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Review

Pharmacological sedation management in the paediatric intensive care unit

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Abstract

Objective This review addresses sedation management on paediatric intensive care units and possible gaps in the knowledge of optimal sedation strategies. We present an overview of the commonly used sedatives and their pharmacokinetic and pharmacodynamic considerations in children, as well as the ongoing studies in this field. Also, sedation guidelines and current sedation strategies and assessment methods are addressed.

Key findings This review shows that evidence and pharmacokinetic data are scarce, but fortunately, there is an active research scene with promising new PK and PD data of sedatives in children using new study designs with application of advanced laboratory methods and modelling. The lack of evidence is increasingly being recognized by authorities and legislative offices such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Conclusion The population in question is very heterogeneous and this overview can aid clinicians and researchers in moving from practice-based sedation management towards more evidence- or model-based practice. Still, paediatric sedation management can be improved in other ways than pharmacology only, so future research should aim on sedation assessment and implementation strategies of protocolized sedation as well.

Introduction

Sedation management is a crucial element of paediatric critical care medicine, aiming at reducing children's anxiety, distress and oxygen demand. Adequate sedation improves patient–ventilator synchrony and prevents auto-extubation in ventilated children.[1] Moreover, it allows tolerance to diagnostic or therapeutic procedures. However, sedation induced by pharmacological agents often leads to adverse events including prolonged mechanical ventilation, tolerance, withdrawal syndrome and even paediatric delirium. Dosing regimens are not always based on PK data or paediatric pharmacological research findings, and even today, more than 80% of drugs used in the paediatric intensive care unit (PICU) are off-label or unlicensed.[2] Still, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have prioritized paediatric pharmacological research efforts to achieve more evidence-based pharmacotherapy.[3]

To date, there is no consensus on sedation management for children.[4,5] This review provides an overview of evidence for the commonly used drugs in paediatric sedation management and inventories ongoing and future research. Table 1 presents an overview of prospective observational studies and randomized controlled trials performed so far.

Sedation Assessment

A 'gold standard' tool to assess the sedation state of children on intensive care units has not yet been identified.[6] Assessment is difficult because signs such as motor restlessness, agitation and increased muscle tone that may point at undersedation are also signs of pain. It is generally accepted that preverbal children are not able to express their pain or discomfort in a way caregivers understand or interpret as such. Furthermore, children may suffer from separation anxiety and fear for strangers and thus show behaviour indicating undersedation.

Table 1 An overview of performed pharmacological studies in paediatric intensive care sedation

Study	Sample size and age	Design	Outcome
Booker *et al.*[149]	*N* = 50, 6 months–9 years	Observational cohort study (midazolam bolus 200 mcg/kg followed by CI 120–360 mcg/kg per h)	Adequate sedation, no major adverse events
Shelly *et al.*[150]	*N* = 50, 0–18 years	Prospective observational cohort study of midazolam CI	Adequate sedation, delayed awakening especially in renal failure patients
Macnab *et al.*[151]	*N* = 23, 6 months–6 years	Prospective observational cohort study of a midazolam loading dose after cardiothoracic surgery	Termination of study after severe hypotension, other participants showed no haemodynamic changes
de Wildt *et al.*[62]	*N* = 21, 0–17 years	Observational cohort PK-PD study with protocolized sedation strategy: start dose midazolam 0.1 mg/kg bolus, followed by 100 mcg/kg per h	No clear PK-PD relationship, adequate sedation reached with protocol No report on toxicity
Rigby-Jones *et al.*[152]	*N* = 26, 0–10 years	Observational cohort PK study, remifentanil and midazolam	Adequate sedation, 1 patient showed hypotension
Ambrose *et al.*[153]	*N* = 30, 0–10 years	Three-step: IV clonidine: low dose vs high dose (variable dose together with midazolam), 3rd group fixed dose	No adverse effects on haemodynamics, sufficient sedation in combination with midazolam
Arenas-Lopez *et al.*[83]	*N* = 24, 0–5 years	Prospective cohort study, oral clonidine as additive to morphine/lorazepam	Opioid and benzodiazepine sparing, safe and effective
Wolf *et al.*[81]	*N* = 129, 0–15 years	Double-blind, randomized controlled trial of IV clonidine vs midazolam	No difference in effectivity, underpowered due to recruitment problems
Hünseler *et al.*[82]	*N* = 219, 0–2 years	Double-blind, randomized controlled trial of IV clonidine vs midazolam	Opioid and benzodiazepine sparing in neonatal age group
Duffett *et al.*[84]	*N* = 50, 0–18 years	Double-blind, randomized controlled trial of oral clonidine vs placebo in addition to physician-driven sedation	No significant difference in effectivity, study with clonidine clinically feasible
Su *et al.*[154]	*N* = 36, 1–24 months	Open-label dose–response study of dexmedetomidine	Reduction of supplementary sedatives, no cardiovascular adverse effects
Hosokawa *et al.*[155]	*N* = 141, 0–15 years	Observational cohort study: dexmedetomidine vs chlorpromazine, midazolam or fentanyl in cardiac surgery patients	Comparable efficacy, more haemodynamic adverse effects in dexmedetomidine group
Aydogan *et al.*[88]	N = 32, 12–17 years	Double-blind, randomized controlled trial of IV dexmedetomidine vs midazolam in adolescents after scoliosis surgery	Decreased pain score, fentanyl consumption and delirium in dexmedetomidine group, more bradycardia in dexmedetomidine group
Diaz *et al.*[156]	*N* = 10, 0–8 years	Observational PK study of dexmedetomidine for postoperative sedation	Hypotension in most cardiac surgery patients
Tobias and Berkenbosch[89]	*N* = 30, 0–8 years	Randomized controlled trial: IV low dose or high dose, dexmedetomidine vs midazolam	Equivalent sedation across 3 groups, lower heart rate in dexmedetomidine group: 1 patient removed from the study after bradycardia
Svensson and Lindberg[157]	*N* = 174, 0–16 years	Prospective observational cohort study: propofol CI in the PICU	No occurrence of PRIS in cohort group
Rigby-Jones *et al.*[158]	*N* = 21, 0–12 years	Observational PK study of propofol CI	Adequate sedation in 17 of 20 scored patients, 1 case of hypotension and metabolic acidosis
Hartvig *et al.*[159]	*N* = 10, 8–30 months	Observational PK study of ketamine CI after cardiac surgery	Adequate sedation, no adverse effects observed

Table 1 *Continued*

Study	Sample size and age	Design	Outcome
Parkinson *et al.*[107]	*N* = 44, 0–15 years	Randomized controlled trial of midazolam IV vs chloral hydrate and promethazine PO	More optimal sedation in chloral hydrate/promethazine group, 1 patient with indication of delirium in chloral hydrate/promethazine group

Roughly, two types of sedation assessment scales are available[6,7]; those that score a number of behavioural indicators of distress and those that consist of one item describing the level of consciousness. Examples of the latter type validated for children are the University of Michigan Sedation Scale (UMSS)[8] and the State Behavioral Scale (SBS).[9] The UMSS assesses level of consciousness from 0 (awake and alert) to 4 (unarousable). The SBS has six levels from −3 (unresponsive) to +2 (agitated). Another one-item scale, the Ramsay scale, has been used mainly for adults and is not applicable to preverbal children as it includes an item 'responds to commands only'.[10,11] To date, the Richmond Agitation–Sedation Scale (RASS)[12] is more often used in adults, but it has not been validated for children as this includes the item 'overtly combative or violent; immediate danger to staff'.

An example of a scale that includes several behavioural indicators of distress is the COMFORT behavioural (COMFORT-B) scale.[10] The COMFORT-B scale can be used both in ventilated and spontaneously breathing patients and has proven to be valid for both pain and sedation assessment. In addition, the scale is able to detect treatment-related changes in pain or distress intensity and therefore can reliably guide pain and sedation management.[13] Still, the COMFORT-B scale cannot be applied in patients with fluctuations in neurological status, pre-existing neurological disorders or patients receiving neuromuscular blocking agents.

A limitation of behavioural assessment tools in general is the difficulty to discriminate between pain, discomfort, withdrawal symptoms or delirium. For example, the Face, Legs, Activity, Cry and Consolability (FLACC) scale, one of the most widely used pain assessment scales, was found wanting in its capacity to discriminate pain and distress.[14]

For a decade, the Bispectral Index Monitor (BIS) was considered promising for objective assessment of sedation. Studies comparing BIS to the COMFORT (or COMFORT-B) scale[15–22] showed correlations ranging from weak[15] to excellent when grouped in a BIS range of 41–60.[17] This wide variation can be partially explained by different study conditions, as the weak correlation was found in patients undergoing endotracheal suctioning, and the high correlation was found during continuous sedation. Depending on the clinical indication, BIS can potentially be used, although it has not proven valid for children under the age of 1 year old as the EEG algorithm has not been validated in infants.[23]

Prolonged administration of sedatives may lead to drug tolerance and physical dependency, leading to iatrogenic withdrawal syndrome after abrupt discontinuation or (too rapidly) tapering down of these drugs. The symptoms of this syndrome overlap with signs of undersedation. The Withdrawal Assessment Tool-1 (WAT-1) and the Sophia Observation withdrawal Symptoms score (SOS) are the most valid and reliable tools to identify withdrawal in the PICU.[24,25] Furthermore, a position statement from the European Society for Paediatric And Neonatal Intensive Care (ESPNIC) provides clinical recommendations for sedation and withdrawal syndrome assessment in the paediatric age group.[26]

Sedation Guidelines

Sedation management in adults has shifted from full unconscious sedation to a more easily arousable state.[27] In this approach, the use of sedation guidelines and protocols was associated with reduced ICU and hospital length of stay (LOS) as well as reduced duration of mechanical ventilation (MV).[28] In paediatrics, however, a systematic review published in 2013[29] showed that some studies also found a reduced ICU LOS and duration of MV in protocolized sedation arms, but concluded that the overall evidence for protocolized sedation remained relatively poor due to the low quality of studies. Children's cognition and behaviour clearly require a different strategy.

One year later, Curley *et al.*[30] reported on the largest multicentre RCT comparing protocolized sedation with physician-driven usual care in a mixed PICU population. The protocolized sedation management had not resulted, however, in shorter MV duration or ICU and hospital LOS. Heterogeneity in outcome measures and pharmacological agents makes it difficult to obtain sufficient evidence for the usefulness of sedation guidelines in paediatric intensive care. A systematic review of Vet *et al.*[31] concluded that optimal sedation is achieved in only around 60% of

sedation assessments and that oversedation is more common than undersedation. Oversedation often was not adequately managed by tapering off medication, indicating that healthcare professionals may be tolerating oversedation. This attitude may diminish the effect of protocolized sedation in trials. It would seem that 'protocolized' does not automatically mean 'uniformity' or 'one size fits all'.[32]

In adults, the method of daily sedation interruption (DSI) seemed promising in reducing ICU LOS and MV duration,[33,34] but conclusive evidence has not yet been found.[35,36] A multicentre RCT comparing protocolized sedation and DSI plus protocolized sedation in the PICU showed no beneficial effects of DSI,[37] in contrast to two other RCTs in children.[38,39] Vet *et al.* compared to protocolized sedation management instead of physician-based sedation management, which may imply a positive effect of the protocolized sedation in the control arm.

Although an optimal level of sedation often cannot be achieved without pharmacological treatment it is also important to consider environmental factors and non-pharmacological interventions. Light and noise, for example, can be disturbing, and care should be taken to let the children wear ear plugs, ask staff to speak softly and prevent ongoing alarm sounds, etc. Non-pharmacological interventions to reduce stress, such as live or recorded music, have been primarily studied in adult critical care.[40] A meta-analysis including three RCTs of music therapy offered to paediatric surgical patients (0–18 years), although not in the intensive care setting, reported significant reduction in pain, anxiety and distress.[41] It would be worthwhile to study non-pharmacological interventions in the PICU setting.

Pharmacological Aspects

Several overviews of commonly used sedatives have already been published.[42–44] Still, the dosing regimens greatly differ. This is not surprising, as most of these sedatives are prescribed off-label.[2] Figure 1 illustrates the mechanisms of actions of the different sedatives. Table 2 provides PK and PD properties of the most common sedatives including proposed dosing strategies.

Low-volume blood collection techniques such as dry blood spot sampling[45] in combination with new analysis techniques such as LC-MS/MS, for which less blood is needed, could help establish optimal paediatric dosing strategies by enhancing pharmacokinetic research. Moreover, comparative effectiveness studies and population PK-PD studies using opportunistic and sparse sampling could further facilitate paediatric drug research.[46]

However, many internal and external factors can alter the PK and PD of sedative drugs. The internal factors include critical illness itself, which has been correlated with altered PK parameters of midazolam[47,48] and other drugs,[49] decreased cardiac output, changes in liver and kidney function and altered distribution, for example, in children with burns.[50] External factors include renal replacement therapy,[51] ECMO[52,53] and hypothermia.[52,54] Increasingly, physiology-based pharmacokinetic (PBPK) studies will offer the opportunity to integrate physiological and pathophysiological changes over time in the drug dosing schedules.

Furthermore, weight-based infusion concentrations are often inaccurate. In a prospective study, 65% of opiate concentrations in a PICU and NICU differed >10% from the

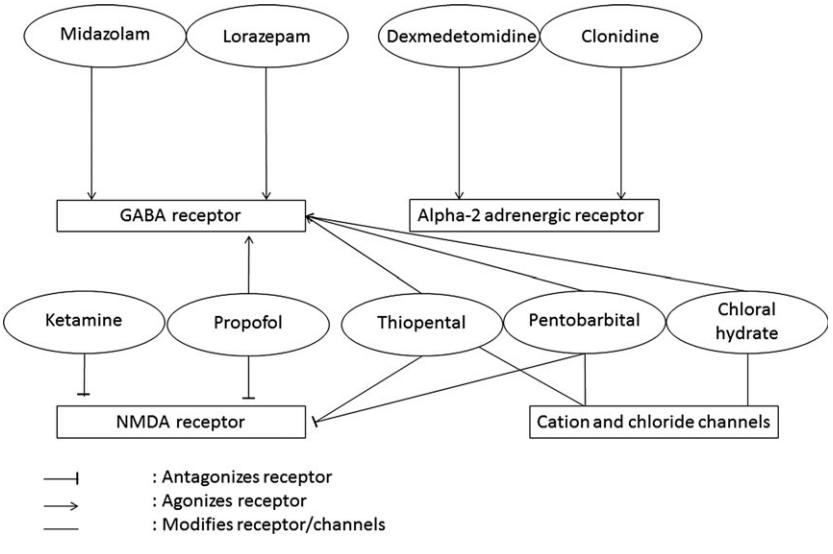

Figure 1 An overview of the sites of action of the most commonly used sedatives in the pediatric intensive care unit.

Table 2 Sedative PK/PD properties

	Elimination half-life	Metabolism	Recommended dose	Advantages	Caveats
Benzodiazepines					
Midazolam	3–4 h	CYP3A4/3A5, glucuronidation of phase I metabolite	IV: Bolus of 0.1–0.2 mg/kg, followed by 0.1–0.6 mg/kg per h CI	Fast-acting	Accumulation in hepatic/renal failure
Lorazepam	10–20 h	Glucuronidation	IV: 0.02–0.1 mg/kg q4–8 h or 0.025 mg/kg per h CI	Metabolism independent of liver and kidney function	Propylene glycol toxicity
Alpha-2-adrenergic receptor agonists					
Clonidine	7–17 h	60% kidney excretion, metabolism by CYP2D6	IV: Bolus of 2 mcg/kg, followed by 0.1–2 mcg/kg per h CI	Preserves respiratory drive and has analgesic properties	Bradycardia and rebound hypertension
Dexmedetomidine	2–4 h	CYP2A6 and glucuronidation	IV: 0.2–2.5 mcg/kg per h CI	Short half-life	Rebound hypertension
Other sedatives					
Propofol	30–60 min	CYP2B6/2C9, glucuronidation	3–15 mg/kg per h	Fast-acting, short half-life	Associated with PRIS at higher doses or prolonged use
Ketamine	2–3 h	CYP3A4/2B6/2A9	IV: Bolus of 1 mg/kg followed by 16 mcg/kg per min (1 mg/kg per h) CI	Preserves respiratory drive and has analgesic properties	Hypertension, raised intracranial pressure
Chloral hydrate	8–35 h (TCE)	Glucuronidation	PO or RC: 25–75 mg/kg q4–6 h	Does not interfere with EEG results	No IV solution available
Barbiturates					
Pentobarbital	15–50 h	Hepatic microsomal enzyme system	IV: 0.5–5 mg/kg per h	Decreases intracranial pressure, profound sedation	Not suitable for haemodynamically unstable patients
Thiopental	6–15 h	Oxidation (CYP2C19) and hydroxylation	IV: Bolus of 4–6 mg/kg followed by 5 mg/kg per h up to a maximum of 10 mg/kg per h	Decreases intracranial pressure, profound sedation	Not suitable for haemodynamically unstable patients

prescribed concentration.[55] This confounder should be taken into account in PK-PD studies, and it should be considered to measure the actual administered infusion concentration.

Not only PK but also PD may be affected by critical illness. An adult study[56] found a significant correlation between disease severity and level of sedation, independent of propofol clearance. It is plausible that this holds also for children.

Pharmacological Agents

Benzodiazepines

Benzodiazepines are the drug class of first choice, often in combination with opioids. An exception must be made, however, for the premature population as a study showed that midazolam was associated with a higher incidence of intraventricular haemorrhage grade III or IV and periventricular leucomalacia compared to morphine.[57] Benzodiazepines have been used for sedation of mechanically ventilated children for many years. The exact mechanism of action is not yet clear, although it is known that all agents from this class share the same site of action. Binding to this site increases the frequency at which the chloride channel is opened by γ-amino butyric acid (GABA), thereby making the neuron more sensitive to GABA. The more chloride is allowed to enter the target neuron, the more it is hyperpolarized, resulting in a decrease in firing rate of this target neuron. This in turn leads to the pharmacological effects of benzodiazepines: sedation, anxiolysis and muscle relaxation.[58] This inhibitory effect of the GABA system is developing during the first weeks of life; therefore, GABAergic agents may be less effective in prematurely born and term born neonates and may even lead to paradoxical reactions such as increased agitation and convulsions.[59]

Midazolam

Midazolam is recommended in UK PICU guidelines as first-choice sedative in most critically ill children. With onset of action occurring within 1–5 min after infusion, its effects last for 30–120 min after a single infusion, and even up to 48 h after one week of continuous infusion.[60] Besides sedation and anxiolysis, midazolam also provides anterograde amnesia, thus minimizing children's recall of unpleasant experiences after a PICU admission.[61] Midazolam is mainly metabolized to the equipotent metabolite 1-OH-midazolam and then glucuronidated to the renally excreted 1-OH-MDZ-glucuronide.

Although a clear PK-PD relationship was not found in a prospective study in 21 PICU patients, effective sedation was achieved within the recommended range.[62] Midazolam dosing can be effectively and simply titrated based on level of sedation. However, as 80% of conjugated 1-OH-midazolam is eliminated renally, accumulation of the metabolites may lead to prolonged sedation in children with renal failure.[63] Furthermore, the sedation strategy for a patient with severe sepsis should take into account that critical illness reduces midazolam clearance independently of serum creatinine levels and could increase sedation depth. Critical illness thus leads to a great variability in midazolam clearance, as was confirmed in a systematic review.[64] It should be clear that this variability greatly affects correct dosing. Ongoing midazolam trials in paediatric long-term sedation or pharmacology are listed in Table 3.

Lorazepam

The longer acting benzodiazepine lorazepam is used much less than midazolam in the PICU but has been included in the Best Pharmaceuticals for Children Act (BPCA) Priority List.[30,65] Its IV formulation contains propylene glycol (PG), which at toxic amounts can lead to lactic acidosis.[43,66] Note should be taken that the PG metabolism is immature in preterm and term neonates.[67,68] It is recommended to carefully monitor the osmol gap.[69] Data on a PK-PD relationship of lorazepam for sedation are lacking. Pharmacokinetics are well-described in children with seizures and status epilepticus[70–72] and a PBPK model underscores the low elimination rate in neonates and the higher elimination rate in children around 2 years of age.[73] Still, a clear evidence-based dosing regimen for critically ill children is not yet available (see Table 3 for ongoing paediatric lorazepam studies).

Alpha-2-adrenergic receptor agonists

If benzodiazepines fail to achieve adequate sedation, adjuncts such as the α2-receptor agonists clonidine and dexmedetomidine can be used, which nevertheless are not labelled for this indication. A2-receptor agonists reduce sympathetic outflow[74] by stimulating presynaptic α2-adrenergic receptors, thereby reducing the noradrenaline release into the synapse. This provides sedation without respiratory depression. Because of its analgesic properties, clonidine is often given as spinal anaesthesia adjunct after surgical procedures.[75] Dexmedetomidine could reduce MV duration and ICU LOS[76] when compared to standard sedation practices, but there is still limited experience with this sedative. In critically ill children, both clonidine and dexmedetomidine exert effects on the cardiovascular system, the latter theoretically to a lesser extent, as this is a more α2-selective agonist. However, both seem to be well-tolerated and the cardiovascular side effects are well-manageable.[77–79]

Table 3 Current trials

Trial register number	Short title	Sedative agent	Type of study	Study population	Comparator (if applicable)	Co-medication
EudraCT 2014-003269-46	PedMicMida	Midazolam	Microdosing PK study	Children on midazolam (0–6 years)	N/A	None
NCT02302391	Morpheus	Midazolam	PK analysis	MV children (1 month–18 years)	N/A	Fentanyl
NCT00109395	Lorazepam sedation for critically ill children	Lorazepam	Double-blind RCT	MV children (0–18 years)	Midazolam	None
NTR5112	PK of lorazepam oral liquid in PICU patients	Midazolam	PK analysis of new oral formulation	Children on benzodiazepine weaning (2 weeks–12 years)	N/A	None
NCT02509273	CloSed	Clonidine	RCT, PK-PD analysis	MV children (0–18 years)	Midazolam	Morphine
NCT02252848	N/A	Clonidine	Phase I trial	Neonates with HIE treated with hypothermia	N/A	None
NCT02249039	N/A	Clonidine	Dose-finding study (phase I–II)	MV infants	N/A	None
NCT01091818	Dexmedetomidine vs midazolam for intensive care sedation of children	Dexmedetomidine	Double-blind RCT	MV children (2–18 years)	Midazolam	None
NCT02296073	The efficacy and the safety of dexmedetomidine sedation on the paediatric intensive unit (PICU) patients	Dexmedetomidine	Open-label RCT	MV children (1–16 years)	Midazolam	Fentanyl
NCT00875550	Study of evaluating safety and efficacy of dexmedetomidine (DEX) in intubated and mechanically ventilated paediatric intensive care unit (PICU) patients	Dexmedetomidine	Double-blind RCT	MV children (1–16 years)	Low dose vs high dose	Fentanyl, morphine, midazolam
NCT02375243	Use of dexmedetomidine in children undergoing cardiac surgery	Dexmedetomidine	Open-label RCT	Children undergoing cardiac surgery (1 month–2 years)	Half-dose co-medication plus DEX vs full-dose co-medication	Midazolam and morphine
ACTRN12615001304527	Cardiac baby SPICE	Dexmedetomidine	Double-blind RCT	Children undergoing cardiac surgery (>6 years)	Midazolam	None
ACTRN12614000225617	Baby SPICE	Dexmedetomidine	Open-label RCT	MV children (0–16 years)	Standard sedation care	None
NCT02529202	Dexmedetomidine pharmacokinetics in neonates during therapeutic hypothermia	Dexmedetomidine	PK analysis	Neonates with HIE treated with hypothermia	N/A	None
NCT01266252	NEODEX	Dexmedetomidine	PK analysis	MV neonates	N/A	None
NCT02544854	Pharmacokinetic/pharmacodynamic model of propofol in children	Propofol	PK-PD analysis	Children (1–12 years) undergoing surgery	N/A	None
NCT01621373	NEOPROP	Propofol	PK-PD analysis	Neonates undergoing INSURE	N/A	None
NCT02040909	NEOPROP2	Propofol	Dose-finding study	Neonates undergoing intubation	N/A	None

Table 3 *Continued*

Trial register number	Short title	Sedative agent	Type of study	Study population	Comparator (if applicable)	Co-medication
ACTRN12611000451909	The pharmacokinetics and pharmacodynamics of propofol infusion in obese children	Propofol	PK-PD analysis	Obese children (5–15 years)	N/A	None
NCT00618397	Pharmacokinetics of low dose ketamine infusion	Ketamine	Phase I trials with PK analysis	MV children (3–18 years)	N/A	None
EudraCT 2008-003293-18	Pharmacokinetics of ketamine in infants	Ketamine	PK analysis	Infants undergoing anaesthesia	N/A	None

An overview of current trials with sedative agents in children. NCT trials are found on www.clinicaltrials.gov, EudraCT trials on www.clinicaltrialsregister.eu, ACTRN trials on www.anzctr.org.au and NTR trials on www.trialregister.nl. PK, pharmacokinetics; MV, mechanically ventilated; RCT, randomized controlled trial; HIE, hypoxic–ischaemic encephalopathy.

Clonidine

Clonidine has a relatively long half-life,[80] and therefore, it is recommended to give a loading dose before a continuous infusion. Only one published trial in children, the SLEEPS study, did use a loading dose[81]; whereas in other trials, a loading dose was not applied.[82–84] This practice could lead to a later onset of action of clonidine.[80]

The SLEEPS study compared clonidine to midazolam and found no significant difference in efficacy. The study was underpowered, however, as recruitment appeared problematic, and true non-inferiority of clonidine therefore was not shown. Genuine PK-PD research has not been performed, but adequate sedation could be reached with a plasma level of 0.9–2.5 ng/ml.[83] PK-PD simulations[80] have shown that this level is reached in the majority of patients receiving 1 mcg/kg per h, but without the use of a bolus dose, it will take up to at least 24 h to reach this level. Dosing recommendations are still not evidence-based, but evidence is gained from an ongoing RCT (the CloSed trial: NCT02509273 on clinicaltrials.gov).

Dexmedetomidine

Dexmedetomidine seems to reduce cardiovascular complications after cardiac surgery.[85] A beneficial effect was found in a meta-analysis[86] of haemodynamic outcomes in children after surgery for congenital heart disease. Three RCTs on dexmedetomidine in children[87–89] showed a decrease in MV duration and an opioid-sparing effect. Many of the children in these trials had bradycardia, but this had no effect on blood pressure. Optimal dosing of dexmedetomidine is unknown. Its clearance is immature during the first 2 years of life, then increases to above adult level when expressed per kg bodyweight and returns to adult levels after 5 years of age.[90] The half-life in preterm neonates is twice that in term neonates.[91] A PK-PD model has been established only for children after cardiac surgery.[92] A target plasma level of 0.6 mcg/l is regarded effective in adults,[93] but a target plasma level for children is unknown. Simulation of doses used in trials based on a pooled population PK analysis[90] estimates the target plasma level to lie between 0.4 and 0.8 mcg/l, but this needs to be confirmed in a larger patient group. Moreover, experience with dexmedetomidine in children is relatively scarce so knowledge on safety is also lacking. Nevertheless, several paediatric studies on dexmedetomidine are underway (see Table 3).

Other sedative agents

Propofol

Propofol is a very rapid-acting and versatile sedative. It is included in the revised priority list of the EMA,[94] for

procedural sedation in the neonatal age group. While often used as sedative in adult ICUs,[95] its long-term use in children is contraindicated as it may lead to a propofol infusion syndrome (PRIS), a metabolic disorder with severe metabolic acidosis, hyperkalaemia, hyperlipidemia, rhabdomyolysis and organ failure, associated with an increased risk of mortality.[60] A fatty acid oxidation disturbance may be the underlying aetiology. Risk factors are doses >4 mg/kg per h with a duration of >48 h, but short-term high doses can be dangerous, too. Other risk factors include a young age, critical illness, high fat and low carbohydrate intake, inborn errors of mitochondrial fatty acid oxidation and concomitant catecholamine infusion or steroid therapy.[96] Wang *et al.*[97] pooled seven paediatric pharmacokinetic studies and evaluated the allometric exponent of 0.75, which is often used to estimate the clearance in individuals of different age. The models gave a clear insight into the PK of propofol in all age groups. Propofol PD is less well-studied. One study found a PK-PD relation[98] with a wide variability in the PD endpoint, for which reason the authors advise dose titration. Four propofol PK-PD trials are being performed (Table 3).

Ketamine

Ketamine is a NMDA receptor-blocking agent, which provides dissociative anaesthesia[99] 'disconnecting' the thalamocortical and limbic systems, that is disconnecting the CNS from outside stimuli.[100] Ketamine preserves the respiratory drive and the blood pressure and is thus suitable for use in haemodynamically unstable patients.[101] It stimulates the release of endogenous catecholamines, producing dose-dependent tachycardia and hypertension. This mechanism is also used in refractory bronchospastic events.[102] Ketamine is contraindicated for patients with a raised intracranial pressure as ketamine may further increase the pressure by intracerebral vasodilation. The blocking of the NMDA receptor may prevent opioid tolerance; therefore, ketamine often serves as an adjunct to sedatives and opioid analgesics, with an opioid-sparing effect.[43,103] Ketamine is available as the racemic mixture of R(−) and S(+) ketamine, but the S(+) enantiomer is twice as potent as racemic ketamine and has fewer side effects.[104] Some European countries have consequently replaced the racemic mixture with S(+) ketamine (esketamine). A PD profile of ketamine has been established in children in an emergency department setting where short-term sedation and analgesia were required for brief painful procedures.[105] The profile shows that a target serum concentration of 1 mg/l provides moderate sedation and that a concentration of 1.5 mg/l provides deep sedation. However, optimal dosing should still be confirmed by a well-designed RCT with adequate long-term sedation as endpoint (for ongoing PK studies, see Table 3).

Chloral hydrate

Chloral hydrate (CH) is a prodrug, rapidly converted by acetaldehyde dehydrogenase to the active metabolite trichloroethanol (TCE), which is either glucuronidated to an inactive metabolite, or oxidized to trichloroacetic acid (TCA) and then excreted by the kidneys.[106] One trial showed better sedation using chloral hydrate with promethazine compared to midazolam intravenously in critically ill children who tolerated nasogastric feeding.[107] However, enteral sedatives are not recommended primarily in this population as the enteral absorption is unpredictable.[108] Plasma levels of CH could be detected after hours in neonates, while in healthy adults, the half-life is very short.[109] A correlation was also found between CH plasma levels and sedation scores, although TCE is the presumed active metabolite. As it is unclear which of the compounds, CH or TCE, provides sedation, pharmacokinetic data are difficult to interpret, and thus, an evidence-based dosing recommendation is lacking.[110] Moreover, neonates may be vulnerable to toxic levels of TCE and TCA because these metabolites have a longer half-life at neonatal age.[111] Chloral hydrate has been associated with a higher incidence of bradycardiac events in prematurely born neonates, which implies that cardiorespiratory monitoring is needed.[112] Future research should be aimed at the efficacy and safety of CH in long-term sedation, preferably by establishing a good PK-PD profile in different age groups. No trials involving CH have been registered yet.

Barbiturates

Pentobarbital

Pentobarbital (pentobarbitone) can provide profound sedation when other first-line therapies fail. Doses are titrated based upon a clear pharmacodynamic endpoint, that is burst suppression on the EEG. However, BIS monitoring, which is easier to perform, could be a valid alternative to EEG monitoring in this indication.[113] BIS monitoring is validated only for children older than 1 year and also has its limitations when used in critical care. For example, BIS is usually recorded on one side of the brain, while asymmetrical intracranial pathology may be present.[114] As the cerebral oxygen demand is reduced, the cerebral blood flow is reduced as well and consequently the intracranial pressure will fall.[115] Pentobarbital is a relatively short-acting barbiturate.[116] It is a very efficient sedative, but has been associated with adverse effects[117] such as hypotension (as it is a direct negative inotrope), oversedation, choreo-athetoid neuromuscular phenomena and withdrawal. The drug may suppress the immune system, which effect could be relevant to critically ill children

with multiple accesses to the blood stream.[118] Its PK and PD have been well-established in adults, but data in children are limited. A population PK study in children after open heart surgery suggested that younger infants would need a relatively higher dose based on body weight due to increased clearance.[92] However, in this study, no link was made to a PD endpoint, so it remains unclear whether dosages should be adapted as there is a clear clinical titration endpoint.

Thiopental

Thiopental (thiopentone) is an ultra-short-acting barbiturate with an onset of action of 20–40 s after intravenous infusion.[119] It is widely used as an anaesthesia induction agent. Like pentobarbital, thiopental is a suitable agent for patients with raised intracranial pressure. PK and PD studies have been rarely performed in children, and most of them date from the 1980s.[120–123] Despite a reported double clearance compared to adults,[121] doses do not need to be doubled.[119] Thiopental dose requirement varies among individuals, and titration to the burst suppression EEG pattern should take place, along with careful therapeutic drug monitoring.[124,125] Effective plasma levels vary between 15 and 35 mg/l (see Table 2 for a proposed dosing strategy).

Discussion

This review shows an increasing interest in research on PICU sedation pharmacotherapy. Still, there is a lack of well-designed studies and consequently many practices are not yet evidence based. This type of research is complicated by different methods of sedation assessment, different pharmacokinetics in different age and weight categories, patient heterogeneity with multiple factors influencing the pharmacokinetics and also by ethical and practical considerations. For ethical reasons, drug studies cannot be performed in healthy children, which implies that illness severity will always be a confounding factor. On the other hand, for PICU practice, we only need information on critically ill children, and there should be always dealt with different severities of illness.

Traditional RCTs come with limitations as well. Results often apply only to a selective study population based on strict inclusion and exclusion criteria for the sake of internal validity. External validity is compromised; however, thus, pragmatic RCTs or cohort studies and well-designed titration studies with an objective and clear PD endpoint should complement classical RCT designs.[126] Moreover, using a classical RCT design with placebo as comparator is unethical in sedation research as then the control group may suffer profound anxiety and agitation. When it comes to safety, children should be followed for decades after drug exposure as long-term effects are important endpoints as well.[127]

PK-PD modelling might overcome several practical issues in paediatric drug research. While in the standard two-stage approach, individual values play a central role in determining PK parameters, and therefore, large patient samples are needed; the nonlinear mixed-effects models (NONMEM) approach provides a Bayesian-based prediction of PK parameters using population data.[128] This approach resulted in a new dosing regimen for morphine in infants[129] with much lower dosing than generally recommended so far, suggesting that neonates have been universally overdosed.

Improvements may also be made in the field of quantifying pharmacodynamics. A study in which the item response theory was applied to the COMFORT scale and the Premature Infant Pain Profile (PIPP) score made clear that the behavioural items corresponded better with pain and discomfort than did the physiological items.[130] A previous study has already made clear that the physiological items in the COMFORT scale have no added value,[10] but the item response theory with its more advanced statistical techniques allows calculating the probability of pain for each item. Thus, when using assessment scales consist of more than one item, it would be worthwhile to collect data on each of the items rather than the total score only.

Another form of *in silico* experiments are PBPK models[73,131] representing a multicompartment model applicable to multiple drugs. Pharmacodynamics can be linked to such models by adding biophase concentrations, but only a few full PBPK-PD models have been developed so far for the administration of midazolam, theophylline, lorazepam and propofol to children.[73,132,133] The validity of these models should be evaluated further. As sedatives act on the CNS, evaluation requires obtaining brain tissue concentrations, which is not possible in routine critical care. Experimental strategies include calculations based on mass balance principles using the net flux of drugs (obtained from arterial and venous concentration differences)[134] or microdialysis.[135] Both strategies are invasive and therefore subject to practical objections and ethical considerations.

Future Perspectives

Apart from optimal dosing strategies, new products may also improve pharmacological sedation management. A promising example is the ultra-rapid-acting benzodiazepine remimazolam,[136] which has a pharmacokinetic profile comparable to that of remifentanil, allowing for fast titration. It has only been studied in adults so far.

Monotherapy with remifentanil was found effective for long-term ICU sedation in adults.[137] In a paediatric study,

remifentanil was as effective as fentanyl for sedation and analgesia and allowed for earlier extubation.[138] However, its use carries the risk of opioid-induced hyperalgesia (OIH) that is a phenomenon seen after opioid administration,[139] notably on account of its short half-life and fast onset of action.[140,141] It has been suggested that ketamine or clonidine as adjuvants could prevent the OIH,[142] but these agents may have unwanted side effects. Gradual remifentanil withdrawal has been suggested as well, but OIH was still observed after cold pressure testing in one study.[143] Moreover, chronic pain may develop after (prolonged) surgery,[144] so more data on these issues are warranted before it is regularly used in children.

In adult intensive care, volatile agents such as sevoflurane, desflurane and isoflurane have a favourable pharmacological profile with short elimination half-lives and low toxicity and could be suitable for long-term sedation.[145] These agents have not been studied in children so far. There is some concern that they may have adverse long-term neurological effects,[146–148] so more conclusive studies on the long-term effects of these agents are needed before efficacy trials may be performed.

Conclusion

A variety of sedatives are used in the paediatric intensive care unit, but evidence and pharmacokinetic data are still scarce. Fortunately, there is an active research scene which yields promising new PK and PD data using new study designs combined with advanced laboratory methods and modelling. However, pharmacology is not the only way that can lead to improved paediatric sedation management. We recommend that future research focuses also on sedation assessment and implementation strategies of protocolized sedation.

Declarations

Conflict of Interest

The authors declared that they do not have any conflict of interest.

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