude and expedition medicine and have a breadth of experience in managing medical conditions in some of the world’s most challenging environments. David Murdoch worked for 2 years in the Everest Region, first at the Himalayan Rescue Organisation’s first aid post at Sheriche, then at Kunde hospital. This makes the handbook occasionally controversial, always authoritative, and full of practical advice on how to overcome the technical challenges of practising medicine in such difficult conditions.

This is a valuable guide to have with you on expedition or any high altitude trek, but also includes valuable pre-departure planning information such as an appendix on what to include in a typical high altitude medicine kit list. Although the handbook is primarily aimed at medical practitioners, its straightforward text makes it accessible to lay travellers and can be highly recommended to anyone considering travelling to high altitude.

F Bellis
Competing interests: A Pollard (book author) and F Bellis (reviewer) are both members of Medex, a medical mountaineering and expedition club

CORRECTION

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