Neuraxial drugs provide robust pain control, have the potential to improve outcomes, and are an important component of the perioperative care of children. Opioids or clonidine improves analgesia when added to perioperative epidural infusions; analgesia is significantly prolonged by the addition of clonidine, ketamine, neostigmine, or tramadol to single-shot caudal injections of local anesthetic; and neonatal intrathecal anesthesia/analgesia is increasing in some centers. However, it is difficult to determine the relative risk-benefit of different techniques and drugs without detailed and sensitive data related to analgesia requirements, side effects, and follow-up. Current data related to benefits and complications in neonates and infants are summarized, but variability in current neuraxial drug use reflects the relative lack of high-quality evidence. Recent preclinical reports of adverse effects of general anesthetics on the developing brain have increased awareness of the potential benefit of neuraxial anesthesia/analgesia to avoid or reduce general anesthetic dose requirements. However, the developing spinal cord is also vulnerable to drug-related toxicity, and although there are well-established preclinical models and criteria for assessing spinal cord toxicity in adult animals, until recently there had been no systematic evaluation during early life.

Therefore, in the second half of this review, we present preclinical data evaluating age-dependent changes in the pharmacodynamic response to different spinal analgesics, and recent studies evaluating spinal toxicity in specific developmental models. Finally, we advocate use of neuraxial drugs with the widest demonstrable safety margin and suggest minimum standards for preclinical evaluation before adoption of new analgesics or preparations into routine clinical practice. (Anesth Analg 2012;115:638–62)

The consequences of inadequate regulation of pain were made evident by early clinical studies showing that anesthesia and analgesia reduced morbidity and mortality after cardiac surgery in the newborn.1,2 As well as deleterious acute physiological consequences, there is an evolving literature indicating that neonatal surgery and/or intensive care can result in prolonged changes in sensory processing3–6 and altered responses to future pain.7–9 Although adequate intraoperative anesthesia and analgesia in the newborn, as in the adult, can be achieved by inhalants and IV drugs, there has long been an appreciation of the benefits of neuraxial analgesics and anesthetic techniques and drugs without detailed and sensitive data related to analgesia requirements, side effects, and follow-up. Current data related to benefits and complications in neonates and infants are summarized, but variability in current neuraxial drug use reflects the relative lack of high-quality evidence. Recent preclinical reports of adverse effects of general anesthetics on the developing brain have increased awareness of the potential benefit of neuraxial anesthesia/analgesia to avoid or reduce general anesthetic dose requirements. However, the developing spinal cord is also vulnerable to drug-related toxicity, and although there are well-established preclinical models and criteria for assessing spinal cord toxicity in adult animals, until recently there had been no systematic evaluation during early life. Therefore, in the second half of this review, we present preclinical data evaluating age-dependent changes in the pharmacodynamic response to different spinal analgesics, and recent studies evaluating spinal toxicity in specific developmental models. Finally, we advocate use of neuraxial drugs with the widest demonstrable safety margin and suggest minimum standards for preclinical evaluation before adoption of new analgesics or preparations into routine clinical practice. (Anesth Analg 2012;115:638–62)

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Accepted for publication May 10, 2012.

Supported by Royal College of Anaesthetists/British Journal of Anaesthesia Project grant and Great Ormond Street Hospital Children’s Charity (SMW) and NIDA 15353 (TLY).

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0b013e31826253f2

CME

Neuraxial Analgesia in Neonates and Infants: A Review of Clinical and Preclinical Strategies for the Development of Safety and Efficacy Data

Suellen M. Walker, MBBS, PhD, FANZCA, FFPMANZCA,* and Tony L. Yaksh, PhD†
infants; (2) highlight current difficulties in evaluating the comparative benefit and potential risk of different spinal analgesic drugs; (3) summarize preclinical models evaluating developmental changes in the pharmacodynamic response to spinal analgesic drugs; and (4) review minimal standards for implementation of spinal drugs in neonates to permit informed assessment between different drugs in terms of efficacy and toxicity in the neonate. The review will consider drugs that block conduction (i.e., local anesthetics), but will focus on those that specifically attenuate the spinal processing of pain information when administered by the intrathecal or epidural/caudal route (i.e., spinal analgesics, also often termed “spinal adjuvants”).

1. CLINICAL USE OF NEURAXIAL ANALGESIA AND ANESTHESIA IN NEONATES AND INFANTS

Neuraxial Delivery
The control of afferent traffic through neuraxial interventions (epidural or intrathecal delivery) can be used in neonates and infants as (i) a sole neuraxial anesthetic technique for abdominal and lower limb surgery, or (ii) as a supplement to reduce intraoperative general anesthetic requirements and manage perioperative pain.

Intrathecal delivery of local anesthetic produces “spinal anesthesia. Use of neonatal spinal anesthesia is increasing in some centers, with large series reporting safe and effective anesthesia and analgesia, including use in high-risk and extremely low birth weight neonates. "Single-shot" spinal anesthesia provides an alternative to general anesthesia for lower abdominal or inguinal surgery; however, the clinical utility of this technique is limited by the duration of action of intrathecal local anesthetics in neonates, and conversion to general anesthesia is often required if surgical duration exceeds 1 hour.

Various techniques have been used in infants and neonates to prolong the duration of intrathecal anesthesia including the following: (i) repeat administration via an intrathecal catheter; (ii) a combined spinal and epidural catheter technique for upper abdominal surgery; (iii) additional local anesthetic administration by the surgeon during myelomeningocele surgery; and (iv) addition of spinal anesthetic adjuvants such as opioids or clonidine.

Epidual analgesia can also be used as a sole technique or as a supplement to general anesthesia for perioperative analgesia for neonatal and infant surgery. Single bolus administration, or infusion via a catheter advanced from the caudal space or inserted at an intervertebral level in the thoracic or lumbar spine, is possible in even the smallest preterm neonate. A range of spinal analgesics are now administered, often in conjunction with local anesthetics, with the aim of (i) improving analgesia, (ii) reducing local anesthetic requirements and associated side effects such as motor block, and (iii) prolonging analgesia after single-shot administration.

Epidemiology
Neuraxial analgesia is used in children of all ages, but the pattern of use and choice of technique varies with age of the child, across institutions, and with time in some centers. In a 1994 survey of regional anesthesia by the French-Language Society of Pediatric Anesthesiologists, neonates comprised 3.3% of the pediatric population, but received 3.4% of caudals, 1.8% of epidurals, and 10.9% of all spinal anesthetics. A similar survey in 2006 found a decrease in the use of caudals, but increased use of epidural catheters and single-shot spinal anesthetics, and a larger proportion of central blocks were being performed at younger ages (5.6% vs 3.4% in neonates; 30% vs 16.5% in infants younger than 6 months). In one French center, the overall proportion of neuraxial blocks decreased from 1989 to 2005, but spinal analgesics in neonates had become the most frequent technique, comprising 30% of the total. The number of epidurals performed annually in children in the United Kingdom (UK) was stable from 2002 to 2005, with 5% of the total 10,633 epidurals performed in neonates and 16% in children aged between 1 month and 1 year.

2. CLINICAL BENEFITS AND RISKS OF NEURAXIAL ANALGESIA

Potential Advantages of Neuraxial Route in Neonates and Infants
In addition to minimizing the potential exposure of the developing brain to general anesthetics, neuraxial analgesia may improve postoperative outcomes for high-risk neonates who are susceptible to respiratory complications (e.g., preterm-born neonates with lung disease and postoperative apnea) or who require major surgery for correction of congenital anomalies. However, the magnitude of benefit of intraoperative or perioperative neuraxial anesthesia is difficult to determine from case reports or series. Even in older children undergoing scoliosis surgery, meta-analysis demonstrated improved analgesia with epidural local anesthetic and opioid versus systemic opioid and sedatives. In younger children, variability in study design (type of surgery; neuraxial anesthesia regimes with local anesthetic in varying concentrations and doses and different types and doses of spinal analgesic) makes systematic analysis of outcomes even more difficult. Reported benefits of neuraxial anesthesia in studies that include neonates and infants are:

Reduction in Respiratory Complications
(i) Postoperative apnea.
Analysis of four trials comparing spinal and general anesthesia in neonates born preterm undergoing inguinal herniorrhaphy found a reduction in the incidence of postoperative apnea only if systemic sedatives were avoided. Neuromuscular block and spinal injections of opioids may have added advantages in neonates with central hypotension which may be associated with respiratory depression. It has been suggested that spinal anesthesia can reduce costs related to postoperative monitoring and hospitalization.

(ii) Postoperative mechanical ventilation.
In a randomized trial of infants undergoing cardiac surgery, caudal morphine and local anesthetic provided some analgesic benefits over systemic morphine, but the study had insufficient power to evaluate effects on early tracheal extubation. In case series comparing perioperative neuraxial anesthesia with systemic opioid analgesia, the proportion of neonates requiring postoperative mechanical ventilation was reduced.
after gastrochisis repair,\textsuperscript{38} lung resection for congenital lung lesions,\textsuperscript{46} and Nissen fundoplication.\textsuperscript{47} Cases of improved respiratory function after major neonatal thoracic surgery with epidural analgesia have been reported.\textsuperscript{46,49}

### Attenuation of Stress Response
Circulating levels of stress hormones such as cortisol,\textsuperscript{50,51} adrenaline and noradrenaline\textsuperscript{25,52} are reduced when supplementary neuraxial anesthesia is added to general anesthesia.

### Cardiac Stability
Maintenance of cardiovascular stability has been demonstrated during neuraxial techniques in neonates,\textsuperscript{53} including combined spinal and epidural anesthesia for upper abdominal surgery,\textsuperscript{24} and in high-risk neonates and infants with congenital cardiac disease.\textsuperscript{54} While these observations support the safety of the technique, improved outcomes in comparisons with general anesthesia have not been confirmed.

### Reduction in Hospital Stay
In uncontrolled trials, epidural rather than systemic analgesia reduced hospital stay after ligation of patent ductus arteriosus in infants\textsuperscript{55} and fundoplication.\textsuperscript{47}

### Improved Surgical Outcome
Wound dehiscence after bladder exstrophy repair in neonates was avoided with prolonged neuraxial anesthesia (mean 15 days) and sedation, but there was no comparison with other analgesic techniques.\textsuperscript{37}

### Potential Disadvantages of Neuraxial Route in Neonates and Infants
#### Complication Rates
Although severe complications after pediatric neuraxial techniques are rare, the incidence is higher in neonates and infants: 0.4% vs 0.1% for all neuraxial blocks\textsuperscript{27} and 1.1% vs 0.49% for epidural blocks alone.\textsuperscript{35} Outcomes may be worse in neonates,\textsuperscript{36,37} with complication rates as high as 4:1000 (including 3 deaths)\textsuperscript{56} initially reported, but more recent surveys report complication rates of 0.29% (95% confidence interval [CI]: 0.21%–0.43%) for central blocks (caudal, epidural, and spinal; \( n = 10,556 \)).\textsuperscript{17} After peripherepidural infusions (\( n = 10,633 \)), the rate of serious incidents approximated 0.5:1000, with an additional 0.75:1000 incidents graded as moderate severity.\textsuperscript{35}

The clinical practice setting, resource availability, and experience of individual practitioners can have a major impact on the relative risk and benefit of neuraxial anesthesia. The lack of intensive care facilities in some practice settings will increase the potential benefit of neuraxial techniques that reduce the requirement for postoperative mechanical ventilation. Management by experienced practitioners may minimize the incidence and severity of adverse events in neonates, because skilled intraoperative resuscitation was required after dural puncture or intravascular injection.\textsuperscript{34} Complications related to the use of wrong equipment (e.g., inappropriate or oversized needles, excessive length of catheter introduced into space) were reported in early series.\textsuperscript{34} Pump programming or prescription errors were more common in young children (0.3% in children younger than 1 year versus 0.07% in 1- to 8-year-olds).\textsuperscript{35} All were corrected before harm occurred, but this emphasizes the need for adequate monitoring and follow-up of patients with epidural infusions.

### Infection
Asymptomatic colonization of epidural catheters is common (35%) but in series of 210 children\textsuperscript{58} or 1458 children,\textsuperscript{59} no local or systemic infections were reported. Age was not a clear factor, although the rate of colonization was higher for caudal than lumbar catheters in the younger than 3 years age group.\textsuperscript{58} In a national audit of 10,633 perioperative epidural infusions, there were 25 cases of local skin infection (ages not reported); epidural abscess was reported in 2 cases (including 1 infant), and an additional 16-year-old patient developed signs of meningism.\textsuperscript{35} In a single center over 17 years, epidural catheter-related infection, limited to the paraspinal or subcutaneous tissue, occurred in 6 of 10,437 patients (0.06%), including 1 neonate and 1 infant.\textsuperscript{60} All presented with back pain, pyrexia, and cellulitis; 5 also had paresthesia visible at the catheter exit site; 3 required surgical drainage; and all recovered without neurological sequelae. Epidural catheters inserted for longer periods for chronic pain management were associated with higher rates of infection (3.2% vs 0.06%).\textsuperscript{60}

### Neurological Injury
Rates of neurological injury after neuraxial analgesia range from 0.13 to 0.4 per 1000 in large series, with higher rates after epidural catheter techniques than single-shot caudals. Transient neuropathy was reported after 2 per 15,013 central blocks\textsuperscript{34} and 6 per 10,633 epidural anesthetic infusions.\textsuperscript{35} In addition, after a programming error that rapidly delivered 15 mL of solution, a 4-month-old preterm-born infant developed cauda equina syndrome with persisting neurological deficit 1 year later.\textsuperscript{35} Suspected nerve injuries occurred after 1 of 364 thoracic, 2 of 1183 lumbar, and 1 of 8493 caudal epidural blocks, with no reported long-term deficits, and children were aged 8 years and older.\textsuperscript{17} Isolated cases of neurological deficit after neuraxial anesthesia of varying severity have been reported in neonates\textsuperscript{61} and older children.\textsuperscript{52–56} The relative contributions of needle trauma, surgical injury, or potential drug-related toxicity to neurological injury are difficult to determine. No neurological sequelae were reported in a retrospective review of 750 children (52% of whom were infants) requiring cardiac surgery and treated with perioperative epidural local anesthetic, opioid, and/or clonidine.\textsuperscript{60} However, as in many studies, the duration of follow-up and the nature and sensitivity of neurological evaluation were not reported. The rates of complications may be underestimated, particularly in young children, who cannot report sensory symptoms, and subtle motor changes are difficult to detect in infants not yet walking. More thorough follow-up of patients after neuraxial blocks has been advocated.\textsuperscript{58}

### Clinical Choice of a Spinal Analgesic: Efficacy Local Anesthetics
The primary drugs delivered neuraxially in neonates are local anesthetics, and examples of the range of preparations used in neonates and infants are included in Table 1. Issues of safety with neuraxially administered local anesthetics...
Table 1. Spinally Administered Local Anesthetics in Neonates and Infants

<table>
<thead>
<tr>
<th>Route</th>
<th>Concentration/dose</th>
<th>Age</th>
<th>Design/sample</th>
<th>Outcome/results</th>
<th>Side effects/complications</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine IT</td>
<td>0.5 mg/kg, 0.5% = 0.1 mL/kg (&lt;5 kg); 0.4 mg/kg (&gt;5 kg)</td>
<td>&lt;1 mo, n = 20; 1–3 mo, n = 26; 3–6 mo, n = 22</td>
<td>Case series; inguinal hernia repair</td>
<td>In youngest: higher proportion (95%) with adequate spinal but less postoperative analgesia</td>
<td>Mild hypotension</td>
<td>288</td>
</tr>
<tr>
<td>IT</td>
<td>Hyperbaric 0.5% 1 mg/kg + epinephrine</td>
<td>Birth 24–40 wk; postnatal age 5–24 wk, n = 20</td>
<td>Case series; 17 inguinal hernia, 2 stoma, 1 teratoma; BIS monitoring</td>
<td>100% successful block; decrease BIS values 15 min postspinal</td>
<td>&gt;20% decrease in BP; HR stable</td>
<td>289</td>
</tr>
<tr>
<td>IT</td>
<td>Isobaric 0.5% bupivacaine vs hyperbaric 0.5% bupivacaine in 8% glucose; 0.5 mg/kg &lt;10 kg, 0.4 mg/kg 11–19 kg, 0.3 mg/kg &gt;20 kg</td>
<td>2–115 mo, n = 100</td>
<td>Double-blind, randomized; lower abdominal and lower limb</td>
<td>Success (complete sensory block) higher with hyperbaric (95% vs 82%); no difference in height of sensory block (but wide variability both groups), degree motor block or postoperative analgesia</td>
<td>Treatment required: 10/100 patients required supplemental O₂; 1 hypotension; 1 bradycardia</td>
<td>290</td>
</tr>
<tr>
<td>IT</td>
<td>Isobaric 0.5%; mean dose 0.68 ± 0.16 mg/kg</td>
<td>Gestational age at operation: 47.6 (28–120) wk; n = 505</td>
<td>Case series; lower abdominal, perineal, lower limb (79% inguinal hernia)</td>
<td>Successful spinal 96%; conversion to GA 1% (surgery &gt;90 min); sedation required 28%</td>
<td>Average spinal tap attempts 1.4 (1–6); bloody tap 12.4%; bradycardia 1.8% (6/9 required atropine); high block 3 patients (2 required intubation)</td>
<td>19</td>
</tr>
<tr>
<td>IT + EP-B (C)</td>
<td>Isobaric 0.5% 1 mg/kg IT in spinal group; all: + caudal 0.25% 2 mg/kg</td>
<td>40 (36–44) wk PCA; n = 10 (n = 14 GA sevoflurane)</td>
<td>RCT; spinal vs GA</td>
<td>Successful spinal 72%; decreased postoperative cardiorespiratory events in spinal group</td>
<td>Unsuccessful spinal 28% (4/14)</td>
<td>291</td>
</tr>
<tr>
<td>IT (CSE)</td>
<td>Isobaric 1 mg/kg 0.5%; caudal catheter (advanced to thoracic): 0.2 mg/kg/h 0.1%</td>
<td>31–53 wk PCA, n = 28</td>
<td>Case series; CSE sole technique for major upper abdominal surgery</td>
<td>Satisfactory surgical anesthesia in 24/28 (4 convert to GA); 20 supplemental midazolam</td>
<td>Multiple spinal attempts 3/24; CVS parameters stable</td>
<td>24</td>
</tr>
<tr>
<td>EP-B (L)</td>
<td>1 mL/kg 0.25% bupivacaine + epinephrine then 1 mL/kg 0.125% every 2 h intraoperatively</td>
<td>36–41 wk PCA repair on 4th or 5th d (1–23 d), n = 23</td>
<td>Case series; bladder extrophy repair</td>
<td>Intraoperative bupivacaine bolus (postoperative lidocaine; see below); 7/23 required intraoperative fentanyl</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>Ropivacaine IT</td>
<td>1.08 mg/kg 0.5% = 0.216 mL/kg (ED₉₀)</td>
<td>&lt;55 wk postmenstrual age, n = 50</td>
<td>Dose finding; inguinal hernia</td>
<td>Effective; motor block shorter duration and variable (cf other drugs)</td>
<td></td>
<td>292</td>
</tr>
<tr>
<td>EPB, EP-I</td>
<td>0.9–2 mg/kg 0.2% (L) + 0.2 mg/kg 0.2% (&lt;6 mo); 0.4 mg/kg/h (≥6 mo)</td>
<td>0–1 mo, n = 11; 1–3 mo, n = 10; 3–6 mo, n = 10; 6–12 mo, n = 14</td>
<td>Case series; major abdominal/thoracic surgery</td>
<td>Decreased clearance in neonates; unbound plasma concentration higher in neonates</td>
<td></td>
<td>293</td>
</tr>
<tr>
<td>EPI</td>
<td>0.2% 0–2 mL/kg/h</td>
<td>Neonate; n = 22</td>
<td>Case series; gastrochisis</td>
<td>Decreased postoperative ventilation in regional versus opioid</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>Levo bupivacaine</td>
<td>1 mL/kg 0.6%</td>
<td>0–12 mo, n = 10; 1–5 y, n = 30</td>
<td>Case series; gastrochisis</td>
<td>Higher plasma concentration in infants</td>
<td>No signs systemic toxicity</td>
<td>294</td>
</tr>
<tr>
<td>EPI</td>
<td>0.5–1.2 mg/kg 0.5%</td>
<td>&lt;55 wk PCA; n = 50</td>
<td>Dose finding; lower abdominal surgery</td>
<td>Recommended dose 1 mg/kg</td>
<td>No significant adverse effects</td>
<td>295</td>
</tr>
<tr>
<td>Levobupivacaine IT</td>
<td>2 mL/kg 0.2%</td>
<td>2 ± 0.7 (0.6–2.9) mo; n = 22</td>
<td>Pharmacokinetic study; inguinal hernia repair</td>
<td>Decreased clearance in infants</td>
<td></td>
<td>296</td>
</tr>
</tbody>
</table>

(Continued)
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Route</th>
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<th>Outcome/results</th>
<th>Side effects/complications</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>EP I</td>
<td>0.8–1 mg/kg/h 0.1%</td>
<td>36–41 wk PCA repair</td>
<td>Case series; bladder extrophy repair; Duration: 15 ± 8 d (4–30 d)</td>
<td>Adjust infusion to maintain plasma concentration &lt;5 mg/L; 22/23 required reduction in infusion in first 48 h. Tunneled catheter: 10/23 early dislodgement at 13 ± 7 (6–28) d</td>
<td>Ref. no.</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>IT</td>
<td>Lidocaine 3 mg/kg + epinephrine; tetracaine 0.4 mg/kg or 0.4 mg/kg + epinephrine</td>
<td>1–12 mo (7/100 &lt; 44 wk PCA; 77/100 &lt; 6 mo); n = 100</td>
<td>Case series; lower abdominal, lower limb (87% inguinal hernia)</td>
<td>Duration motor block: lidocaine + epinephrine 56 ± 2.5 min; tetracaine 86 ± 4 min; tetracaine + epinephrine 128 ± 3 min. Sedation: methohexital 78; ketamine 4</td>
<td>297</td>
</tr>
<tr>
<td>IT/CSE</td>
<td>Mean dose 0.65 mg/kg; postoperative caudal catheter: bupivacaine 0.25 mg/kg/h ( neonates) or 0.5 mg/kg/h (infants)</td>
<td>29 wk PCA to 7 mo; 1.5–7.8 kg; n = 19</td>
<td>Case series; major abdominal surgery + CSE bupivacaine via caudal catheter</td>
<td>4–30 d</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>IT</td>
<td>Mean dose 0.56 mg/kg; 0.5% in dextrose 5%</td>
<td>Neonates, n = 14</td>
<td>Case series; repair meningomyelocele</td>
<td>Additional doses by surgeon</td>
<td>298</td>
<td></td>
</tr>
<tr>
<td>IT</td>
<td>1 mL/kg 0.5% tetracaine (or 0.5% bupivacaine) + 5% glucose + adrenaline</td>
<td>24–42 wk gestational age, n = 62</td>
<td>Case series; bladder extrophy</td>
<td>Spinal success 89%</td>
<td>299</td>
<td></td>
</tr>
<tr>
<td>IT</td>
<td>0.5 mL/kg 0.5% tetracaine + 5% dextrose + epinephrine</td>
<td>24–37 wk gestational age, n = 142</td>
<td>Case series; 95% inguinal hernia; 5% urology</td>
<td>Spinal success 96%</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>IT</td>
<td>Hyperbaric; mean dose 0.54 ± 0.2 mg/kg (+ epinephrine in 91% (excluding PDA) [0.4% cases: hyperbaric bupivacaine or lidocaine]</td>
<td>Neonates and infants (&lt;12 mo); 650 g to 13 kg; n = 1554</td>
<td>Case series; abdominal, lower abdominal, and lower limb; urology; myelomeningocele; (55% inguinal hernia)</td>
<td>Spinal adequate for surgery 95%; supplemental LA by surgeon 2.7%</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>IT</td>
<td>Hyperbaric 0.5% in 5% dextrose + epinephrine; mean dose 2.4 mg/kg</td>
<td>Neonates mean PCA 33 (28–41) wk; 1276 (650–2965) g, n = 14</td>
<td>Case series; PDA repair intubated and high dose to aim for total spinal; CVS stable</td>
<td>Mean cumulative requirement 2.8 ± 1 mL/kg/h</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>EP B + I (C)</td>
<td>1 mL/kg 3% ± 0.3 mL/kg bolus to establish + 1 mL/kg/h</td>
<td>Ex-preterm 35–49 wk PCA; n = 10</td>
<td>Case series; feasibility in awake, inguinal hernia (sole)</td>
<td>Mean cumulative requirement 2.8 ± 1 mL/kg/h</td>
<td>BP mild decrease; 1 apnea (preexisting episodes)</td>
</tr>
<tr>
<td>EP B + I (C)</td>
<td>1–1.5 mL/kg 3% bolus + 1–1.5 mL/kg/h</td>
<td>Neonates, 1–28 d; 2.2–4.9 kg; n = 25</td>
<td>Case series; major abdominal surgery (regional anesthesia as supplement to general anesthesia)</td>
<td>CVS stable</td>
<td>Caudal space on first or second attempt; CVS stable</td>
<td>29</td>
</tr>
</tbody>
</table>

IT = intrathecal; EP = epidural bolus administration; EP I = epidural infusion; (L) = lumbar injection; (L/T) = lumbar or thoracic insertion/injection; (C) = caudal injection; ED50 = 95% effective dose; GA = general anesthesia; BIS = Bispectral Index; RCT = randomized controlled trial; SaO2 = arterial oxygen saturation; Bx = biopsy; BP = blood pressure; HR = heart rate; PCA = postconceptional age; CVS = cardiovascular system; PDA = patent ductus arteriosus; LA = local anesthetic; CSE = combined spinal and epidural. NOTE: studies with local anesthetic combined with opioid of adjuvant reported in Table 2.
have tended to focus on systemic toxicity and high plasma concentrations that precipitate neurological and cardiovascular complications (i.e., convulsions and arrhythmias). Age-related alterations in pharmacokinetics result in higher free drug concentration after a bolus and accumulation of local anesthetic during infusion in neonates. As a result, infusion duration tends to be limited in the youngest patients. In one study of neonates after bladder extrophy repair, epidural lidocaine was infused for an average of 15 days (range 4–30 days), but with regular monitoring of plasma lidocaine concentration. As will be reviewed below, it should be emphasized that although widely used, there have until recently been no systematic studies as to potential adverse effects on the developing spinal cord, and no comparative studies of different local anesthetics.

Spinal Analgesics and Clinical Study Design
Few studies have directly compared the efficacy of different spinal analgesic drugs in children of different ages. This, and the lack of systematic safety data (discussed below), make it difficult for practitioners to make an evidence-based choice between different drugs, thus contributing to the wide variability in current clinical practice. Evaluating data from current controlled trials is hampered by variation in methodology, particularly in the sensitivity of the outcome measures and end points used to measure the duration and efficacy of analgesia. In neonates and infants, sample sizes are frequently small because recruitment of large homogeneous samples is difficult, and may be further constrained by ethical issues. Additional variability in the type, sensitivity, and specificity of pain assessment tools used may further reduce the power of the study.

Prolongation of Analgesia
If analgesia is being titrated against individual requirements, differences in pain scores should not be seen, and therefore differences in the duration of analgesia or supplemental analgesia requirements are often used as outcome measures. The most frequent comparison is between the same dose of local anesthetic with or without a spinal analgesic, and relatively few studies evaluate the ability of spinal analgesics to reduce the required concentration of local anesthetic or the impact of different doses of local anesthetic. Time to first analgesia will be influenced by the sensitivity, frequency, and interrater reliability of pain assessment (particularly after discharge when reliance is placed on parental interventions); the trigger for administration; and the type of supplemental analgesic. Meta-analyses have demonstrated statistically significant prolongation of analgesia with caudal clonidine and ketamine. The remaining question is whether the degree of change is clinically, as well as statistically, significant. Because reported increases in duration range from 2.3 to 5.3 hours, analgesia may be receding soon after the patient leaves the postanesthesia care unit or when ambulatory patients are leaving the hospital, and this needs to be considered when providing instructions to ward staff and parents regarding supplemental analgesia.

Supplemental Analgesia
The clinical significance of a reduction in supplemental analgesia as an outcome depends on the total dose, side-effect profile, and relative risk of the different treatments. A reduction in opioid requirement with addition of spinal analgesics has the potential to reduce opioid-related side effects such as nausea and vomiting. However, many pediatric studies have been conducted after day-case surgery, where postoperative pain scores and/or analgesic requirements are low, making it difficult to demonstrate a difference between 2 active treatments. A reduction in the use of mild analgesics such as acetaminophen or nonsteroidal antiinflammatory drugs provides evidence of an analgesic effect, but the relative risk of the spinal adjuvant must be weighed against that of the additional supplemental analgesia. We would question whether avoiding 1 or 2 doses of acetaminophen over a 24-hour period justifies the risk of neuraxial administration of a drug that has not been evaluated for spinal toxicity. In addition, studies may report only the proportion of children requiring analgesia, or the total number of doses in the whole treatment group, and therefore dose requirements and relative benefits or risks for individual patients cannot be assessed.

Route of Administration
Neuraxial analgesic administration has the potential to produce analgesia at doses lower than required with systemic administration, thus reducing side effects. In several studies, epidural morphine (12–50 μg/kg) improved analgesia and although early systemic absorption was detected, analgesia was evident 1 and 3 hours later when plasma levels were lower than required for a systemic analgesic effect. Lower doses (2–5 μg/kg) are effective intrathecally. The degree of dose sparing depends on the chemical properties of the drug, and for more lipophilic opioids such as fentanyl, the difference between equipotent epidural and systemic doses may be less. Minimal dose sparing has also been demonstrated with ketamine, because 0.5 to 1 mg/kg is used in caudal studies and the same dose systemically provides procedural sedation and analgesia, albeit for a shorter duration. Similarly, analgesia was prolonged when comparing caudal and IV administration of 2 mg/kg tramadol. Clonidine via the intrathecal or caudal route has a greater effect on analgesic duration than the same dose IV, but effects on general anesthetic requirements and early postoperative sedation are seen with neuraxial and systemic administration.

Addition of caudal adjuvants after unilateral hernia repair in children often aims to reduce local anesthetic requirements and associated motor block, but less-invasive techniques such as local infiltration and ilioinguinal block are also effective in the early postoperative period. Few studies have directly compared different local anesthetic techniques. Compared with dorsal penile block for circumcision, caudal bupivacaine plus ketamine was found to have no advantage, or to produce mild prolongation of analgesia (7.6 vs 6.2 hours) at the cost of increased motor block.
Spinal Analgesic Drugs

In the following section, we will provide a commentary on the use of analgesics that are delivered by the intrathecal or epidural/caudal route, with the aim of producing spinally mediated analgesia (i.e., spinal analgesics or spinal adjuvant analgesic drugs), and which are typically used in conjunction with local anesthetics. Table 2 provides a systematic summary of the reported literature relevant to the several families of adjuvant analgesics. In each case, the reported dosing is provided. In many cases, there is limited information related to the concentration of the different drugs within the injectate, but when coadministered with local anesthetic, the desired spread and volume of local anesthetic is often the deciding factor.

Opioids are the most frequently used spinal analgesics, but increased knowledge of spinal pharmacology has led to drugs such as α2-adrenergic agonists (clonidine), NMDA antagonists (ketamine), γ-aminobutyric acid (GABA)A agonists (midazolam), and neostigmine being used alone or in combination as spinal analgesics in adults. Use of spinal analgesics has expanded to pediatric practice, but there is marked variability in the availability of different preparations and in the clinical use of these drugs. Surveys of pediatric anesthetists in the UK reported that 16% added clonidine, 15% ketamine, and 9% epinephrine to epidural infusions. The proportion using clonidine as a caudal analgesic has increased (26% in 2002 and 42% in 2009), whereas use of ketamine and midazolam remained relatively constant at 32%–37% and 0.5%–1%, respectively. A survey of 25 international pediatric centers found an increased use of clonidine (18 to 23 of 25 centers) whereas use of ketamine had significantly decreased from 12 to 4 centers. Although the majority of controlled trials have been conducted in children older than 6 months, many spinal analgesics have been used in neonates and infants younger than 6 months (Table 2), despite limited evaluation of age-related changes in the pharmacodynamic profile of these drugs and no systematic evaluation of toxicity in the developing spinal cord.

Opioids

μ-Opioids have been administered by epidural bolus and/or infusion and also as an intrathecal additive with local anesthetic. Morphine or fentanyl has been used most frequently in neonates and infants, but the use of a wide range of opioid drugs has been reported in children 6 months and older including alfentanil, sufentanil, buprenorphine, butorphanol, diamorphine, hydromorphone, and tramadol. In surveys of UK pediatric anesthetists, 85% used opioids for epidural analgesia, but variability in the drug chosen (fentanyl, morphine, or diamorphine) was noted in this and an earlier survey (21% adding fentanyl and 13% adding diamorphine to caudal anesthetic blocks). Although many practitioners had a minimum age for the use of epidural opioids, the cutoff varied from the neonatal period to 5 years of age.

Clonidine and Dexmedetomidine

Meta-analyses of caudal studies in children older than 6 months of age reported prolongation of analgesia with addition of 1 to 2 μg/kg clonidine to local anesthetic for 2.4 hours (95% CI: 2.6–5.5 hours), 3.98 hours (95% CI: 2.84–5.13 hours), and 3.68 hours (95% CI: 2.65–4.7 hours). Many studies reported minor sedation after clonidine, which was more severe and associated with cardiovascular side effects at higher doses (5 μg/kg). Case reports of side effects of apnea, oxygen desaturation, and bradycardia have been reported in neonates given doses of caudal clonidine (1.25–2.2 mg/kg) that are tolerated by older children. Continuous infusion of epidural clonidine 0.08 to 0.12 μg/kg/h produces dose-dependent analgesia when added to local anesthetic infusions, and higher doses of clonidine alone (0.2 μg/kg/h preceded by bolus of 2 μg/kg) provide analgesia at rest after abdominal surgery. When added to intrathecal local anesthetic in neonates, relatively large doses of clonidine (up to 2 μg/kg) prolonged analgesia. A subsequent observational study with longer follow-up (24 hours) found more than half of the patients were sedated in the immediate postoperative period, and the proportion of neonates developing self-limiting apnea increased postoperatively. This dosing represents concentrations up to 5 μg/mL being used for both caudal and intrathecal single-shot injections and 0.6 to 1 μg/mL for continuous epidural infusion.

The more selective α2-adrenergic agonist dexmedetomidine (1 μg/kg) prolonged analgesia when added to caudal bupivacaine, and reduced supplemental analgesic requirements by 1 to 2 doses of acetaminophen 10 mg/kg in the first 24 postoperative hours. Similar analgesia was reported when comparing caudal dexmedetomidine and clonidine in children aged 6 months and older. Because there has been limited evaluation of neurotoxicity with this drug, further testing is required before routine clinical use.

Ketamine

Caudal ketamine has been used for perioperative analgesia in children, including neonates and infants. Dose-ranging studies using 0.25 to 1 mg/kg reported 0.5 mg/kg as the optimum dose, with increasing side effects at 1 mg/kg. Recent meta-analyses evaluating addition of ketamine to caudal local anesthetic reported prolongation of analgesia for 2.26 hours (95% CI: 1.53–2.98 hours) or 5.3 hours (95% CI: 5.45–5.76 hours). Acute psychomimetic effects were reported in 2 of 7 trials, but the difference was not statistically significant in the other analysis (OR = 1.72, 95% CI: 0.69–4.26). A reduction in supplementary analgesics was demonstrated in studies using non-opioid analgesics or acetaminophen (paracetamol), but not in studies in which perioperative opioids were required. Ketamine 0.5 to 1 mg/kg was diluted with 0.5 to 1.0 mL/kg local anesthetic or saline resulting in final concentrations approximating 0.5 to 1.3 μg/mL. Systemically administered S-ketamine has increased potency over the racemic mixture. Dose sparing has not been evident in caudal studies, with S-ketamine used in doses of 0.5 mg/kg or 1 mg/kg. Ketamine solutions may contain benzethonium chloride, but there is limited information about the injectate preparation in some studies, whereas others report using a preservative-free solution of racemic S-ketamine.
<table>
<thead>
<tr>
<th>Table 2. Spinally Administered Analgesics in Neonates and Infants (≤6 mo)</th>
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<tbody>
<tr>
<td><strong>Opioids</strong></td>
</tr>
<tr>
<td>morphine</td>
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<td>hydromorphone</td>
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<td>diamorphine</td>
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<td>fentanyl</td>
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(Continued)
### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Route</th>
<th>Concentration/dose</th>
<th>Age</th>
<th>Design/sample</th>
<th>Outcome/results</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clonidine IT</strong></td>
<td>1 μg/kg clonidine + hyperbaric bupivacaine 0.5 mg/kg versus 1 μg/kg fentanyl + bupivacaine versus 1 μg/kg clonidine plus fentanyl + bupivacaine versus bupivacaine alone</td>
<td>Infant’s 2–11 mo (ex-preterm excluded); n = 61 (15–16 per group)</td>
<td>RCT double-blind; lower abdominal surgery under SA block (80% inguinal hernia)</td>
<td>Sensory block height T4-8</td>
<td>Sedation score higher and intraoperative propofol requirement lower in BC and BCF groups; CVS stable</td>
</tr>
<tr>
<td>IT</td>
<td>0.25, 0.5, 1, or 2 μg/kg (+ 0.5% isobaric bupivacaine 1 mg/kg)</td>
<td>38–46 wk PCA, n = 75</td>
<td>RCT; inguinal hernia</td>
<td>Duration increased by 1 and 2 μg/kg; recommend 1 μg/kg</td>
<td>MAP decreased by 22%–40% (higher proportion MAP &lt; 40 mm Hg in C2); HR decreased 12%–27% all groups; no difference early apnea. Limited follow-up until PACU discharge</td>
</tr>
<tr>
<td>IT</td>
<td>1 μg/kg (+ 0.5% isobaric bupivacaine 1 mg/kg)</td>
<td>Premature versus term (29–50 vs 39–53 wk current PCA), n = 67 vs 57 = 124</td>
<td>Prospective observational; inguinal hernia</td>
<td>Success rate 84%</td>
<td>Unsuccessful block 30%; high block and respiratory impairment 1</td>
</tr>
<tr>
<td><strong>Ketamine EP-I (L/T)</strong></td>
<td>Bolus 2 μg/kg + 0.2 μg/kg/h OR 0.2 μg/kg/h + ropivacaine 0.1% (0.2 mL/kg/h)</td>
<td>3–98 mo; n = 35</td>
<td>Randomized, nonblinded; major abdominal surgery</td>
<td>“Good analgesia” in both groups; rescue analgesia required for cough and movement</td>
<td>Clonidine bolus increased sedation and hypotension; HR and RR stable</td>
</tr>
<tr>
<td><strong>Ketamine EP-B (C)</strong></td>
<td>Sketamine 1 mg/kg ± 1 or 2 μg/kg clonidine (3 groups)</td>
<td>1–72 mo (mean 26 ± 24 mo)</td>
<td>RCT; inguinal hernia</td>
<td>K + C longer duration; supplemental analgesia in 24 h: 63% vs 16% with combination (paracetamol? single dose)</td>
<td>CVS stable; “no adverse CNS effects” (?criteria); 24 h follow-up</td>
</tr>
<tr>
<td>EP-B (C)</td>
<td>Sketamine 0.5 mg/kg ± 1 mL/kg levobupivacaine 0.15% or 0.175% or 0.2%</td>
<td>3 mo to 6 y (mean 3 y), n = 164 (52-56 per group)</td>
<td>RCT DB; lower abdominal or urology (57% inguinal hernia)</td>
<td>Adequate analgesia on incision 162/164 0.175% + K; lower analgesic requirement (22/52 vs 38/56 vs 30/56) 10/15 in ketamine group vs 3/15 no additional analgesia</td>
<td>Postoperative agitation 34/164; no “excess agitation or odd behavior”; 6 h postoperative follow-up</td>
</tr>
<tr>
<td>EP-B (C)</td>
<td>Bupivacaine 0.125% 0.2 mL/kg ± Sketamine 0.5 mg/kg</td>
<td>1 mo to 9 y (mean 2.7 y), n = 30</td>
<td>RCT DB; lower abdominal or urology (60% inguinal hernia)</td>
<td>CVS stable, no emergence delirium or unexplained distress</td>
<td>CVS stable; no difference in sedation; no motor block at 6 h</td>
</tr>
<tr>
<td>EP-B (C)</td>
<td>Sketamine 0.5 mg/kg versus 1 mg/kg versus bupivacaine 0.25% 0.75 mL/kg with epinephrine</td>
<td>3 mo to 6 y; n = 49</td>
<td>RCT DB; inguinal hernia repair</td>
<td>Ketamine 1 mg/kg = LA &gt; 0.5 mg/kg; 33 vs 30 vs 72% supplemental paracetamol</td>
<td>(Continued)</td>
</tr>
</tbody>
</table>
In some regions, the number of centers using neuraxial ketamine in children has reduced in recent years.111,150

**Midazolam**

Midazolam is a GABA<sub>A</sub> agonist with potential analgesic actions in the spinal cord, but major concerns have been raised about the safety of neuraxial administration in both adult151,152 and pediatric practice.153 Addition of midazolam 50 µg/kg to caudal local anesthetic prolonged analgesia and increased sedation in children aged 1 to 12 years.154 Some report using a preservative-free solution,148,155 but others give no details of the pharmaceutical preparation,154,156 although one reported using a solution with a pH of 6.2 rather than 3.3 to 3.9 as used in previous studies.157 Solutions of 0.1% to 0.5% midazolam were administered with 0.5 to 1.0 mL/kg local anesthetic or saline resulting in final concentrations approximating 50 to 100 µg/mL.145,155,157,158

**Neostigmine**

Neostigmine produces analgesia after neuraxial administration in adults,159,160 but the incidence of side effects has led to its role in pediatric practice being questioned.161 Doses of caudal neostigmine ranging from 1 to 4 µg/kg have been administered in children from 5 months of age162–166 and prolong analgesia by 9.9 hours (95% CI: 7.8–122 hours) but without a clear dose-response relationship.86 The relative risk (RR) of postoperative nausea and vomiting is significantly increased (RR 1.78, 95% CI: 1.11–2.85),86 with incidences from 30%,167 and up to 60% with higher doses.168 Preparations containing methylparaben and propylparaben148,169 and preservative-free solutions170 have been used. Prolongation of hyperbaric bupivacaine block has also been demonstrated with intrathecal neostigmine 0.75 to 1 µg/kg in infants.171 This dosing represents concentrations of 2 to 4 µg/mL for caudal injections and 10 µg/mL administered intrathecally.

**Clinical Choice of Spinal Analgesic: Safety**

For the last 2 decades, there has been an increasing appreciation that there needs to be a specific intent to define the safety of neuraxially delivered drugs before routine clinical use in adults.172,173 We, and others, have argued that systematic preclinical assessment of potential for spinal toxicity in validated models should be performed before clinical delivery into the neuraxial space of neonates and children.150,161 Without safety data, it is impossible to confirm a favorable risk-benefit ratio for neuraxial administration, or to compare the relative safety, of this wide range of drugs and preparations, and clinical trials must be undertaken with caution. So significant has become this issue, that several major journals involved in pain and anesthesia have provided specific guidelines on the acceptability of work that uses the off-label neuraxial use of novel drugs, indicating that systematic preclinical safety should be available or specific FDA approval gained before undertaking the trial.174–177 In the following sections, we review the information that does exist regarding spinal adjuvant use in human infants; however, we emphasize that in and of itself, such information does not qualify the drug being delivered as safe. Often it reflects retrospective series and limited follow-up, and the primary metric of the safety study (i.e., spinal histopathology) cannot be assessed.
Evaluation of Risk
Concerns regarding the potential for toxicity after neuraxial analgesic administration have been raised in multiple reviews and editorials with calls for further preclinical testing. “It is essential to undertake extensive animal testing with further evaluation of any neurotoxic effects before pediatric use.”153 Although preservatives in preparations of midazolam justifies extensive preclinical testing may seem burdensome, the risk-benefit relationship for epidural midazolam justifies the need.153 Although preservatives in preparations of neostigmine178 and ketamine179 may contribute to potential toxicity, using a preservative-free solution does not guarantee safety. Authors reporting the use of caudal ketamine acknowledge that “as yet, no permanent neurological injury has resulted from single-shot caudal ketamine use but caution is warranted,”97 and that conclusive safety studies are required.84,180 This is particularly important because isolated cases of postoperative neurological injury have been reported in children, and neuraxial analgesia may be implicated in medicolegal claims even if other potential factors (such as peripheral compression neuropathy related to positioning) are subsequently identified.180

It was suggested several years ago that performance of neuraxial anesthesia in healthy children required demonstration of a high therapeutic ratio and additional advantages.181 Although complications are rare,35 without information regarding tissue toxicity, it is difficult to determine whether the drug administered contributes to the risk. Extensive clinical use does not preclude the potential for cases of toxicity,79 as seen in adult practice with chloroprocaine182 and lidocaine and cauda equina syndrome.183 It has also been noted that a single case of neurological injury may be sufficient to change clinical practice, bring a particular technique in general use into disrepute, and thus deny many children the benefits of neuraxial analgesia.161 Therefore, further specific data comparing the efficacy and relative safety of currently available and potential new spinal analgesic drugs are essential to inform clinical choice. New alternatives should only be used if improved analgesia, combined with an acceptable safety and side-effect profile, can be demonstrated.151 It should be stressed that the neuraxial route of delivery exposes local tissues (meninges, roots, spinal parenchyma) to extraordinary concentrations of drug (mg/mL), which, because of local restrictions in redistribution, may persist for extended intervals. Accordingly, the specific assessment of the potential toxicity of the drug must be of the highest priority. In the next sections, we will review the existing preclinical data related to the safety of spinal anesthetic and analgesic drugs in neonatal models.

3. PRECLINICAL MODELS OF NEURAXIAL ANALGESIA: DEVELOPMENTAL PHARMACODYNAMIC RESPONSES

Neonatal Neuraxial Delivery Models

Intrathecal and Epidural Delivery Techniques

Bolus intrathecal drugs in neonatal and infant rats can be delivered with a technique similar to that described in adult mice.184 The spinal column or pelvic girdle is stabilized by one hand, and percutaneous injection is performed at the level of the cauda equina in the L5-S interspace (rodents have 6 lumbar vertebrae) with a 30-gauge needle attached to a syringe calibrated to deliver microliter volumes. Correct placement is typically demonstrated by a tail flick on needle insertion. Although it is likely that such a response represents contact with a nerve root and is a potential source of pathology,185 appropriate control studies in neonatal rats have revealed no untoward anatomical pathology related to this technique.186 Systematic training with the injection of dye and confirmation of spread within the cerebrospinal fluid (CSF) on postmortem dissection ensures that each experimenter can consistently perform the technique.184,186 In addition, we recently used in vivo imaging after intrathecal injection of a fluorescent dye to confirm that our technique was reliable and reproducible in rat pups as young as 3 postnatal days with an average weight of approximately 10 g.186

Intrathecal catheters have been inserted via a lateral thoracic laminectomy in pups as young as postnatal day 3. An injectate volume of 4 μL of methylene blue produces spread from the caudal cervical to the lumbar/sacral region,187 but associated motor deficits limit behavioral analysis to the contralateral limb.

Single-shot percutaneous epidural injections can also be performed in rat pups, with correct epidural placement (spread along vertebral segments but lack of staining in CSF) confirmed by injection of Evans blue dye and postmortem dissection.188–190

Distribution of Injectate

The distribution of the neuraxially delivered drugs must be defined in any preclinical model. The volume must be adequate to deliver drug to the appropriate dermatomes used to evoke pain behavior (e.g., lumbar segments for evaluation of hindlimb withdrawal reflex sensitivity) but insufficient to acutely produce supraspinal redistribution. Recently, we confirmed that segmental spread of intrathecal dye covaried directly with injectate volume and inversely with age in rat pups.186 An injectate volume of 0.5 μL/g resulted in fluorescent dye extending into vertebral segments but lack of staining in CSF) confirmed by coinjection of Evans blue dye and postmortem dissection.188–190

Radioactive labeling in the spinal cord has also been used to characterize neuraxial injections. Percutaneous intrathecal injection of 2 μL in postnatal day 3 rats, or 7 μL of 3[H]-gabazine in postnatal day 21 rats, produced binding throughout the thoracolumbar cord.184 Epidural injection of 3[H]morphine at postnatal day 3, postnatal day 10, or...
postnatal day 21 produced similar levels of binding in the cord, all of which, as expected, were much higher than levels seen after systemic administration of the same dose.189

An important indirect assessment of correct placement is the observation of an appropriate behavioral response after injection of an analgesic or local anesthetic. Whereas overly large volumes promoting supraspinal redistribution are to be avoided, very small volumes may in fact lead to an inadequate movement of the injectate to the spinal segments regulating the processing of afferent traffic. Accordingly, demonstration of a reliable and dose-dependent change in pain behavior is a critical component of validating dosing volumes in a preclinical model. Neuraxial local anesthetic effects may be assessed by motor and/or sensory changes, and thoracolumbar spread can be assumed by maintenance of adequate respiration, motor block restricted to the hindlimbs, and/or lack of a hindlimb withdrawal response to a suprathreshold stimulus.26,186

Developmental Pharmacodynamic Profile of Spinal Analgesics

We have postulated that evaluation of the relative safety (or toxicity) of different spinal drugs is best made in the context of the therapeutic ratio, i.e., the dose that produces toxicity or the maximum tolerated dose versus the dose that is required to have a therapeutic analgesic effect.186,195,196 Accordingly, it is appropriate to consider the utility of neonatal models of neuraxial delivery in defining dose-related analgesic and behavioral effects. Developmentally regulated changes in the structure and function of nociceptor pathways, and in the expression and distribution of receptors, have a significant impact on analgesic efficacy and dose requirements during postnatal life.197 Studies in developmental models, particularly the rat pup, allow systematic assessment of a variety of specific nociceptive end points and the degree of alteration by analgesic drugs.

Analgesic Efficacy and Age-Dependent Dosing

Increases in the mechanical withdrawal threshold or thermal withdrawal latency threshold of an uninjured hindlimb can be used to evaluate age- and dose-dependent antinociceptive analgesic effects. The efficacy of spinal analgesics has also been evaluated by nociceptive behaviors to local irritants such as formalin198 or mustard oil,199 and also in facilitated hyperalgesic states such as carrageenan-induced inflammation.188,190,196

In early life, an enhanced sensitivity to opioids is demonstrated whether given by systemic,200 epidural,189,201 or intrathecal186,202 administration, and lower dose requirements with neuraxial administration confirm selective spinal analgesic effects.186 Changes in opioid receptor distribution in the dorsal root ganglion (DRG) and spinal cord are likely to contribute, and may also explain modality-specific differences in efficacy against thermal and mechanical stimuli,189,202–204 Lower doses of opioid,186,201 local anesthetic,188 NMDA antagonist,196 and α2 agonist190,199,205 reverse injury-induced hyperalgesia and/or increase withdrawal thresholds in neonatal rat pups when the dose is adjusted for weight.

Side Effects

Effects unrelated to analgesia may be usefully considered as those which are reversible and those that are irreversible. Side effects such as sedation, motor impairment, and cardiovascular changes can often limit dose escalation. These dose-dependent effects can be evaluated in laboratory studies and compared with analgesic doses to determine the therapeutic window (difference between dose producing side effects and the analgesic dose) at different ages. In humans, such side effects may represent (i) a spinal action (e.g., inhibition of the micturition reflex after spinal morphine)206, (ii) a direct neuraxial redistribution to the brain (as with the behavioral disruption reported after intrathecal ziconotide)207; or (iii) systemic redistribution of the neuraxial dose after intrathecal delivery (e.g., rapid sedation after intrathecal lipophilic drugs such as sufentanil).208 Side effect end points may vary with age. Thus, in preclinical models, in addition to lower antihyperalgesic dose requirements with epidural dexmedetomidine, the dose that significantly prolonged the righting reflex or reduced heart rate was lower in the youngest animals, resulting in a narrower therapeutic window in early life.190,199 It should be stressed that these side effects are adverse events that are related to the physiological and reversible pharmacodynamic profile of the particular competitive drug. Support of function, such as respiration and arterial blood pressure, until drug clearance or reversal will often prevent any further deterioration. These events are important because they limit the useful dose range of the drug and may be safely exposed. This would be defined as the maximum tolerable dose.

In contrast, drugs at some concentration or dose exposure may exert a direct effect on cellular function and lead to irreversible changes in cellular viability and thus represent tissue toxicity. Such end points would be, for example, expression of apoptosis or necrosis, frank demyelination, or changes in endothelial cell function. Some of these effects may be manifest by changes in spinally mediated behaviors or physiology, such as seizures, paralysis, or anesthesia. However, where the tissue injury is delimited or where changes are slow and initiate compensatory actions, such effects may not be associated with functional or behavioral changes in the preclinical model. An example of this is the slowly growing, space-occupying granuloma.209 Here, the appropriate criteria are the systematic postmortem assessments of target tissues (spinal cord, nerve, and DRG). Without this, the absence of negative functional signs can be a false negative for tissue toxicity.

Preclinical Spinal Drugs: Developmental Toxicity Impact of Postnatal Age

Preclinical models for assessing intrathecal and epidural drug safety have been established in adult animals,210 but there has been little effort until recently to develop models for assessing spinal toxicity throughout the early postnatal period of development. It is crucial that although persistent changes in behavior after neuraxial drug treatment may be a signature of direct tissue toxicity, absence of such changes cannot be construed as being an absence of toxicity. Such an
assertion requires demonstration of absence of neuropathology, e.g., histological signs, increases in apoptosis, and alterations in glial response in exposed tissues. We argue that an important element in considering drugs for neuraxial delivery in human neonates and infants is their appropriate preclinical evaluation. In the following sections, we will consider several variables that we believe affect the preclinical assessment of developmental toxicity of neuraxially delivered drugs.

**Activity-Dependent Neural Development**

There are well-established critical periods in early postnatal life when the normal development of neuronal circuits is activity-dependent, and alterations in neural activity can produce long-term consequences that are not seen after the same perturbation in the adult. Neural activity promotes synaptic strengthening and network formation, whereas lack of activity and failure to form appropriate synaptic contacts can result in programmed cell death (apoptosis). In contrast to excitotoxic cell death, apoptosis is a normal developmental process for activity-dependent matching of pre- and postsynaptic populations and the refinement of neural circuits. However, during these critical periods, exposure to drugs such as general anesthetics that reduce excitation (NMDA antagonists) or enhance inhibition (GABA agonists) may trigger excessive degrees of apoptosis in many brain areas. The degree and distribution of apoptosis change during the first 2 postnatal weeks, with peak susceptibility in the cortex around postnatal day 7. Prolonged general anesthesia in postnatal day 7 pups increases apoptosis not only in the brain but also in the spinal cord. Changes outlined below also emphasize the significant plasticity of the developing cord. As such, neuraxially administered anesthetics and analgesics which alter neural activity in the cord may also produce specific patterns of toxicity that differ from those seen at older ages.

**Developing Spinal Cord Structure and Function**

During postnatal development, there are significant structural and functional changes in nociceptive circuitry in the spinal cord. A-fiber afferent terminals initially project throughout the dorsal horn and only gradually withdraw to deeper laminae over the first 3 postnatal weeks in the rat as C-fiber projections mature. The normal postnatal development of A- and C-fiber innervation in the spinal cord is activity-dependent and can be altered by changing input at critical stages. Blockade of synaptic activity by a neuraxially administered slow-release NMDA antagonist prevents the structural reorganization of A-fiber terminals, and the neonatal pattern of low mechanical withdrawal thresholds and large dorsal horn receptive fields persists into adulthood.

The somatotopic organization of primary afferent terminal fields can also be altered by changing neural input during the neonatal period. Cell death in the DRG is a normal developmental phenomenon and is balanced by proliferation in early life. However, cell death occurs more rapidly and to a greater extent after sciatic nerve section in neonatal compared with adult animals. Importantly, responses to neonatal injury such as inflammation or surgical injury have been associated with long-term functional consequences and an enhanced sensitivity to future injury.

The balance between excitatory and inhibitory activity in the spinal cord changes during the postnatal period. Excitatory glutamate receptors (AMPA, NMDA, and metabotropic glutamate receptors) are highly expressed and tend to be more widely distributed in the neonatal spinal cord. Developmental changes in subunit expression of the NMDA receptor are associated with changes in channel kinetics and increased calcium influx that further increase excitatory effects, and may influence the potential for toxicity. GABA-mediated inhibition is functional at a cellular level, but there is minimal glycine-mediated inhibition in the neonatal spinal cord and a delay in the overall maturation of inhibitory networks, and local GABA-mediated inhibition in the cord is initially dominated by descending excitatory effects. Ketamine and propofol have been shown to increase cell death and alter dendritic arborization of GABAergic neurons in vitro, but effects in spinal networks have not been directly evaluated.

**4. Standards for Preclinical Evaluation of Efficacy and Toxicity of Spinal Analgesics**

Preclinical safety evaluations by definition use surrogate models with key characteristics that mirror those of the human condition; in this case, the mammalian neonate during the early postnatal phases of development receiving spinal drug exposure in a validated model. As reviewed above, the minimal component to an appropriate assessment of toxicity is the systematic consideration of pathology in the neuraxis as compared with the appropriate neuraxial vehicle control. Methods used in recent developmental spinal toxicity studies are summarized in Figure 1.

**Validated Model and Drug Delivery**

The principal developmental toxicity model used for neuraxial delivery has been percutaneous delivery in rat pups, but the model (i.e., the animals and the delivery system) must be validated. This implies that the drug delivery has been reliably demonstrated to occur within the intrathecal space (an important issue where the delivery has been percutaneous puncture) and that the injection protocol (needle placement, volume) results in an adequate and reliable distribution of the injectate. As discussed earlier, preliminary studies are required to ensure reliability of the technique in the hands of each investigator, and to avoid confounding effects of dyes in toxicity studies, correct placement can be confirmed by measuring a predetermined dose-dependent acute behavioral change (e.g., increase in hindlimb withdrawal threshold or motor block). In addition, the model should have the ability and sufficient sensitivity to reveal a profile of toxicity that has been previously described (e.g., apoptosis or demyelination).

It is of fundamental importance that appropriate control groups are included to statistically differentiate between the effects of the interventions and effects of the intervention plus drug. A saline injection group will demonstrate effects related to the technique, needle trauma, or volume of injectate. In addition, comparison with a naïve group ensures that effects are not related to the brief anesthesia, handling, or maternal separation required for the procedure.
Spinal toxicity in adult models has been evaluated after both epidural and intrathecal delivery. Although both intrathecal and epidural delivery have been demonstrated in the neonatal rat, current toxicity models focus on intrathecal delivery. Higher doses or concentrations of epidural drug are frequently required to achieve similar concentrations at target sites within the spinal cord. As such, the worst-case scenario is the intrathecal delivery of an intended epidural drug, not only because of the risk of increased acute side effects but also because of the exposure of the cord to an increased dose or concentration of drug. Cases of unrecognized dural puncture and inadvertent total spinal have been reported in large series (2 per 10,633 cases35 and 1 per 10,098 cases17). In addition, the overall incidence of dural taps has been reported at 0.12%,16 and 0.1% (95% CI: 0.05%–0.19%),17 and 6 of the 10 dural taps in the latter survey were associated with caudals in babies. This further emphasizes the need to establish a safety profile for all neuraxial drugs, whether epidural or intrathecal delivery is planned.

Figure 1. Methods used in the evaluation of anesthetic and analgesic toxicity in the developing spinal cord. Preclinical studies in the postnatal rat have used a range of functional/behavioral and histopathological tests to evaluate spinal cord responses to analgesic and anesthetic drugs. 1, Experimental groups include a range of intrathecal drugs. Appropriate control groups include intrathecal saline and naïve animals. Positive control groups are required to ensure adequate sensitivity of the tissue analysis when evaluating drugs with no or limited toxicity. 2, A measurable behavioral response is required to confirm correct intrathecal placement. Analgesic response curves are schematic examples of dose-dependent reversal of hyperalgesia and of age- and dose-dependent changes in mechanical withdrawal threshold. 3, Neuronal apoptosis and acute histopathological change can be evaluated by a range of methods. Images are representative examples of spinal cord sections stained for activated caspase-3 immunoreactivity with positive cells identified by brown DAB staining, and Fluoro-Jade C staining with apoptotic or dying neurons identified by green immunofluorescence. 4, Histopathological responses to drug exposure, and demyelination following local anesthetics (LAs), are evaluated at later time points. Images represent spinal cord sections stained with hematoxylin and eosin (H&E) to assess histopathology and apoptotic cell counts, Iba1 immunoreactivity to evaluate microglial reactivity (green), and glial fibrillary acidic protein (red) to evaluate astrocytes. 5, Measurement of spinal reflex sensitivity, analysis of gait, and length of time on a rotarod have been used to evaluate spinal cord functional outcomes in later life. P = postnatal day; I.T. = intrathecal; NMDA = N-methyl-D-aspartate.

Animal Age

The infant rodent is frequently used as a model for evaluating the progress of postnatal mammalian development. Although direct translation of different developmental ages from rodents to humans and the specific timing of events after birth continues to be debated, the sequence of development of sensory and reflex systems in rodents correlates with that of human infants.241 Statistical models have been developed to translate development across species242,243 but are predominantly based on structural measures and acknowledge that, because peak synaptogenesis is more complex and more prolonged in the human, the model cannot account for activity-dependent modification after birth.244 In terms of spinal processing, many approximate a postnatal day 3 rat with a preterm human neonate, postnatal day 7 with an infant, postnatal day 21 with an adolescent, and postnatal day 35 with young adulthood.197,245,246 Translational developmental models based on correlating behavioral measures support these estimates.241 In both humans and rats, locomotor capabilities develop postnatally, with a...
gradual rostrocaudal pattern of maturation. Rat pups ambulate through use of forelimbs and the upper torso by postnatal day 3 to 4, crawling behavior peaks approximately postnatal day 7, body weight is fully supported by postnatal day 12 to 13, and rearing without foreleg support is achieved by postnatal day 18.241 Spinal reflexes, which comprise both sensory and motor development, also show similarities in the sequence of development in the postnatal rat and human infant.247,248 with gradual maturation from low threshold,190,249–251 large receptive fields,251,252 poorly directed and generalized responses250,251,253 in both rodent and human infant early life. Clear relationships between the intensity of the stimulus and the degree of reflex withdrawal response229,254,255 are maintained at all ages, thus facilitating evaluation of the response to injury and/or analgesia.

Vulnerability to apoptosis in the brain coincides with rapid synaptogenesis or the brain growth spurt, which occurs predominantly in the first 2 postnatal weeks in the rodent, but may extend from midgestation to several years after birth in the human infant.216 The majority of preclinical studies evaluating general anesthetic effects in the brain have focused on postnatal day 7 because apoptosis peaks in the cortex at this age, and drug effects are most apparent in regions where spontaneous apoptosis is occurring.217,256 Spontaneous apoptosis occurs in the postnatal spinal cord, occurs predominantly in the dorsal horn, and peaks at a slightly earlier developmental stage than seen in the cortex with the number of apoptotic cells highest at postnatal day 2 to 5, and decreasing by postnatal day 8 to 10.196,257–259 Because peak apoptosis occurs at an earlier age in the spinal cord (postnatal day 3 rather than postnatal day 7) than the cortex, the period of susceptibility to proapoptotic drugs may be shorter, but prolonged general anesthesia does increase apoptosis in the cord at postnatal day 7.76,218 In addition, because there are ongoing changes in the structure, function, and synaptic connectivity of neural networks in the spinal cord throughout the first 3 postnatal weeks,232 assessment of developmental neuraxial toxicity should include a range of ages. This also addresses the potential uncertainty in the precise parallels between the postnatal development in the human and rodent.

**Evaluation and Outcomes**

In this review, we do not seek to cover the appropriate histopathology in detail, but experts in the fields of neuropathology will argue that to define the absence of pathology, one must satisfactorily address a number of specific issues and tissue targets.

Blinded assessments. Evaluation must include an analysis that is made independent of knowledge of tissue/animal treatment, with groups that at a minimum include vehicle versus drug treatment cohorts with tissue harvested at predetermined intervals after drug exposure.

Histopathology. Analysis of pathology requires appropriate selection of histopathological targets and indices.

(i) At the minimum, it is reasonable to systematically examine hematoxylin and eosin sections to note necrosis, gliosis, and inflammation. Such examination typically includes spinal cord and meninges and may also include DRG. Evaluation of nerve roots and demyelination is particularly relevant for assessing effects of local anesthetics.

(ii) Evaluation of apoptosis and neuronal cell death is an important additional component in early development. Although a range of potential techniques is available,262 activated caspase-3, an enzyme in the apoptotic cascade that marks neurons progressing beyond the point of commitment to cell death253 has been frequently used to identify apoptosis in the brain and also the spinal cord.76,186,196,218 Fluoro-Jade C is an additional marker of neuronal degeneration,264 and we found a pattern of staining that correlated with activated caspase-3 immunohistochemistry.196,196

(iii) Activation of non-neuronal cells by the use of specific astrocyte glial fibrillary acidic protein and microglia (IBA1 or OX42) markers can provide further indicators of altered function and the response to injury.

(iv) Evaluation of potential nerve injury requires assessment of the state of myelination. Previous work has shown that local anesthetics can produce signs of demyelination of the cauda equina.265,266 Because myelin is in the developing stage up through postnatal day 3, acute effects on myelin may be difficult to assess. Others have focused on apparent changes in the root at later time points, or in the dorsal column, which represents the ascending collaterals of large primary afferents.76

(v) As mechanisms associated with developmental anesthetic toxicity are further clarified, additional factors requiring evaluation in the developing spinal cord may be identified. As noted earlier, ketamine and propofol have effects on the dendritic tree of cultured cortical and hippocampal neurons.240,267,268 Because changes in dendritic morphology in the spinal cord have been noted in developmental neurological disorders and have a role in synaptic plasticity after nerve injury,269,270 similar mechanisms may be relevant for developmental toxicity in the spinal cord. Neurotrophic factors and actin depolymerization have been associated with apoptosis in cultured neuronal cells exposed to propofol271 and isoflurane,272 but effects in vivo273 and relevance to analgesic toxicity in the spinal cord have not yet been established.

(vi) A corollary to this commentary is that evaluation of the potential for spinal toxicity must involve the use of in vivo animal models. Such models may be complemented by the study of drug effects in ex vivo or in vitro models, as has been widely used to study local anesthetic toxicity. Changes in DRG cell function, or clonal cell viability or ex vivo nerve exposure.274–277 all provide important approaches to define potential mechanisms. However, as useful as the ex vivo system is for characterizing local drug effects, care must be taken in extrapolating these results to the intact organism, because they can just as easily provide false-positive indications that may not be relevant to in vivo safety or pathology related to a given drug (see Ref. 278).
Age at time of exposure. An important issue relates to the developmental age at initial drug exposure. As reviewed above, critical postnatal periods of neural development are represented by the onset of innervation, development of myelination of the long tract and primary afferents, and the time course of spontaneous apoptosis. On this basis, we have argued that appropriate ages in the rat are postnatal day 3, postnatal day 7, and postnatal day 21, with postnatal day 21 reflecting an animal that has essentially reached a steady state for the end points indicated.

Survival time postexposure. Initiation of cell death may begin as early as 6 hours after toxin (drug) exposure, and caspase-3 immunoreactivity may be reduced at later time points as the cell decomposes. In the spinal cord, we found increased apoptosis 6 hours after intrathecal ketamine at postnatal day 3, and significant increases were maintained at 24 hours. However, glial reactions and evidence of demyelination may not be maximal until a later time point. Accordingly, an optimal characterization would include both an early (6- to 24-hour) and later (7-day) interval of posttreatment recovery. Longer-term effects on functional outcomes must also be considered, and be sufficiently sensitive to detect changes that are related to any observed structural or histological defects. For example, because general anesthetics at postnatal day 7 increase apoptosis in the hippocampus, long-term effects on learning and memory have been evaluated. Although prolonged general anesthesia increased apoptosis in the spinal cord, motor performance on the rotarod at postnatal day 30 was not altered. Whereas local anesthetic toxicity or demyelination may result in changes in motor function, spontaneous apoptosis in the ventral horn occurs mainly before birth. Spontaneous apoptosis and increases after intrathecal ketamine at postnatal day 3 occur predominantly in the dorsal horn, with associated long-term changes in mechanical thresholds for hindlimb withdrawal, and in static but not dynamic variables of gait. This suggests that alterations in sensory and motor function should be included when evaluating long-term effects of neuraxial drugs.

Drug Exposure and Dose
To have credibility as a robust assessment paradigm, the drug exposure must occur at neuraxial doses, which by the metric of concentration and dose, equal or exceed those destined for the human condition. One limitation of percutaneous administration is that effects of dose are limited to single administrations rather than ongoing infusion and chronic exposure. Intrathecal catheterization has been reported in pups as young as postnatal day 3, but motor deficits and histological damage have been noted ipsilateral to the catheter, thus limiting the utility of this method for assessing toxicity. The use of a single dose runs the evident risk that a drug will be observed to have pathology at a dose that is well beyond any reasonable clinical exposure. Nevertheless, the higher the dose examined without pathology, the more confident we can be that the assertion of “no toxicity” is valid.

Translation of Drug Exposure and Dose
An important question relates to the expression of the dosing, and the translation of dosing in the surrogate to the target species. After systemic delivery, the typical metric for dose response is the body mass (e.g., mg/kg). However, it is widely appreciated that across large ranges of body weight, a more appropriate metric may be body surface area (BSA), particularly when precise dosing is required to maximize the therapeutic response while minimizing the likelihood of unacceptable toxicity (e.g., chemotherapy dosing) (Table 3). Because BSA has also been shown to correlate across mammalian species with physiological functions (such as metabolic rate, blood volume, and renal function), BSA rather than body weight has been used when converting doses across species to humans. The factor (body weight in kg divided by BSA in m²) is often incorporated in formulae for species conversions: e.g., human equivalent dose (mg/kg) = animal dose (mg/kg) x [animal Km/human Km]. Such calculations aim to produce a comparator that generates a proportional plasma level and are important for converting no adverse effect levels established in preclinical studies to doses used in clinical trials. However, the FDA also acknowledges that this approach has limited applicability when drugs are administered into anatomical compartments, such as the intrathecal space, where there is little subsequent distribution and where there may be as much as 2-fold difference in local volume. Considering the spinal dose in terms of mg/kg in 2 adult humans that may differ by a factor of 2 in body mass may be appropriate for avoiding systemic toxicity or side effects associated with redistribution or inadvertent injection into vascular structures. However, variability in intrathecal volume is likely to be less, and because toxicity may be more dependent on the compartmental volume (i.e., CSF volume and/or its turnover), it is the local concentrations to which the tissue is exposed that is important. The problem is yet more complicated where one compares across species, and different methods for dose conversion are shown in Table 3. When expressed as age-specific concentrations (total dose in µg per µL CSF volume), analgesia is achieved at twice the concentration of morphine and 42 times the concentration of ketamine and clonidine in neonatal pups. The maximum tolerated doses of intrathecal morphine and clonidine did not produce toxicity in the rat, despite being delivered in concentrations approximating 600 or larger than 10,000 times, respectively, than concentrations required for clinical analgesia. By contrast, intrathecal ketamine produced toxicity at <150 times the clinical concentration. Although these conversions require some assumptions, and are approximate because only limited dose intervals were assessed, they provide comparisons of different drugs, and again demonstrate the reduced safety margin of ketamine compared with morphine and clonidine.

The Therapeutic Ratio of Toxic to Analgesic Dose: A Way Forward?
The relative efficacy and safety of different treatments, and the potential benefits and risks for individual patients, are essential for choosing the most appropriate drug in clinical practice. Safety studies frequently appreciate that every drug examined neuraxially will at some point display pathology. The issue is that the drug must have a therapeutically lower than the dose that produces...
in early life was drug. In recent studies, we showed that the therapeutic ratio produce a therapeutic effect of the intrathecally delivered without tissue toxicity and the minimum dose required to tions. In this case, one notes the quotient of the minimum dose therapeutic ratio of the several drugs under identical condi-

have a deleterious action? One strategy is to define the what algorithm might we use to select the one least likely to produce a similar therapeutic end point (e.g., analgesia), neonates requiring surgery. However, if several drugs it is clearly not appropriate to withhold anesthesia for patient is deemed to outweigh this risk. Similarly, despite concerns about proapoptotic effects of general anesthetics, this particular strategy provides a rationale in the current environment to minimize the potential complications secondary to direct tissue toxicity, particularly when old drugs are being given by a new route (e.g., neuraxial) or when new drugs or preparations are being considered for neuraxial use. As noted above, with ongoing clinical use, it can become apparent that even frequently used drugs may lead to pathology as seen after intrathecal infusion of local anesthetics and chronic intrathecal morphine. Although the ratio can vary for different reasons across end points and laboratories, we would argue that in a given assessment paradigm, if 2 drugs have similar analgesic efficacy, but differ in their therapeutic ratio, the drug with the higher therapeutic ratio will be preferred, all other things being equal.

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CONCLUSION

We acknowledge that neuraxial anesthesia is an important component of perioperative pain management in children

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Table 3. Comparison of Intrathecal Doses Assessed in Neonatal Humans and Rats Expressed in Terms of Total Dose, Body Mass, Body Surface Area, CSF Volume, and CSF Turnover

<table>
<thead>
<tr>
<th>Analgesic Dose</th>
<th>Human newborn</th>
<th>Neonatal rat pup (3–5 d)</th>
<th>MTD or toxic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal body weight (kg)</td>
<td>3500 g Neonate = 0.2 m²</td>
<td>12 g 0.0035 m²</td>
<td>36</td>
</tr>
<tr>
<td>20 kg</td>
<td>0.8; 60 kg adult = 1.6</td>
<td>0.12 m²</td>
<td>10</td>
</tr>
<tr>
<td>CSF volume/mL</td>
<td>25 mL/d (305)</td>
<td>0.12 m/L/d</td>
<td>300</td>
</tr>
<tr>
<td>CSF turnover (µL/min)</td>
<td>17 µL/min</td>
<td>0.34 µL/min (305)</td>
<td>1000</td>
</tr>
<tr>
<td>Analgesics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose, µg/kg</td>
<td>24.5–70</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>µg/mL CSF vol</td>
<td>0.12–0.35</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td>µg per µL/min CSF turnover</td>
<td>0.5–1.4</td>
<td>1 (2×)</td>
<td></td>
</tr>
<tr>
<td>Elimination µg/mL × µL/h</td>
<td>1.44–4.1</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose, µg</td>
<td>350</td>
<td>36</td>
<td>120</td>
</tr>
<tr>
<td>µg/kg</td>
<td>IT ~100</td>
<td>3000 (3 mg/kg)</td>
<td></td>
</tr>
<tr>
<td>µg/mL CSF vol</td>
<td>1.75</td>
<td>10.2</td>
<td>3.42</td>
</tr>
<tr>
<td>µg per µL/min CSF turnover</td>
<td>7</td>
<td>300 (42×)</td>
<td>1000 (142×)</td>
</tr>
<tr>
<td>Elimination µg/mL × µL/h</td>
<td>20.1</td>
<td>105</td>
<td>100</td>
</tr>
<tr>
<td>Clonidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose, µg/kg</td>
<td>7.3</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>µg/kg</td>
<td>1(27)</td>
<td>30</td>
<td>1000 (10 mg/kg)</td>
</tr>
<tr>
<td>µg/mL CSF vol</td>
<td>0.017</td>
<td>0.103</td>
<td>3.42</td>
</tr>
<tr>
<td>µg per µL/min CSF turnover</td>
<td>0.07</td>
<td>3 (42×)</td>
<td>1000 (14285×)</td>
</tr>
<tr>
<td>Elimination µg/mL × µL/h</td>
<td>0.021</td>
<td>1.05</td>
<td>352</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose, µg/kg</td>
<td>1750–3500</td>
<td>3.75(77) P7: 16 g</td>
<td></td>
</tr>
<tr>
<td>µg/mL CSF vol</td>
<td>0.5(28b)</td>
<td>0.5% solution</td>
<td></td>
</tr>
<tr>
<td>µg per µL/min CSF turnover</td>
<td>8.75–17.5</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>Elimination µg/mL × µL/h</td>
<td>35–70</td>
<td>500 (7–14×)</td>
<td>176</td>
</tr>
</tbody>
</table>

References are shown superscript in parentheses.

IT = intrathecal; CSF = cerebrospinal fluid; ED = effective dose; MTD = maximum tolerated dose.

* Adult analgesic doses: 0.2–0.5 mg/kg epidural analgesia; 0.1 mg/kg intrathecal. As 0.5 mg/kg caudal epidural is also analgesic in neonate, assume 20% dose effective intrathecal.

* Dose data from 7-day rat pup.
of all ages, and particularly in neonates and infants as inadequately controlled pain in early development may also have adverse long-term effects.197 Our aim is not to discourage use of neuraxial anesthesia, but rather to encourage use of drugs with demonstrated efficacy and the widest possible safety margin. Clinical studies are well suited to assessing tolerability and efficacy, but cannot reliably confirm safety and an absence of morphological effects.136 Therefore, we complete this overview of neonatal neuraxial analgesic use by emphasizing 4 points.

First, we believe it is evident that the potential for spinal drug toxicity may present a greater problem in early life because of the dynamic properties intrinsic to neuraxial development.

Second, given the above issues, we believe that advances in this area require systematic preclinical assessments of the comparative safety of candidate drugs with attention being given to the therapeutic ratio of the neuraxially delivered drug, the developmental time of exposure to the drug, and assessment of neuropathology (apoptosis, myelination, gliosis, and dendritic morphology) and long-term functional outcomes. Furthermore, the research must recognize that the critical periods of development that occur (e.g., synaptogenesis, myelination, and apoptosis) differ for brain and spinal cord. Of equal importance, because the algorithm relating rodent and human neonatal development cannot be precisely matched, preclinical safety evaluations must review a range of developmental ages in their respective models.

Third, there is a need for a greater appreciation by IRBs regulating clinical trials, and by editors and reviewers of scientific publications, of the issues of potential toxicity and the degree to which the clinician-investigator has adequately addressed these concerns.

Finally, we must entertain a high index of suspicion of potential toxicity when drugs are administered neuraxially. Because children are rarely subject to detailed assessment after day-stay surgery, there is the potential to underestimate the rate of complications.67 This is particularly important in neonates and infants who may not only be more susceptible to perturbations in neural development, but who are also unable to report sensory symptoms, and because they are not walking, subtle motor deficits may be missed. We agree with others that more thorough follow-up of children after neuraxial analgesia is required,68 with longer-term epidemiological studies to establish clinical safety.296 Integrating preclinical and clinical data has also been the focus of studies evaluating adverse neurodevelopmental outcomes after general anesthetic exposure in early life. In this situation, the clinical benefits of diagnostic investigations and surgery with adequate anesthesia outweigh the risks identified in laboratory studies, and although modifications in practice have been suggested,287 current data do not support significant changes in clinical practice or provide clear evidence of a better alternative.11,215 However, when considering the choice of spinal analgesic adjuvants, many provide similar analgesia but not all have undergone systematic evaluations of spinal toxicity, and changing practice to include only drugs with the widest demonstrable safety margin can be achieved without compromising clinical care. It is essential to ensure that every step is taken to evaluate both the benefits and the safety of new and existing spinal drugs, before routine clinical use, to minimize the risk of an unexpected and untoward outcome.

**DISCLOSURES**

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Contribution: This author cowrote the manuscript.

Name: Tony L. Yaksh, PhD.

Contribution: This author cowrote the manuscript.

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