Canadian Agency for Drugs and Technologies in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Title: Administration of Intravenous Medications to Pediatric Patients: Guidelines and Safety of Intravenous Push

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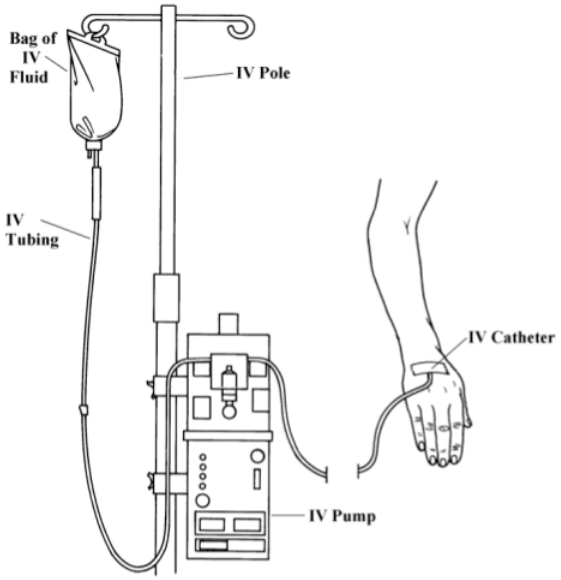
Context and policy issues:

Intravenous (IV) therapy is the delivery of liquid substances directly to a vein. Standard infusion sets are comprised of a pre-filled, sterile container of fluids with an attached drip chamber, and long sterile tubing with a clamp to regulate or stop the flow (Figure 1, Ohio State University Medical Center).[1] The IV tubing may be put through a pump to control how fast the fluid flows into the vein.



Peripheral IV therapy can be given as a bolus injection (IV push), intermittent infusion, or continuous infusion (Table 1).[2] To administer IV push, a syringe is connected to the IV access device and the medication is injected into the fluid stream of the IV tubing. A second fluid injection is often used to flush the tubing and push the medicine into the bloodstream more

quickly. To reduce the risk of fluid overload in pediatric patients, a soluset or buretol (chamber that holds a small volume of fluid) may be used to deliver IV medications. A nurse injects the medication into a soluset, runs it through the IV tubing until the soluset is empty, and flushes to ensure complete delivery of the medication.[3]

Each route of peripheral IV therapy holds potential risks to patient safety ranging from minor complications to death.[2] Infection, phlebitis (irritated vein), infiltration or extravasation (drug leaks to surrounding tissue), and anaphylaxis/anaphylactoid reactions (life-threatening allergic reaction) are common risks associated with all IV routes.[2] While complication rates are difficult to determine due to lack of consistent definitions for complications; infiltration, leaking and occlusion account for 95% of IV device removals.[4] Neonates and very young children are at greater risk of phlebitis, infiltration and extravasation than other patient groups.[2,4,5] The incidence of catheter-related infection is between 0% to 7.5% in neonates.[4] While it is important to reduce risks by ensuring that the right drug be given to the right patient at the right dose, IV push calls for the right flush, at the right speed with appropriate monitoring.[6] The Royal College of Nursing (2003) guidance recommends pulsatile flush to create turbulence inside the catheter lumen to flush adhering substances.[7] The flush rate should be no faster than the medicine that has been administered.[2]

Table 1: Rationale and Risks Associated with Route of IV Therapy

Route	Rationale	Risks
IV push	Quick response needed High blood concentration required Patient is fluid overloaded Medicine is not chemically stable in solution	Anaphylaxis/anaphylactoid reactions Speedshock (systemic reaction when a foreign substance is rapidly introduced) Infiltration or extravasation Phlebitis Infection
Intermittent Infusion	High blood concentration required Patient is fluid overloaded Medicine not chemically stable for continuous route Reduces risk of adverse reactions, for example, bolus antibiotics	Anaphylaxis/anaphylactoid reactions Infiltration or extravasation Phlebitis Fluid overload Medicine error-rate too fast or slow Infection
Continuous Infusion	Constant blood level required Constant effect required	Anaphylaxis/anaphylactoid reactions Infiltration or extravasation Phlebitis Fluid overload (higher rate or larger volume than system can absorb or excrete) Medicine error-rate too fast or slow Incorrect rate-overdose Infection

Health Canada publishes Pediatric Clinical Practice Guidelines for Nurses in Primary Care containing procedures for intravenous access in children aged one to six years.[8] The guidelines cover general restraint, procedures, vascular access sites, needle types complications and intraosseous access but they do not reference IV push.[8] A quality improvement audit showed 33% of 145 neonates admitted to the neonatal intensive care unit receive peripheral IV.[4] Infants underwent a median of 4.6 insertions requiring a median of two attempts during their hospitalization; however, no evidence was found regarding preferred cannulation sites, optimal care techniques or strategies to minimize complications.[4]

In 2005, 1,410 neonates (0 days to 27 days) and 453 infants (1 month to11 months) died in Canada, resulting in a mortality rate of 5.4 per 1,000 live births.[9] No information was provided regarding the number of deaths due to IV push medication errors in infants. Between 1987 and 2003, Health Canada received reports of 425 incidents involving infusion pumps.[10] Twenty deaths and 135 injuries were suspected to have been caused by the pump.[10] The Institute for Safe Medication Practices issued safety alerts highlighting the lack of free-flow protection mechanisms that can result in serious consequences if the user fails to use the manual roller clamp on the infusion line.[11] A national hospital survey conducted in 2003 indicated that several facilities still use pumps without adequate free-flow protections.[11] Based on the reported incidents, Health Canada made recommendations regarding training, free-flow protection, ergonomics, programming safeguards, patient-controlled analgesia, prevention of tampering, and licensing of devices.[10] In 2007, subsequent safety alerts were issued for all IV administration sets indicated for use with the Alaris® Pump module and Gemini™ Infusion Pumps.[12] Further recommendations were made to reinforce the intended use of the roller clamp as the primary means of regulating and preventing flow to the patient upon priming or use outside the pump.[12]

A retrospective analysis of deaths related to medications reported through the United States FDA Adverse Event Reporting System from 1993 to 1998 suggested half of the deaths were due to an injectable drug.[6] Approximately 41% of deaths were due to incorrect doses (overdoses), 16% were due to the wrong drug, and 10% of deaths occurred because the medication was administered via the wrong route.[6] In some cases, the wrong amount of diluent or active ingredient was given or administered at the wrong rate.[6] A study of the incidence and severity of intravenous drug errors conducted in the United Kingdom suggests errors occur in 49% of all IV medications administered.[13] Of these, 73% occurred when giving IV push doses, and in 95% of those cases, the dose was given faster than recommended.[13] IV fluids are the most commonly cited product involved in medication errors reported to the United States Pharmacopeia Medication Errors Report Program.[14] Due to safety concerns, evidence is sought to support the administration of medications IV push to pediatric patients under the age of two years.

Research questions:

1. What is the clinical effectiveness and safety of administering medications IV push versus continuous infusion to pediatric patients under the age of two years?

2. What are the guidelines for administering medications intravenously to pediatric patients under the age of two years?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, Ovid MedLine, The Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and February 2008, and are limited to English language publications only. A filter was applied to the guidelines for administration of IV medications search to limit the retrieval to guidelines but limited hand searching was also conducted. No filters were applied to the clinical effectiveness and safety of administering IV push to pediatric patients search.

Summary of findings:

The literature search yielded a protocol for a systematic review,[15] and an observational study comparing administration of IV medications by continuous infusion versus bolus.[16] The observational study was an open-label case series with historic controls,[16] No clinical practice guidelines, health technology assessments, meta-analyses or randomized controlled trials were identified. Study details are provided in appendix A. Other studies evaluating bolus infusions without comparison with continuous infusion are detailed in appendix B.

Health technology assessments, clinical guidelines, meta-analyses

No health technology assessments, clinical guidelines, meta-analyses, or randomized controlled trials were identified that specifically addressed the safety and efficacy of administering medications IV push to pediatric patients under the age of two years. Identified by hand searching, Canadian Pediatric Clinical Practice Guidelines for Nurses in Primary Care provides guidance on general restraint, procedures, vascular access sites, needle types complications and intraosseous access regarding IV therapy but they do not reference IV push.[8]

Infusion versus Bolus

Systematic reviews

A protocol for a Cochrane systematic review was identified.[15] The primary objective of the review is to determine whether a continuous infusion of indomethacin is as effective as a course of intermittent bolus infusions for symptomatic patent ductus arteriosus closure in preterm infants. Secondary objectives include a review of complications associated with these regimens. Subgroup analyses are planned based on gestational age, birth weight, dose, and method used to diagnose a patent ductus arteriosus (PDA).[15]

Observational studies

The effectiveness of continuous indomethacin infusion versus bolus infusion for patent ductus arteriosus (PDA) closure was evaluated in an open-label case series with historic controls (bolus group) matched for gestational age.[16] Ductal closure rates in 16 preterm infants treated with continuous indomethacin infusion were compared to 16 historic controls that received the same dose by bolus. PDA closed in seven of 16 preterm infants in the continuous indomethacin group and 13 of 16 infants in the bolus group (p=0.033).[16] Two of eight infants weighing less than 1000 g in the continuous group and 10 of 10 infants weighing less than 1000 g in the bolus group demonstrated closure (p=0.002).[16] Continuous infusion was more likely to be associated with closure failure than bolus injection (OR: 19; 95% CI 1.5, 247; p=0.023).[16] All PDA closure failures in the continuous group occurred when glucose 5%, not NaCl 0.9%, was used to dissolve the indomethacin, which may confound the results. Side effects were similar in both groups.[16] A larger number of infants in the bolus group produced less urine than those in the continuous group (5 of 16 versus 1 of 16), but this was not significant.[16] Necrotizing enterocolitis (stage II-A) occurred in three infants that received continuous infusions.[16] The authors concluded that continuous infusions of indomethacin may be less effective in closing PDA than bolus infusions, especially in low birth weight infants.[16] Confounding factors may have affected the ductal closure rates in this case-control study. Small differences between groups may be significant enough to make clinical differences to this small study. Historical controls are also a limitation as changes in treatment other than the method of indomethacin administration may have occurred over time.

Limitations

The open-label case series study demonstrating continuous indomethacin infusion is less effective in closing PDA than bolus infusion is limited by small study size, confounding factors, and the use of historical controls.[16]

Conclusions and implications for decision or policy making:

No health technology assessments, clinical guidelines, meta-analyses or randomized controlled trials were identified that specifically addressed the safety and efficacy of administering medications IV push to pediatric patients under the age of two. The Canadian Pediatric Clinical Practice Guidelines for Nurses in Primary Care provides guidance on general restraint, procedures, vascular access sites, needle types complications and intraosseous access regarding IV therapy but it does not reference IV push.[8] A single open-label case series study suggests bolus injection is more effective at PDA closure than continuous indomethacin infusion.[16] However, results of this study are limited by small study size, confounding factors and historical controls. There is no compelling evidence to support the administration of IV medications by bolus compared to continuous infusion, at this time.

While deaths and injuries have been suspected with use of infusion pumps, several facilities still use pumps without adequate free-flow protections.[11] Based on the reported incidents, Health Canada made recommendations regarding training, free-flow protection, ergonomics, programming safeguards, patient-controlled analgesia, prevention of tampering, and licensing of devices improve pump safety.[10]

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Appendix A: Clinical Effectiveness and Safety of Administering Medications IV Push to Pediatric Patients

Author, Year, Country	Study Design	Participants	Intervention versus Comparator	Outcomes	Results	Conclusions and Limitations
Clinical Effectiveness						
Observational Studies						
De Vries et al. 2005 The Netherlands[16]	Observational Open-label Case series Retrospective control (bolus) Study period: Continuous: December 2001-June 2002 Bolus: November 2000-December 2001	N=32 preterm infants with PDA by echocardio-graphy n=16 continuous n=16 bolus historic controls Males: 18 Females: 14 Median gestational age (continuous): 27.3 (25.4, 29.6) weeks	Continuous indomethacin infusion: 0.5 mL/h over 36 hours versus bolus indomethacin infused over 3-5 minutes	PDA closure based on echocardio-graphy 36 hours after indomethacin	Closure rates were 7 of 16 (continuous) versus 13 of 16 bolus (p=0.033)[16] Of those weighing < 1000 g, 2 of 8 continuous and 10 of 10 bolus recipients showed closure (p=0.002).[16] Continuous infusion was more likely associated with closure failure than bolus (OR: 19; 95% CI 1.5, 247; p=0.023).[16] More infants produced less urine in the bolus group compared to the continuous group (5 of 16 versus 1 of 16), but this was not significant.[16] Necrotizing enterocolitis (stage II-A) occurred in three infants that received continuous infusions.[16]	The authors concluded that continuous infusions of indomethacin may be less effective in closing PDA than bolus infusions, especially in low birth weight infants.[16] All PDA closure failures in the continuous group occurred when glucose 5%, not NaCl 0.9%, was used to dissolve the indomethacin.

Author, Year, Country	Study Design	Participants	Intervention versus Comparator	Outcomes	Results	Conclusions and Limitations
		Median gestational age (bolus): 27.2 (25.7, 29.3) weeks Dose: by age, amount by weight based on infusion rate of 0.5 mL/h during 36 hours Bolus: infused in 3-5 minutes Sampling: controls were sampled consecutively retrograde				Confounding factors may affect the ductal closure rates in this case-control study. Small differences between groups may be significant enough to make clinical differences to this small study. Historical controls are also a limitation as changes in treatment other than the type of indomethacin may have occurred over time.

Appendix B: Clinical Effectiveness and Safety of Administering IV Medications Bolus

Systematic reviews

A systematic review was conducted to assess the benefit of administering an IV bolus of albumin or normal saline to normovolaemic neonates with metabolic acidosis.[17] While study methods provided information about the literature search, selection criteria, and outcome measures for the systematic review, no detail was given regarding the number of reviewers that selected studies, extracted data or assessed quality. An unblinded, RCT and a non-randomized, retrospective cohort study were included in the review. While both studies reported improvements in the pH and base deficit with volume expansion as outcome measures, neither included survival, morbidity, length of hospital stay or neurodevelopment disability. The authors concluded that there was insufficient evidence to support the benefit of administering an IV bolus of albumin or normal saline to normovolaemic neonates with metabolic acidosis.[17]

Randomized controlled trials

Between 1999 and 2001, a randomized, double-blind study was conducted in five district hospitals in the North West Thames region of the United Kingdom to determine the relative efficacies of aminophylline and salbutamol in severe acute childhood asthma.[18] Forty four children aged one to 16 years were randomized to receive a short IV bolus of salbutamol (15 µg/kg over 20 minutes) followed by a saline infusion or an aminophylline infusion (5 mg/kg over 20 minutes) followed by an infusion of 0.9 mg/kg/hr. An intent to treat analysis showed no significant difference in asthma severity scores between groups two hours after dosing [median (inter quartile range); 6 (6,8) versus 6.5 (5, 8) for salbutamol and aminophylline, respectively, p=0.93)].[18] A similar improvement in asthma severity scores was observed in the two groups [mean difference of -0.08, 95% CI -0.97, 0.80].[18] There was a trend towards a longer duration of oxygen therapy in the salbutamol group compared to the aminophylline group (17.8 hours [95% CI 8.5, 37.5] versus 7 hours [95% CI 3.4, 14.2]; p=0.07). A significantly longer length of hospital stay was observed in salbutamol recipients compared to aminophylline recipients (85.4 [95% CI 66.1, 110.2] hours versus 57.3 hours [95% CI 45.6, 72.0]; p=0.02). No significant difference in the number of adverse events was noted in salbutamol and aminophylline groups (22.2% versus 36%; p=0.5). The most frequent adverse events were nausea, vomiting, and abdominal pain. The authors suggested that there was no significant difference in the effectiveness of a bolus of salbutamol and an aminophylline infusion in the first two hours of treatment; however, aminophylline infusion significantly reduced the length of hospital stay.[18] This study is limited by small study design, imbalanced allocation between groups, and large range in age compared to the population of interest.[18]

Observational studies

The pharmacokinetics of propofol have been studied in adults and pediatric patients but administration of propofol is off-label in neonates.[19] The variability in propofol pharmacokinetics in preterm and term neonates was evaluated in an observational study involving 25 neonates receiving an IV bolus of propofol (3 mg/kg over 10 seconds).[19] Median weight was 2930 (range 680 to 4030) grams, postmenstrual age was 38 (27 to 43) weeks, and postnatal age was 8 (1 to 25) days. Based on 235 arterial concentration time points collected in 25 neonates up to 24 hours after bolus, propofol clearance at 38 weeks (post menstrual age) was 0.029 L/minute.[19] The authors concluded that post menstrual age and post natal age contribute to the inter-individual variability of propofol clearance, suggesting preterm neonates and those in the first week of postnatal life are at risk of an increased risk for accumulation during intermittent bolus

or continuous administration of propofol.[19] This study is limited by study design and small sample size. Results may not be generalizable to the Canadian population as this study was set in Belgium.

Propofol pharmacokinetics in preterm and term neonates following a single IV bolus were compared to that of toddlers and young children in another observational study.[20] Prospectively collected observations following administration of IV bolus propofol in 9 preterm and full-term(?) neonates (aged 4 to 25 days) were compared to previously reported pharmacokinetic estimates in 22 children (aged 1 to 7 years).[20] Median weight was 2.51 (range 0.9 to 3.8) kg and postmenstrual age was 36 (27 to 43) weeks in the neonates. Median clearance was 13.6 (range 3.7 to 78.2) ml/minute/kg.[20] Compared to previously reported observations in toddlers and children [43 (35-74) mL/minute/kg in one study; 28.2 (21.5-44.4) mL/minute/kg another study], median clearance was significantly lower in neonates ($p<0.01$).[20] The authors conclude that propofol disposition was significantly different in neonates compared to toddlers and young children, reflecting development and differences in body composition. Based on the reduced clearance of propofol, longer recovery time is expected for neonates.[20] This study is limited by design and small sample size. Results may not be generalizable to the Canadian population as this study was set in Belgium.

An observational study was conducted to determine the pharmacokinetic profile of a single bolus of propofol in 35 Chinese children (aged 4 months to 9 years).[21] Arterial blood samples were collected at 12 time points following a single bolus IV injection of 3 mg/kg propofol.[21] Plasma concentrations were measured using high-performance liquid chromatography and a population model was used to estimate the pharmacokinetics. Clearance was 0.185 L/minute for a child with an average weight of 13.7 kg. No significant age effect could be demonstrated on clearance or volume of distribution parameters after weight was accounted for.[21] The authors concluded that the pharmacokinetic properties of propofol do not differ substantially across Chinese children of different ages after weight was taken into account.[21] Generalizability of these findings to the Canadian context is limited by study design, small sample size, few patient characteristics and uncertainty as to how patients were sampled.

The pharmacokinetics of oxycodone were evaluated in an observational study involving 22 infants (aged 0 to 6 months).[22] Infants undergoing surgery were given a post-operative IV bolus of 0.1 mg/kg oxycodone hydrochloride. Patients were grouped by age. Group one comprised 10 patients under 1 week old, group two comprised six patients aged 1 week to 2 months, and group three consisted of six patients aged 2 to 6 months. Plasma samples were collected for analysis up to 24 hours post injection. The median (range) values for clearance were 9.9 (2.3-17.2), 20.1 (3.7-40.4), and 15.4 (14.8-80.2) mL/minute/kg, respectively by group.[22] Clearance and half-life were correlated by age ($p<0.05$), with clearance time and half-life being prolonged in younger infants.[22] Thirteen patients were on mechanical ventilation at the time of oxycodone administration; spontaneously breathing infants did not hypoventilate or need assistance.[22] The authors concluded that routine dosing of oxycodone in young infants is dangerous and oxycodone should be titrated individually.[22] Small sample size and the use of other medications may limit generalizability of results.

The effects of terlipressin treatment in four paediatric patients (aged 4 months, 2, 3, and 6 years) with catecholamine-resistant hypotensive septic shock were reported as case reports in a pediatric unit of a university hospital.[23] In each case, teripressin was added to standard treatment, by IV bolus at a dose of 0.02 mg/kg every 4 hours during a maximum of 3 days with the aim of achieving mean arterial pressure within normal limits for age.[23] Terlipressin

administration was maintained at least 48 hours and was prolonged up to 72 hours in cases where norepinephrine was still needed. In all four cases, terlipressin induced rapid, sustained improvement in mean arterial pressure allowing lessening or withdrawal of norepinephrine infusion.[23] No adverse effects were detected. The authors concluded that terlipressin may be considered as a rescue therapy for hypotension resistant to catecholamines in children with septic shock.[23] Generalizability is limited due to study design, small number of case reports and indication.

Limitations

While the first RCT regarding suggested the efficacies of aminophylline and salbutamol in severe acute childhood asthma were equivalent two hours post dosing, findings are limited by small study design, imbalanced allocation between groups, and large range in ages compared to population of interest.[18] The population pharmacokinetic study suggests propofol clearance at 38 weeks post menstrual age is 0.029 L/minute; however, small sample size and geographic location limit the generalizability of these results to a Canadian setting.[19] A subsequent population pharmacokinetic study suggested a median clearance of 13.6(range 3.7 to 78.2) mL/minute/kg in neonates with reduced clearance compared to toddlers and children.[20] However, results of this study are limited by design, small sample size and generalizability within the Canadian context. While a Chinese observational study showed clearance of propofol was 0.185 mL/minute for a child of 13.7 kg, and this did not differ by age as weight was accounted for, results are limited by study design, sample size and generalizability to a Canadian setting.[21] A prospective observational study suggests oxycodone be individually titrated for infants; however, generalizability of these results is limited based on small sample size and other medications administered.[22] Four case reports suggest that an IV bolus of terlipressin may be considered as a rescue therapy for hypotension resistant to catecholamines in children with septic shock.[23] Generalizability of these findings is limited due to study design, small number of case reports and indication.

Appendix B: Characteristics of Bolus only Studies

Author, Year, Country	Study Design	Participants	Intervention vs. Comparator	Outcomes	Results	Conclusions and Limitations
Clinical Effectiveness						
Roberts et al. 2003 United Kingdom[18]	RCT Multi-centre Study period: 1999-2001 Follow-up: 2 hours Intent to treat analysis Study numbers assigned by random number table.	N=44 patients aged -16 years with acute asthma n=18 (salbutamol) n=26 (aminophylline) Males: 32 Females: 12 Median age (salbutamol): 3.85 [1.32, 15.55] Median age (aminophylline): 4.12 [1.19, 13.13]	Intervention: single bolus IV salbutamol (15 µg/kg over 20 minutes) followed by an infusion of saline Comparator: continuous aminophylline infusion (bolus of 5 mg/kg over 20 minutes followed by an infusion of 0.9 mg/kg/hr)	Primary end point: asthma severity score (ASS); saturation levels, adverse effects Outcome measures were validated. Outcome assessors were blinded to treatment allocation. The mean difference between scores assigned by each observer was 0.1 (-1 to +1)	No significant difference in ASS was observed between groups 2 hours after dosing [median (inter quartile range); 6 (6,8) versus 6.5 (5, 8) for salbutamol and aminophylline, respectively, p=0.93)].[18] A similar improvement in ASS was observed in the two groups [mean difference of -0.08, 95% CI -0.97, 0.80].[18] A trend towards a longer duration of oxygen therapy was observed in the salbutamol group (17.8 hours [95% CI 8.5, 37.5] versus 7 hours [95% CI 3.4, 14.2]; p=0.07).[18] Longer hospital stay was observed in salbutamol recipients (85.4 [95% CI 66.1, 110.2] hours versus 57.3 hours [95% CI 45.6, 72.0]; p=0.02).[18] No significant difference in adverse events was noted between salbutamol versus aminophylline recipients (22.2% versus 36%).[18]	The authors concluded there is no significant difference in the effectiveness of bolus IV salbutamol versus an aminophylline infusion in the first 2 hours of treatment. Aminophylline infusion significantly reduced length of hospital stay.[18] Three early withdrawals, one from aminophylline group refused a cannula and 2 from salbutamol group were given additional treatment. Findings are limited by small study design, imbalanced allocation between groups and large range in age compared to population of interest.

Author, Year, Country	Study Design	Participants	Intervention vs. Comparator	Outcomes	Results	Conclusions and Limitations
Observational Studies						
Allegaert et al.2007 Belgium[19]	Observational Prospective Case series Study period: 2001-2003	N= 25 neonates undergoing elective chest tube removal (n=15) semi-elective chest tube placement (n=2) or endotracheal intubation (n=8). Male: 21 Female: 4 Median postmenstrual age: 38 (27-43) weeks Median postnatal age: 8 (1-25) days Median weight: 293 (680-4030) grams Sampling: neonatologist decided on propofol use, considered for inclusion if an arterial line was available to enable sequential collection of blood samples	Propofol bolus 3 mg/kg over 10 seconds	Blood samples collected by arterial line 1, 5, 15, 30, 60, 90 minutes, and 2, 4, 8, 12, and 24 hours post propofol bolus	Propofol clearance at 38 weeks (postmenstrual age) was 0.029 L/minute.[19]	The authors concluded that postmenstrual age and post natal age contribute to the inter-individual variability of propofol clearance. Preterm neonates and those in the first week of postnatal life are at risk of an increased risk for accumulation during intermittent bolus or continuous administration of propofol.[19] This study is limited by study design and small sample size. Results may not be generalizable to the Canadian population.

Author, Year, Country	Study Design	Participants	Intervention vs. Comparator	Outcomes	Results	Conclusions and Limitations
Allegaert et al. 2007 Belgium[20]	Observational Prospective (neonates) Retrospective (toddlers, children) Study period: NR	N=31 N= 9 neonates undergoing elective chest tube removal, semi-elective chest tube placement, or endotracheal intubation. N=22 children from two previously reported studies Males: NR Females: NR Neonate median postmenstrual age: 36 (27-43) weeks Neonate median weight: 2.51 (0.91-3.8) kg Sampling: considered for inclusion if an arterial line was available to enable sequential collection of blood samples	Propofol bolus 3 mg/kg over 10 seconds	Blood samples collected by arterial line 1, 5, 15, 30, 60, 90 minutes, and 2, 4, 8, 12, and 24 hours post propofol bolus	Median clearance was 13.6 (range 3.7 to 78.2) ml/minute/kg.[20] Compared to previously reported observations in toddlers and children [43 (35-74) mL/minute/kg in one study; 28.2 (21.5-44.4) mL/minute/kg in another study], median clearance was significantly lower in neonates ($p<0.01$).[20]	The authors concluded that propofol disposition is significantly different in neonates compared to toddlers and young children, reflecting ontogeny and differences in body composition. Based on reduced clearance of propofol, longer recovery time is expected for neonates.[20] This study is limited by study design and small sample size. Results may not be generalizable to the Canadian population

Author, Year, Country	Study Design	Participants	Intervention vs. Comparator	Outcomes	Results	Conclusions and Limitations
ShangGuan et al. 2006 China[21]	Prospective Observational Study period: February-September 2002	N=35 children undergoing general or urinary surgery for congenital megacolon, urinary tract defects, or undescended testis Males: 33 Females: 2 Age range: 4 months-9 years Sampling: NR	3.0-5 µg/kg fentanyl and 3.0 mg/kg propofol within 20 seconds, and 0.1 mg/kg vecuronium; additional bolus muscle relaxant as per clinical judgment	Arterial blood samples at 2, 4, 5, 6, 8, 10, 20, 30, 45, 60, 90, 120 and 180 minutes after a bolus propofol	Clearance was 0.185 L/minute for a child with an average weight of 13.7 kg. No significant age effect could be demonstrated on clearance or volume of distribution parameters after weight was accounted for.[21]	The authors concluded that the pharmacokinetic properties of propofol do not differ substantially across Chinese children of different ages after weight has been taken into account.[21] Small sample size, few patient characteristics. Uncertain how patients were sampled.
Marja-Leena et al. 2005 Finland[22]	Prospective Observational Study period: NR	N=22 infants undergoing surgery n=10 aged <1 week n=6 aged 1 week to 2 months n=6 aged 2-6 months Males: NR Females: NR 9 patients on mechanical ventilation Sampling: NR	Post operative IV bolus of 0.1 mg/kg oxycodone over 1 minute; further analgesia as clinically indicated, with IV morphine 0.1 mg/kg or paracetamol	Arterial and venous blood samples 10 minutes before injection and 2, 10, 30, 60, 120, 180, 240, 360, 480, 600, 720, 1080, and 1440 post injection	The median (range) values for clearance were 9.9 (2.3-17.2), 20.1 (3.7-40.4), and 15.4 (14.8-80.2) mL/minute/kg, respectively by group.[22] Clearance and half-life were correlated by age ($p<0.05$).[22]	The authors concluded that routine dosing of oxycodone in young infants is dangerous and oxycodone should be titrated individually.[22] Small sample size and the use of other medications may limit generalizability of results.

Author, Year, Country	Study Design	Participants	Intervention vs. Comparator	Outcomes	Results	Conclusions and Limitations
Rodriguez-Nunez et al. 2004 Spain[23]	Observational Case reports Study period: NR	n=4 patients with catecholamine-resistant septic shock Males: 4 Females: 0 Aged 4 months, 2, 3, and 6 years	IV bolus terlipressin at a dose of 0.02 mg/kg every 4 hours during a maximum of 3; maintained at least 48 hours up to 72 hours where norepinephrine was still needed.[23].	Mean arterial pressure	In all four cases, terlipressin induced rapid, sustained improvement in mean arterial pressure allowing lessening or withdrawal of norepinephrine infusion. No adverse effects were detected.[23]	The authors concluded that terlipressin may be considered as a rescue therapy for hypotension resistant to catecholamines in children with septic shock.[23] Generalizability is limited due to study design, small number of case reports and indication.

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