New Drugs in Pediatric Anesthesia

Anne M. Lynn MD
Seattle Children’s Hospital
University of Washington School of Medicine

There’s nothing like a nice, focused topic to start this meeting. So many drugs, so little time! Given the breadth of possibilities, I feel I should start with an apology if I haven’t chosen a newer drug you wanted discussed.

In focusing on drugs with relevance to pediatric anesthesia practice, I will review current information on three different types of agents, starting with anti-emetics, using aprepitant and dolonosetron as examples, then on a new type of muscle-relaxant reversal agent, suggamadex, and finally an update on recent issues with the sedative agents, propofol and dexmedetomidine. I considered including a review of older agents which may become necessary when manufacturing problems make newer agents unavailable, but didn’t as there will not be sufficient time to explore this issue. My plan is to present fairly basic information – dose, metabolism, efficacy, problems in studies to date, with pediatric information if any is available. The conceptual framework for pharmacologic studies will be presented by Dr. Davidson and the problem with use of drugs not approved for pediatric use will be discussed by Dr. Tobin.

Anti-emetics

One of the incompletely-solved dilemmas in anesthesia is control of postoperative nausea and vomiting. A Pubmed search under nausea/vomiting treatment and pediatric anesthesia lists 247 entries showing this is still an active area of clinical study. Adult studies delineate factors associated with high-risk for postoperative nausea/emesis (PONV) which include patient (female gender, non-smoker, history of PONV or motion sickness), anesthetic (volatile agents, N2O, intraoperative opioids) and surgical (lengthy procedure) factors. Peak incidence in children occurs at puberty with several surgeries considered high-risk: strabismus, tonsillectomy, hreniorraphy, orchidopexy, middle ear procedures. In children risk scores increase with surgeries over 30 minutes, age over 3 y, strabismus surgery and history of PONV from 10% risk with one factor to 70% with four factors.

Many stimuli induce or modify the process of vomiting including input from abdominal viscera via the vagus nerve, vestibular system, the chemoreceptor trigger zone (CTZ) in the area postrema. The nucleus tractus solitarius melds this input. Antiemetics work by blocking receptors for the neurotransmitters in these areas: serotonin 5-HT3, dopamine D2, histamine H1, muscarinic cholinergic and neurokinin NK1. Effectiveness of antiemetics can also be modified by genetic variations in metabolic enzymes like the CYP450 system.
Cholinergic blocking drugs and antihistamines are used less often now due their undesirable side effects like dry mouth and sedation even though they are effective antiemetics. Similarly the dopaminergic blockers (phenothiazines, butyrophenones) also have high incidences of sedation. Many investigators feel low dose droperidol is a very effective and long-lasting antiemetic and side effects are small at low dose (0.625-1.25 mg in adults). Use of droperidol decreased dramatically after the FDA required a “black box” warning of cardiac arrhythmias (torsades de pointe) associated with its use. This remains a controversial issue. Many agents used in anesthesia can affect the QTc interval.

The current gold standard antiemetic is the 5-HT3 blocker ondansetron. The effectiveness of this drug has led to its widespread use in adult and pediatric anesthesia. Its effect is most clearly seen in early phases of PONV. Because it is not universally effective, another agent is commonly added in a multimodal approach. Dexamethasone has been used in this way and reported to help decrease late PONV. Ondansetron has a reported half-life of 3.5-5.5h although its pharmacodynamic effect lasts longer at 9h, felt to reflect the binding affinity of the drug for the 5-HT3 receptor.

A newer “second-generation” 5-HT3 antagonist palonosetron has stronger binding affinity (100x ondansetron) for the receptor than other 5-HT3 agents and a much longer half-life. Clearance in healthy subjects is 2.67 ml/min/kg resulting in an elimination half-life of 40 h. Its effect on QTc interval is less than ondansetron or dolasetron. The minimum effective dose for PONV in adults is 0.075mg based on 2 trials. It was also effective in decreasing late (24-72h) PONV. Studies in children have not been reported yet.

To address the issue of late PONV, use of NK1 antagonists has also been added. Gan reported a randomized, controlled trial of ondansetron 4 mg iv, to oral aprepitant 40 mg or 125 mg preoperatively in 805 patients. Complete responders were similar in all groups but 90-95% of patients treated with aprepitant had no vomiting versus 74% of ondansetron-treated patients in the first 24 h after surgery. The only pediatric report of aprepitant is in 46 adolescent patients receiving chemotherapy where triple therapy with apreptant, dexamethasone and ondansetron versus the latter 2 agents increased complete responses from 5.6% to 35.7%.

Most recently a phase II study of a newer oral NK1 antagonist, casopitant has been found effective used with ondansetron 4mg IV in 702 high-risk females having gynecologic or gallbladder surgery. Complete response at 0-24 h was seen in 58-62% of casopitant/ondansetron-treated women versus 40% in the ondansetron only group.

**Reversal of neuromuscular blockade, sugammadex**

Neuromuscular block using non-depolarizing agents such as rocuronium or vecuronium are an integral part of anesthesia for many major surgeries. Reversal of residual muscle block has been
accomplished with anticholinesterase agents such as neostigmine or less commonly edrophonium. These agents increase acetylcholine concentrations allowing return of neuromuscular function by acetylcholine displacing the muscle blocker but are not successful in the face of profound levels of neuromuscular blockade. They require the concomitant use of antimuscarinic agents (atropine, glycopyrrolate) to block their side effects on the cardiovascular system but these also have undesirable side effects.

Recent studies have focused on a different mechanism to reverse neuromuscular blocks by encapsulating the drug in plasma, making it unavailable to bind to active sites and establishing a concentration gradient to move rocuronium from bound sites at the neuromuscular junction back into plasma.

Suggamadex is a modified gamma-cyclodextrin, designed to specifically encapsulate the aminosteroid, nondepolarizing muscle blocker rocuronium. Its circular structure and side chains completely engulf the rocuronium molecule and render it inactive. The similar structure of vecuronium allows reversal of its blockade as well. Suggamadex is available for use in the EU, Australia, New Zealand and Norway but has not yet been approved for use by the FDA in the US.

Dose ranging studies in adults report reversal from “shallow” block (recovery of 2 twitches in TOF stimulation) within 1-3 minutes after suggamadex 2 mg/kg or after 4mg/kg for reversal of “deep” block (two twitches only after post-tetanic TOF stimulation). Effects on QTc interval were not seen and liver or kidney function was not affected. Pharmacokinetic parameters show linear dose-responses over the range 1-16 mg/kg (iv bolus). Volume of distribution is 18L and suggamadex does not bind to plasma proteins, clearance is 84-138 mL/min with an elimination half-life of 1.8h in healthy adults. Renal excretion is the route of elimination. Suggamadex increases the renal excretion of rocuronium by 2-3-fold. Elimination of suggamadex-rocuronium complexes is decreased in patients with renal impairment but reversal of blockade was not affected and recurrence of block was not seen. Until further information is available, it is not recommended for use in patients with renal dysfunction. Severe liver disease effects on suggamadex handling have not been studied.

Pediatric study has been limited to one investigation to date. Plaud’s study in infants (n=8), children (n=24), adolescents (n=31) and adults (n=28) found time to TOF 0.9 after rocuronium 0.6 mg/kg block and suggamadex 2mg/kg given at shallow block (return of 2 twitches in TOF) was 1-2 minutes in children and adults versus 19-29 minutes with placebo. Only 2 infants received suggamadex >2mg/kg so dosing guidelines in patients under 2y are not available. No serious adverse events related to suggamadex were found.

Adverse effects reported have been mild to moderate with procedural pain, nausea/vomiting and change in taste most common. Recurrence of muscle block was only seen in patients given doses of suggamadex <2mg/kg. In early phase 1 trials, 6 volunteers given high doses (32mg/kg) in one
study and one given 8mg/kg in another study had symptoms consistent with hypersensitivity (skin flushing and rash). Since the exposed population is relatively small (~2000) the extent of this concern is unclear. Two patients with asthma had severe bronchospasm after sugammadex 4mg/kg. If re paralysis is needed within 24 h after use of sugammadex, use of nonsteroidal muscle relaxants like succinylcholine or cisatracurium are recommended. The issue of hypersensitivity reactions appears to be the main factor in the FDA asking for more studies in 2008.

**Propofol problems / Dexmedetomidine update**

Propofol has become ubiquitous in most pediatric centers as an iv anesthetic induction agent and is often used as a major element in total intravenous anesthetics (TIVA). Its rapid onset/offset, usefulness in allowing spontaneous ventilation while decreasing airway irritability have earned it a prime place in pediatric anesthesia despite its high incidence of pain on injection. This became apparent this spring when manufacturing problems at Hospira and TEVA led to a shortage throughout the US. Because many anesthesia practitioners have more exposure to dexmedetomidine (dex) as an alternative sedative than to the older short-acting barbiturates, a review of some recent studies of dexmedetomidine use seemed appropriate.

Shukry recently reported a compilation of studies of dexmedetomidine in non-intubated patients (pediatric and adult). His review emphasizes that when dex is used for airway procedures, topical anesthesia is mandatory for satisfactory conditions. Loading doses ranged from 0.5 to 5 mcg/kg given over 10 min with infusion doses of 0.2 to 10 mcg/kg/hr. Many of his references include pediatric studies, despite this being an off-label use. FDA approval of dex for non-intubated patients occurred in 2008, facilitating randomized controlled studies. Olutoyin et al reported such a prospective, randomized, double-blind study in 109 children having tonsillectomy and adenoidectomy (T&A). Four groups received either dex 0.75 mcg/kg or 1 mcg/kg or morphine 0.05 mg/kg or 0.1 mg/kg at anesthesia induction looking at postoperative rescue morphine, time to first rescue analgesic, sedation (by Ramsay score), vital signs, emergence agitation and discharge readiness. The total postoperative morphine was similar in all groups with the dex 1mcg/kg and morphine 0.1mg/kg groups showing later time for first rescue analgesic and fewer needing >1 dose of rescue drug in PACU. As the authors note, their study may well have been underpowered to show difference in postoperative morphine use. Patel looked at a similar patient population, 122 children having T&A comparing intraoperative dex load and infusion to bolus dose fentanyl during sevoflurane anesthesia. Dex children needed less intraoperative rescue fentanyl (9.8% vs. 36%), as well as less PACU morphine (16.3% vs. 47.5%). Emergence agitation on admit to PACU was less (18% vs. 45.9%) and desaturation to <95% was lower in the dex group. Whether the differences between the 2 studies relate to more dex being given in the Patel study or its use throughout the anesthetic as an infusion will reveal themselves as more research is done.
References

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