13 The Evidence-Based Safety of Pediatric Regional Anesthesia and Complications

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In the first edition of "Complications in Regional Anesthesia," Broadman[1] produced a chapter that essentially reported a synopsis of all of the complications that were available at that time in the English-language literature that were associated with the placement of regional blocks in infants and children, and the limited safety record associated with caudal block placements. The caudal block safety record was based on three moderately sized series, 750–7800 blocks, which had been safely performed by anesthesiologists that are now recognized authorities in the field of pediatric regional anesthesia.[2–4] All of the potential problems or complications associated with the placement of regional anesthesia blocks at the time of the first writing were unfortunately derived from single case reports.

In this chapter, your authors, Broadman and Holt, will focus their attention on the established safety record of pediatric regional anesthesia. This evidenced-based safety record was derived from data contained in the very large French (ADERPEF) study,[5] the most recent ASA Closed Claims Review,[6] the first 2000 adverse events reported in the Australian Incident Monitoring Study,[7] the 2001 Italian literature review on caudal block safety,[8] and a single-center experience with 1132 spinal anesthetics.[9] Finally, we will update the case report section on specific complications by adding new relevant cases that were reported in the peer-reviewed literature after 1997.

The Evidenced-Based Safety Record of Pediatric Regional Anesthesia

Perhaps the best single article on the overall safety of pediatric regional anesthesia is the 1-year prospective, multicenter (ADARPEF) study.[5] In this study, Giaufré, Dalens, and Gombert collected data on the complications encountered by 164 of the 309 ADARPEF members (French-Language Society of Pediatric Anesthesia) who voluntarily agreed to participate in this 1-year study. The members worked at hospitals in France, Belgium, and Italy, and the study ran from May 1, 1993 to April 30, 1994. Data were collected and evaluated from a total of 85,412 anesthetics, of which 61,003 involved general anesthesia only. These general anesthetics were excluded from further analysis. The remaining 24,409 cases contained some element of regional anesthesia (local infiltration, neuraxial, or peripheral blocks), and the anesthesia

B. T. Finucane (ed.), *Complications of Regional Anesthesia*

records from cases in which a complication or adverse outcome occurred were subjected to a very detailed analysis. Eighty-nine percent of the aforementioned blocks were placed under general anesthesia.

Peripheral blocks and local infiltration techniques were used in 9396 (38%) of the 24,409 regional cases. Local infiltration was the single most common "peripheral block technique" and was safely performed 5306 times. Surprisingly, there were no complications with either the placement of any of the peripheral blocks or the local infiltration cases, and many of these blocks were placed in the youngest patients.

All of the complications in this large series (23/24,409) occurred during the placement of central blocks. A total of 15,013 central blocks were placed, accounting for 61.5% of all regional anesthetic block placements. The caudal block was the most common central block. Twelve thousand one hundred eleven caudal blocks were placed and only 12 adverse incidents were encountered, for an incident rate of 1/1000 blocks. Heretofore, caudal blocks were viewed as the most simple pediatric regional technique and it was assumed that they were virtually free of any untoward outcomes. Based on the evidence contained in the Giaufré study,[5] this may not be the case and the same vigilance that one uses when placing more demanding central neuraxial blocks may be warranted when placing "routine" caudal blocks. There were no complications associated with any of the 372 thoracic epidural blocks. It can only be assumed that all of these blocks were placed by the most skilled pediatric anesthetists. The lumbar epidural block was associated with the highest adverse outcome odds ratio of 5/1000. There were 10 adverse incidents associated with the placement of the 2024 lumbar epidural blocks. Again, all 23 of the adverse events occurred during placement of neuraxial blocks and there were no complications associated with the placement of either peripheral nerve blocks or thoracic epidurals.

Two of the 23 complications recorded by Giaufré et al.[5] occurred in one patient. Dural puncture was the most frequent complication. Of the eight dural punctures, four resulted in total spinals. Two of the eight inadvertent dural punctures caused the patients to have postdural puncture headaches (PDPHs). There were six intravascular injections resulting in two seizures, two cardiac arrhythmias, and two that did not produce any adverse reactions. The seizures and arrhythmias took place despite there being a previous negative test dose in five of the six cases. Two complications were directly related to needle placement and management of a catheter. One rectal puncture and one kinked catheter were also reported. The two sacral postoperative paresthesias were likely the result of positioning because they took place after lumbar epidurals and completely resolved very early in the recovery process. There were three overdoses in the series. Two of these occurred with local anesthetic solutions and one with morphine. There was one "delayed block." Finally, there was one burn-related necrotic lesion over the gluteal region of a child after placement of a caudal catheter. This burn likely occurred secondary to cautery grounding pad placement over an area of skin that had been cleansed with surgical alcohol just before the placement of the caudal catheter. This first-degree burn resolved within 3 days and did not require any form of treatment. Again, it should be noted that two complications occurred in the same patient during their caudal block placement.

Several conclusions can be drawn from the Giaufré study data.[5] It should be noted that the use of improper equipment was blamed for the cause of the adverse event in 11 cases. It is imperative that our readers only use a needle of the correct length, gauge, and bevel for every pediatric block. One could also draw the conclusion that experience could have prevented many of these complications; however, it should be noted that 18 of the complications resulted from blocks placed by experienced practitioners. The majority of thoracic epidurals were performed in infants younger than 6 months of age, and one can only surmise that these blocks were placed by very experienced pediatric anesthesiologists. A similar situation may have existed for peripheral nerve blocks leading to their perfect safety record. Based on the Giaufré data,[5] one should consider a peripheral nerve block whenever possible as

opposed to a neuraxial block because they seem to be associated with fewer adverse outcomes.

The American Society of Anesthesiologists' Closed Claims Analysis provides a potential source for defining specific risks of regional anesthesia. In 1999, Cheney et al.[6] reviewed 2651 claims not previously reviewed since 1990, and 445 of these claims were the result of nerve injuries; however, *none of the claims involved pediatric patients.*

The first conclusion that one can deduce from this closed claims update[6] is that there is often no cause and effect relationship between anesthesia/surgery and perioperative nerve injuries. This is especially true with ulnar neuropathies. All of the ulnar neuropathies occurred in older patients and may have been related to positioning during surgery. There were eight patients who had lower-body procedures performed under a neuraxial block who sustained ulnar neuropathies. Therefore, one should be cautious when positioning all patients for surgery, and this should include pediatric patients. Similar injuries also occurred to the long thoracic nerve in adult patients who were awake during epidural anesthesia and in patients receiving brachial plexus or lumbosacral plexus blocks. Perhaps the reason one does not see such injuries in children is that they are more flexible and can tolerate positioning-related nerve stretching without sustaining any injury.

There were only 13 claims in adult patients for brachial plexus injuries, and in only four of the cases was a paresthesia reported at any time during any of these block placements. This should be somewhat reassuring to pediatric anesthesiologists because most pediatric brachial plexus blocks are placed under light general anesthesia, and even if these pediatric brachial plexus blocks were placed in awake or lightly sedated children most of the younger children would be unable to report a paresthesia. This closed claims report would suggest that there is a very low correlation between patients sustaining a paresthesia during block placement and resultant nerve injury. More importantly, virtually all pediatric peripheral blocks are now placed with either a nerve stimulator or ultrasonic guidance and a paresthesia is not needed to ensure block success.

There were 50 adult claims for spinal cord injury during regional anesthesia. The most common etiologies included spinal hematoma, chemical injury, anterior spinal artery syndrome, and meningitis. Thirteen of the claims resulted from block placements in anticoagulated placements. For the most part, children do not receive anticoagulation therapy and those who do are usually undergoing cardiac anesthesia. This may explain why there are no spinal, caudal, or epidural closed claims in children.

Ninety-three percent of the 67 lumbosacral adult nerve root injuries occurred during neuraxial anesthesia. Major risk factors included the elicitation of paresthesias during block placements and multiple attempts at block placement. It should be noted that 13 of the 23 sciatic injuries were associated with patient positioning. When performing lower-extremity nerve blocks in children, one should glean the following messages from the adult closed claims data: accurate needle placements must be obtained with either a nerve stimulator or ultrasonic guidance, and one should have a low threshold to abandon blocks when placement difficulties are encountered.

The Australian Incident Monitoring Study (AIMS) provides another opportunity to evaluate the safety and risks associated with the use of regional anesthesia. Fox et al.[7] took data from the first 2000 incidents that occurred in the AIMS program and scrutinized the cases that were done under regional anesthesia. There were a total of 160 cases in which regional anesthesia was associated with a complication; however, *none of these cases involved pediatric patients.* The cases were then subdivided into six groups according to the type of regional block that was performed. The groups were epidural, spinal, brachial plexus, intravenous regional anesthesia, ocular blocks, and local infiltration. Not surprisingly, circulatory problems were frequently seen in the spinal and epidural groups. These complications included hypotension, bradycar-

dia/tachycardia, and cardiac arrest. One would expect that similar problems would only be rarely encountered in the pediatric patients. Hypotension is not a problem in children younger than 7 or 8 years of age even when they develop a high spinal or epidural block.[9] Unintentional dural puncture was also a common complication in the AIMS study, and it frequently resulted in the development of a PDPH which required treatment with an epidural blood patch. PDPHs are rarely seen in pediatric patients younger than 10 years of age.[10] Pediatric PDPHs will be discussed in detail in a later section of this article.

All of the remaining incidences reported by the AIMS study[7] could potentially occur in pediatric patients with the same frequency as Fox and colleagues found in adults. There were 24 drug errors in AIMS. The small size of pediatric patients would likely make small drug errors that much more clinically significant. In this study, there were three incidences of delayed hypoxia/respiratory depression which occurred after the injection of epidural morphine. Respiratory depression, apnea, bradycardia, and periodic breathing are all major concerns when one anesthetizes former premature infants. In fact, the use of the caudal/epidural agent clonidine has been implicated as the causal agent in a recent postoperative apnea case report.[11]

An interesting conclusion one can draw from the AIMS study[7] is the very low incidence of perioperative mortality which was found in patients who received the benefits associated with having had a regional anesthetic. Unfortunately, only the numerator is known in the AIMS study, so one cannot make sweeping statements about the morbidity and mortality rate associated with regional versus general anesthesia. There was only one death in the 2000 AIMS patients and it was directly attributable to surgical hemorrhage. There were one case of pulmonary edema following hypotensive resuscitation and one case of neuraxial block–induced cardiac arrest. Both of these patients were successfully resuscitated.

Brachial plexus block–related complications were usually the result of local anesthetic toxicity. The AIMS study authors emphasized that the majority of these complications occurred in ASA class I–III patients and most of the incidents were immediately recognized and treated by a vigilant anesthetist. Infants younger than 6 months of age are particularly sensitive to the toxic effects of local anesthetics, and the AIMS study highlights the risks of using excessive doses to place brachial plexus blocks or the failure to recognize intravascular injections.

The Safety Profile of Spinal Anesthesia

Further support for the safety and efficacy of pediatric neuraxial anesthesia can be found in the low incidence of complications recently reported in a rather large series of 1132 spinal anesthetics by Puncuh and colleagues.[9] The children in this study ranged in age from 6 months to 14 years. Older patients were sedated with oral midazolam (0.6 mg/kg) whereas younger children received this drug via the rectal route. The maximum dose of midazolam was 15 mg irrespective of the patient's weight. An intravenous line was then inserted before placing a hyperbaric bupivacaine spinal with a 25-gauge Sprotte needle. The authors reported a success rate of 98%, which was defined as "not having to induce general anesthesia." All blocks took less than 5 minutes to perform, and complications or problems were only rarely encountered during any of the block placements. Seventeen children had intraoperative hypotension (defined as a decrease in systolic blood pressure by 20% or more from baseline). As expected, this phenomenon was rarely noted in children younger than 10 years of age (9/942) or less than 1% of the children in this younger age group. Seven children had transient oxygen desaturation, and this was likely the result of excessive intraoperative sedation with propofol, midazolam, or thiopental. Finally, one child developed bronchospasm for unknown reasons. The incidence of postoperative complications was also very low. Five children developed a PDPH; unfortunately, the ages of these children were not reported, but none of them required an epidural blood patch. Nine

of the children reported a transient self-limited backache. There were no neurologic deficits or mortalities in any patient in this study.

A Summary of Specific Complications Including Recent Reports

Air Loss of Resistance to Locate Epidural Space

Air loss of resistance techniques for caudal or epidural blockade should be avoided in pediatric patients. Reports indicate that children can develop a life-threatening venous air embolism from small quantities of air used during loss of resistance identification of the caudal epidural space.[12] Schwartz and Eisenkraft[13] reported circulatory collapse in a 9-month-old infant who had 3.0 mL of air injected into the lumbar epidural space. In fact, children may be at more risk than adults because of their high incidence of probe-patent foramen ovale (up to 50% in children younger than 5 years of age).[14]

Because of the lower extension of the dural sac, the risk of dural puncture theoretically is higher in infants and small children than in adults or older children. However, this complication is technique dependent and easily recognized if gentle aspiration is performed after placement of the needle and before the first injection of drug. If a dural puncture is noted, it would be prudent to abandon attempts at caudal blockade because of the risk of total spinal block.[15]

Infection and Associated Risks

One of the most feared complications of neuraxial anesthesia is infection, and it has been recently shown by Holt et al.[16] that a significant number of long-term indwelling catheters will ultimately become infected. The Holt study involved adult patients in whom about 1000 long-term indwelling epidural catheters were followed prospectively for a 17-month period of time. These catheters were left in place from 1 to 270 days and 147 catheter tips were sent for culture for various reasons. Seventy-eight of the 147 catheter tips were ultimately shown to be culture positive. Sixty-four of these 78 tips (82%) grew either *staphylococci* or *corynebacteria*; both of these bacteria are common skin flora. However, only 59 of the 78 patients were suspected of having an epidural-related catheter infection at the time the catheter tip was sent for culture. Twenty of these 59 patients had both insertion site– and catheter tip–positive cultures. Twenty-three other catheter tip–positive patients had systemic signs and symptoms of infection which could have been caused by the epidural catheter, such as meningitis, neurologic deficits, epidural abscess, back pain, or fever. Twelve of these 23 patients died during the study period, but it was not reported if the cause of death was the result of the catheter-related infections or the patients' underlying disease. These authors, Holt et al.,[16] demonstrated that the longer one leaves an epidural catheter in place the more likely it becomes that any given patient will ultimately develop a catheter-related infection. Epidural catheter infections are extremely rare if catheters are left in place for 2 days or less, but the incidence increases dramatically over the next 2 weeks. It should be noted that the average duration of catheterization for patients with only local symptoms was 8 days, whereas those with generalized symptoms had their catheters in place for an average of 15 days. Again, 82% of the infections were caused by normal skin flora supporting the conclusion that local spread is the most common route for the development of catheter tip–positive cultures/infections. Moreover, in the majority of central nervous system infections, localized signs and symptoms were present before the development of these more serious infections. This emphasizes the need for all anesthesiologists and pain medicine physicians to promptly remove catheters that appear to be infected. Finally, these authors recommended that cryptic and overt catheter-related infections, including meningitis and epidural abscess, be promptly diagnosed via lumbar puncture and magnetic resonance imaging studies.

More germane to the pediatric population is a recent study by McNeely and colleagues[17] in which they prospectively studied and cultured the lumbar epidural (n = 46) and caudal catheter tips (n = 45) from pediatric patients in whom all 91 catheters had been placed under aseptic conditions in the operating room and then used to provide short-term postoperative analgesia.[16] On discontinuation of the epidural infusion, the skin was decontaminated with 70% alcohol and then cultured. The distal catheter tip and hub were also cultured. Nine of the caudal catheter tips (20%) were colonized, whereas only two of the lumbar epidural tips (4%) grew bacteria ($P < .02$). Staphylococcus was the predominant skin and catheter tip organism in both groups, but only the caudal catheters grew gram-negative organisms (4/9) (42%). The results of this study suggest that the risk of producing a clinically significant epidural infection is quite low when one uses either a lumbar epidural or caudal catheter to provide short-term postoperative analgesia in the pediatric population. However, the incidence of catheter tip colonization significantly increases when the caudal route is used and it is more likely that the tip will be colonized with more pathogenic gram-negative organisms.

A novel approach to reducing or eliminating caudal catheter tip colonization and localized infections has recently been reported by Fujinaka et al.[18] These researchers demonstrated that by subcutaneous tunneling caudal catheters, infections and catheter tip colonizations could be eliminated. They prospectively studied 18 infants and toddlers in whom caudal catheters were left in place for an average of 3.9 days. Surprisingly, there was a zero incidence of either catheter tip colonization or the development of localized infection in any child. However, one must use caution when attempting to apply these data to the management of long-term indwelling chronic pain catheters because the length of catheterization was brief and the number of patients enrolled in this study was very small.

An older study by Strafford and colleagues[19] also substantiates the belief that epidural infections following the administration of protracted epidural analgesia via indwelling catheters is a very rare event in infants and children. These authors retrospectively reviewed the records of 1620 caudal/epidural catheter placements in infants and children over a 6-year period. The catheters were left in place for as long as 14 days, median 2.4 days. Seventy catheters (3.7%) were placed via the caudal approach; however, the majority of these catheters were lumbar epidural catheters (93%). A combination of bupivacaine and fentanyl was the most common perfusate. This study reported a 0% incidence of clinically significant infections in postoperative patients, a rate that is not statistically different from the spontaneous abscess rate of 0.2–1.2 cases per 10,000 hospital admissions.[20] Epidural abscess was not a reported complication in any of the patients in the Strafford study[19] who received postoperative analgesia via a caudal/epidural catheter. However, one terminally ill child with a necrotic epidural tumor did develop *Candida* colonization of her epidural space.

Meunier and colleagues[21] reported two cases in which infants with biliary atresia developed localized skin infections at their lumbar epidural puncture sites. Both children had undergone Kasai procedures and had received epidural analgesia for the first 48 postoperative hours, at which time the catheters were removed. On the fifth postoperative day, each child was noted to have an area of induration and a small pustule at the catheter entry site. In each case, the pus was evacuated and sent for culture. No organisms were isolated in the first case, so antibiotic therapy was not instituted. The second child was noted to have a recurrent collection of fluctuant subcutaneous material in the area of catheter insertion and underwent surgical incision and drainage of his subcutaneous abscess on postoperative days 6 and 12. His *Staphylococcus aureus* infection was also treated with an appropriate course of oxacillin.

However, the most distressing pediatric infection-related case report in the literature is by Larsson and colleagues.[22] These authors document the formation of an epidural abscess in a 1-year-old boy with severe visceral pain secondary to a rare

condition, chronic intestinal pseudoobstruction. His pain could not be managed with parenteral narcotics and over a 6-month time span, from when he was 7 months old until he was 1 year of age, he had three lumbar epidural catheters placed for pain control. Each remained in place from 3 to 12 days. The child's third catheter had been deliberately placed more cephalad than previous ones in order to better target the area of nonoperative chronic visceral pain and to minimize bupivacaine infusion requirements. It had been placed through a L1–L2 puncture site and the catheter tip had been threaded cephalad to T11–12. Eleven days after the placement of this third catheter, the concentration of bupivacaine had to be increased from 0.125% to 0.375%. Despite the large dose of bupivacaine being infused (1.1 mg/kg/h), the child's pain could not be adequately controlled and parenteral narcotics were administered. The next day (day 12), tender swelling was noted at the epidural catheter penetration site. The catheter was immediately removed. A bacterial culture from the epidural catheter tip revealed the growth of *Pseudomonas aeruginosa* which was sensitive to tobramycin. A magnetic resonance imaging confirmed the presence of an epidural abscess extending T5 to L5. The abscess was noted to be deforming and dislocating the medulla in this area. Surprisingly, the child had not developed any neurologic symptoms. He was treated nonsurgically with intravenously administered antibiotics. The abscess could not be detected on a follow-up computed axial tomography study 11 days after the institution of antibiotic therapy. He survived this event without sequelae. These authors provide the following invaluable tip. When one notes a sudden and otherwise unexplained decrease in the ability of previously effective epidural catheter to continue to provide adequate pain control, an epidural abscess should be included in the differential problem list.[22]

Larsson and colleagues[22] suggest that their patients' continuous bacteremia from his necrotizing enterocolitis may have led to the seeding of his epidural catheter and the subsequent development of his epidural abscess. Likewise, both children in the Meunier report[21] were known to have congenital biliary atresia and had undergone a recent Kasai procedure; as such, they probably had ascending cholangitis and bacteremia.

It is the opinion of Broadman and Holt that children with known or suspected bacteremia/septicemia are probably not suitable candidates to receive neuraxial anesthesia or analgesia.

It is common practice for many pediatric anesthesiologists and their dental colleagues to induce anesthesia in children with congenital heart disease, start a peripheral intravenous line, and then have the surgeons perform a dental block before having completed the infusion of prophylactic antibiotic therapy (SBE prophylaxis). However, an article by Roberts et al.[23] demonstrated a significant increase in bacteremia after buccal infiltration analgesia (16%), modified intraligamental analgesia (50%), and intraligamental analgesia (97%). All of these blocks are common techniques used by pedodontists to supplement general anesthesia and to provide postoperative analgesia. The Roberts study involved 143 children varying in age from 23 months to 19 years. Fifty consecutive children had blood cultures drawn after the induction of anesthesia but before any dental manipulation (baseline). The remaining 93 children were randomized to receive a dental block via one of three aforementioned techniques and a postblock blood culture was obtained 30 seconds after each injection. Therefore, each child had only one blood culture drawn. There were 4/50 children who had spontaneous or "background" bacteremia (8%); this finding was quite surprising and suggests that children with congenital heart disease may be at ongoing risk for the development of endocarditis from dental-based bacteremia. There was a significant increase in bacteremia from all of the dental blocks ($P < .0001$) when compared with baseline values. This study certainly has implications for the timing of SBE prophylaxis administration and the performance of dental blocks. The authors conclude that the modified technique should be used when possible in children at risk for developing endocarditis. Based on the findings of Roberts et al.,[23] Broadman and Holt believe

that SBE prophylaxis should be started in all at-risk children before any dental blocks or manipulations are undertaken.

The Advantages of Caudal Catheters

Lumbar and thoracic epidural anesthesia poses certain advantages over caudal anesthesia in infants and children undergoing upper abdominal and thoracic procedures. Both of the former techniques allow for the targeting of local anesthetic solutions at the site of surgery and therefore reduce the potential for toxic drug reactions and other morbidities. Although both of these techniques, lumbar and thoracic epidural catheter placements, have been well described in children in the older literature,[24,25] it was the belief that both of these blocks were technically difficult and even hazardous to perform in infants and children. However, a recent report by Giaufré and associates[5] refutes these early opinions and clearly demonstrates that thoracic epidural blocks are quite safe when placed by a skilled pediatric anesthetist. However, caudal catheters are very easy to place and the catheter tips may be threaded cephalad to the desired level, thereby affording one the opportunity to provide thoracoabdominal anesthesia/analgesia without the associated risks of either spinal cord trauma or local anesthetic toxicity.[26,27]

Problems Encountered During the Cephalad Advancement of Lumbar Epidural Catheters

An article by Blanco and colleagues[28] demonstrated that it is very difficult and sometimes impossible to advance a catheter that has been placed in the lumbar epidural space cephalad to a thoracic level in infants and children older than 1 year of age. The Blanco group studied 39 infants and children who ranged in age from 0 to 96 months. They used an 18-gauge Tuohy needle and air loss of resistance techniques to properly identify the epidural space at the L-4/L-5 interspace in all study patients. Unfortunately, only 7/39 (18%) of the 19-gauge, unstyletted, polyethylene, multiorifice catheters could be advanced cephalad to the T-12 level. Twenty-three of the 39 catheters (59%) simply formed a loop at or about the L-4/L-5 region. Eight of the catheters were difficult to place. The fact that a catheter was easy to place did not positively correlate with the ability to advance the catheter tip cephalad. There were no inadvertent dural punctures and all catheters were removed without difficulty.

Why did the Blanco group[28] encounter so much difficulty passing 19-gauge catheters cephalad, and Bösenburg et al.[26] and Gunter and Eng[27] did not? Perhaps it relates to the fact that Bösenburg et al.[26] placed their catheters in infants younger than 1 year of age, and one would suspect that most of the infants in the Bösenburg study had not yet assumed upright posture. Therefore, they had not developed lumbar lordosis and 19/20 of Bösenburg's catheters easily passed cephalad.

Gunter and Eng[27] circumvented this problem in older infants and children by using wire styletted microcatheters. Broadman, Holt, and their colleague David Rosen have been using a wire styletted, open-end, microcatheter for several years and coiling has not been a problem (Sims 20/24 Micro Catheter System®).

Postdural Puncture Headache

The incidence of PDPH in children following spinal anesthesia or an inadvertent "wet tap" during placement of an epidural block is quite low, and Wee and Colleagues[10] suggest that the problem rarely occurs in children younger than 10 years of age. However, these authors point out that PDPH is quite common in older pediatric patients and the incidence increases with age. Wee et al.[10] prospectively studied 105 children with malignant disease who ranged from 3 to 18 years of age. All of the children were having a lumbar puncture performed under general anesthesia, and all of the punctures were performed with a 22-gauge spinal needle with a "cutting point."

The parents of each child were given a questionnaire to answer over the 3-day period after the diagnostic/therapeutic lumbar puncture and the questionnaire was targeted to answer the following questions: What was the incidence of PDPH in children and did such headaches spontaneously resolve with time and hydration? Ninety-seven questionnaires were returned (92%). *None of the children younger than 10 years of age developed a PDPH.* Of the children aged 10–12 years, 2 of 17 developed a headache (11.8%). The older children aged 13–18 years had an incidence of 50% (5/10). Adolescent girls in this study had headaches twice as frequently as did boys and this sex-related difference is consistent with the incidence of PDPH reported by Raskin[29] in adults. The reason for the low incidence of PDPH in children younger than 10 years of age is unknown, but it may be related to the lower CSF pressures found in this age group.[30]

A case report by McHale and O'Donovan[31] suggests that there is a role for the use of epidural blood patch techniques in pediatric patients with PDPHs that fail to respond to conservative therapy. McHale and O'Donovan injected 8 mL of blood into the epidural space of a 39-kg boy (0.2 mL/kg) while he was under general anesthesia and his classic PDPH symptoms promptly resolved. The child had had a classic PDPH for 4 days following an inadvertent subarachnoid puncture during a lumbar epidural catheter placement with an 18-gauge Tuohy epidural needle. The volume of blood used in this report is consistent with the amount found in earlier case reports.[32,33] However, the best single reference to help one manage the placement of an epidural blood patch in infants and children is an article by Kumar and colleagues.[34] These authors point out that an epidural blood patch provides effective treatment for PDPH in pediatric patients when the child has not responded to conventional therapy and symptoms persist for more than a week. Sedation and EMLA® cream may be beneficial adjuncts to reduce the pain and emotional trauma of blood patch therapy. Practitioners should consider the child's age and level of maturity when determining whether conscious or deep sedation will be required. The volume of autologous blood recommended varies from 0.5 to 0.75 mL/kg, and should be injected slowly.[34]

Problems with Test Dosing

There is no effective test dosing method or other technique for the reliable detection of the intravascular injection of local anesthetic solutions during block placements in children simultaneously undergoing general anesthesia with volatile agents. Desparmet and colleagues[35] studied 65 children, ranging in age from 1 month to 11 years of age, and found that children who received an intravenous epinephrine-containing solution without atropine pretreatment did not demonstrate a consistent increase in their heart rates. Furthermore, 94% of children who received atropine premedication followed by intravenous epinephrine had only a brief heart rate increase of greater than 10 bpm, (peaking at 45 seconds and lasting to 60 seconds postinjection).[35] It must be emphasized that the atropine injection in this study was given to patients with a stable end-tidal halothane concentration of 1.0%. Increases in heart rate of 10 bpm or more may be noted after needle placements in children who are not so deeply anesthetized. Perillo and colleagues[36] performed a similar study comparing two intravenous doses of isoproterenol (0.05 μg/kg and 0.075 μg/kg). As in the epinephrine study by Desparmet and colleagues,[35] Perillo et al.[36] were unable to show any consistent or predictable relationship between the infusion of the aforementioned test doses of isoproterenol and increases in heart rate.

As in adults, it is important to administer the local anesthetic solution in small increments and carefully monitor for signs of systemic toxicity rather than to rely completely on a test-dosing technique.

The Toxicity of Local Anesthetics

Bupivacaine is one of the most frequently used local anesthetic agents for pediatric caudal and epidural blocks. This agent can be used safely if maximum dosage guide-

lines are followed. However, complications relating to neurologic and cardiac toxicity have been reported.

Whereas the toxic plasma bupivacaine level for adults is estimated to be 4.0μg/mL,[37] the level in infants and children is not known. Plasma levels that are less than 2.0μg/mL are thought to be safe in children and have not been associated with neurologic or cardiac toxicity.[38] However, a number of factors indicate that one should use caution when applying adult toxicity data to children. The metabolism of local anesthetics is greatly reduced in the neonate, because of both decreased plasma pseudocholinesterase and decreased hepatic microsomal activity.[39,40] Also, alpha$_1$-acid glycoprotein (AGP) concentrations are quite low in infants younger than 2 months of age and they do not reach adult levels until after the first year of life.[41] Alpha$_1$-AGP is important because it is the primary binding substrate for cationic drugs such as local anesthetics. Albumin and other plasma proteins only have a very minor role in the binding of local anesthetic solutions. Reduced levels of alpha$_1$-AGP allow for more of the local anesthetic solution to remain in the unbound or free form, and it is only the unbound fraction of local anesthetics that can precipitate toxic reactions such as seizure activity and myocardial depression.

Children eliminate drugs faster than newborns and infants but more slowly than adults. This slower rate of elimination requires particular attention to continuous infusions of local anesthetic. The larger cardiac output of pediatric patients is a factor in the relatively rapid increase of local anesthetic blood levels, especially in the vessel-rich organs such as the brain and heart.

Other factors that have been noted to potentially increase susceptibility to bupivacaine toxicity include concomitant administration of volatile agents,[42] acidosis,[43] hypoxia,[44] and hyponatremia and hyperkalemia,[45] as well as rapid increases in plasma bupivacaine levels.[46]

Several studies have evaluated bupivacaine plasma levels following the administration of single bolus doses to pediatric patients. After lumbar epidural administration of 0.25% bupivacaine (3.0mg/kg), Eyres and colleagues[47] noted that plasma levels peaked at 20 minutes and ranged from about 1.0 to 2.0μg/mL. Ecoffey et al.[24] studied 10 infants and children who ranged in age from 3 to 36 months. Six of the infants had thoracic epidural catheters and four had lumbar catheters. Peak plasma levels occurred in these infants 20 minutes after the bolus administration of 0.5% bupivacaine (3.75mg/kg). All of their plasma levels were less than 1.8μg/mL with the exception of one child who had a plasma level of 2.2μg/mL.[24] Eyres and coworkers[48] found that plasma bupivacaine concentrations ranged from 1.2 to 1.4μg/mL after the caudal injection of 0.25% bupivacaine (3mg/kg) in children. Stow and colleagues[49] also noted that peak plasma bupivacaine concentrations were reached at around 20 minutes after caudal administration to children. In each of the aforementioned studies,[24,47–49] the peak plasma levels of bupivacaine were less than those that are considered to be toxic in adults, and all of the peak plasma levels occurred 20 minutes after administration by caudal, lumbar, and thoracic injections.

Desparmet and colleagues[50] evaluated plasma bupivacaine levels in six children who were given a loading dose of 0.25% bupivacaine (0.5mL/kg) without epinephrine injected into the lumbar epidural space, followed in 30 minutes by an infusion of the same drug at a rate of 0.08mL/kg/h. Plasma bupivacaine levels were assayed from specimens obtained at 4-hour intervals between 24 and 48 hours after the start of the infusion, and then every 2 hours until 10 hours had elapsed following termination of all infusions. Plasma levels in these six children were highly variable, ranging from 0.2 to 1.2μg/mL. No increase was noted in plasma levels between 24 and 48 hours. However, research on adults has shown that continuous epidural infusions of bupivacaine produce constant plasma levels until approximately 50 hours after the start of infusion when a dramatic increase occurs.[51]

McIlvaine et al.[52] evaluated plasma bupivacaine levels in children receiving intrapleural infusions at rates of 0.5–2.5mg/kg/h. Plasma bupivacaine levels ranged from 1.0 to 7.0μg/mL. None of these children were noted to experience any signs of toxicity;

however, this may be attributable either to the small number of patients in the series, or to the fact that some of the children received diazepam within the first 24 hours after surgery.

Agarwal and colleagues[53] reported two cases of neurotoxicity related to continuous bupivacaine infusions. Both patients received 0.25% bupivacaine with 1:200,000 of epinephrine. The first case involved a 9.4-kg 3-year-old girl with chronic interstitial lung disease who was scheduled for a right middle lobe lung biopsy. During the procedure, an intrapleural catheter was placed. It should be noted that systemic absorption of local anesthetic agents is far greater in the intrapleural space than in either the intercostal or caudal epidural space. One hour after a bolus dose of 0.66 mg/kg of bupivacaine was administered, an infusion of 0.25 mg/kg/h was begun. Five hours later the infusion was increased to 0.5 mg/kg/h because of complaints of increased discomfort. Twenty-one hours after the start of the infusion, the patient had two tonic-clonic seizures which were treated with intravenous phenobarbital (100 mg). The patient's bupivacaine plasma level was 5.6 μg/mL at the time of her seizures. The second patient to develop seizures from systemic accumulation of bupivacaine was a 26-kg 9-year-old girl with cerebral palsy. She was a former premature infant, but at the time of the report, she was an otherwise healthy child, scheduled for selective dorsal rhizotomy. After a bolus of bupivacaine (1.25 mg/kg) was injected into her caudal epidural catheter, an infusion at the rate of 1.25 mg/kg/h was started. Fifty-six hours after the start of the infusion, the patient had three tonic-clonic seizures that were successfully treated with phenobarbital. The patient's plasma bupivacaine level at the time of the first seizure was 5.4 μg/mL.

Of interest in the report by Agarwal and colleagues[53] is the complete absence in both cases of prodromal warning signs, which might have alerted caregivers of the impending onset of acute bupivacaine neurotoxicity. Both patients were reported to be calm, cooperative, and restful just before the onset of their seizure activity. The only unusual complaint was from the second patient, who reported a "falling" or "tumbling" sensation several hours before the onset of her seizures.[53] Early central nervous system manifestations of toxicity may not be apparent in children because they are less likely to articulate their symptoms. In infants and toddlers who are awake, these symptoms may be misinterpreted as irritability or "fussiness." The first signs of local anesthetic toxicity in a pediatric patient may be dysrhythmias or cardiovascular collapse.[54,55]

McCloskey and colleagues[56] reported three cases in which children experienced toxic side effects from their continuous epidural bupivacaine infusion. Bupivacaine 0.25% with 1:200,000 of epinephrine was used in all three patients. The first case was a 3.89-kg 1-day-old newborn scheduled for direct closure of exstrophy of the bladder. Bupivacaine solution in bolus doses of 2.5, 1.87, and 1.87 mg/kg was administered at hours 0, 1.5, and 3.0, respectively. At hour 4.5, an infusion was begun at the rate of 2.5 mg/kg/h. Ten hours after the start of the infusion, the patient developed bradycardia and hypotension. The infusion was discontinued and the newborn was quickly intubated. Bag and mask ventilation with oxygen was instituted and epinephrine (10 μg/kg) was given intravenously. The sinus bradycardia suddenly changed to ventricular tachycardia, which partially responded to three bolus doses of lidocaine (1.0 mg/kg) and one dose of sodium bicarbonate (1.0 mEq/kg). Normal sinus rhythm was reestablished through the intravenous infusion of phenytoin (5.0 mg/kg). However, 2 hours later, the patient's rhythm reverted once again to ventricular tachycardia and generalized tonic-clonic seizure activity was noted. Both were treated successfully with intravenous diazepam, 0.25 mg/kg and serially administered phenytoin for a total dose of 7.0 mg/kg. The plasma bupivacaine level at the time the infusion was discontinued was 5.6 μg/mL, and 12 hours later it had only decreased to 3.7 μg/mL. The child had no neurologic sequelae as a result of the aforementioned events and enjoyed an uneventful recovery.

The second patient reported by McCloskey and colleagues[56] was a 45-kg 8-year-old child scheduled for bladder augmentation. Bolus doses of bupivacaine 1.40, 0.83, 0.55, and 1.00 mg/kg were given at 0, 1.5, 3.5, and 5.5 hours, respectively, via his epidural catheter. An infusion of 1.67 mg/kg/h was begun at hour 9.5. After another 25 hours, the patient experienced two generalized tonic-clonic seizures which responded to diazepam. The plasma bupivacaine level shortly after the seizure was 6.6 μg/mL. The third patient was a 12-kg 4-year-old girl with bilateral knee trauma resulting from a motor vehicle accident. There were no signs of head trauma. The patient received bupivacaine boluses during surgery of 2.50, 1.67, 1.67, and 1.67 mg/kg at hours 0, 2.0, 4.0, and 5.5, respectively. A bupivacaine infusion was begun 3.0 hours after the last intraoperative dose at the rate of 1.67 mg/kg/h. At hour 26, the patient's level of analgesia decreased from T-10 to L-2. A leak at the catheter insertion site was noted, and the catheter was replaced. A 0.42 mg/kg bolus was given and the infusion was reinstituted at 2.0 mg/kg/h. Eight hours later, the patient experienced a generalized tonic-clonic seizure which resolved with diazepam. The patient's plasma bupivacaine level was 10.2 μg/mL at the time of her seizure. Neurologic examinations of all three patients after seizure activity resolved were normal.

The infusion rates for all three patients in the aforementioned case report were excessively high. This led McCloskey and colleagues[56] to develop infusion guidelines based on extrapolations from linear pharmacokinetic projections for bolus caudal and epidural bupivacaine levels. They suggested 0.4 mg/kg/h for infants younger than 6 months and 0.75 mg/kg/h for older children.[56] However, lower infusion rates, which provide adequate analgesia, yet pose less potential for toxic complications, have been established by Berde.[57] The Berde recommended dosage guidelines for epidural bupivacaine infusions include a loading dose of 2.0–2.5 mg/kg and an infusion rate not in excess of 0.4–0.5 mg/kg/h in older infants, toddlers, and children and less than 0.2–0.25 mg/kg/h in neonates.

The second complication related to bupivacaine toxicity is cardiac dysrhythmia. This is perhaps a more serious complication because it may be refractory to conventional treatment. Maxwell and colleagues[55] have successfully used phenytoin in the treatment of two neonates with bupivacaine-induced cardiac toxicity. The first patient in the Maxwell article[55] is the same 3.89-kg 1-day-old newborn with exstrophy of the bladder presented by McCloskey et al.[56] The second patient was a 4.4-kg full-term infant, also with exstrophy of the bladder, who received three caudal bolus doses of bupivacaine, 2.50, 1.25, and 1.75 mg/kg, at 0, 2.5, and 4.5 hours, respectively. Five minutes after the third dose was administered, the patient developed a wide-complex tachydysrhythmia. All anesthetic agents were discontinued, and 100% oxygen was administered. After bretylium 5.0 mg/kg was administered, the patient's heart rate increased from 120 to 240 bpm and his blood pressure decreased from 90/60 to 65/40 torr. Normal sinus rhythm was reestablished after phenytoin was administered in divided doses for a total dose of 7.0 mg/kg.

Broadman and Holt suggest that if inadequate analgesia persists after the maximum dose of bupivacaine has been administered and incorrect needle placement and other technical problems have been ruled out, it is unwise to administer additional bupivacaine. Either an epidural opioid can be added to the local anesthetic solution or a systemic opioid can be used in conjunction with the epidural infusion. Moreover, it may simply be more prudent in such cases to simply discontinue the epidural catheter/infusion and use systemic opioids or other analgesics.

An older report[55] suggests that a continuous infusion of caudal or epidural lidocaine may be preferable to bupivacaine because of the ability to rapidly and easily monitor plasma concentrations of the former agent in most hospital laboratories. Unfortunately, many hospital laboratories no longer perform in-house lidocaine assays; therefore, there may not be any advantage to using a long-term lidocaine infusion. More importantly, the newer isomer-specific agent ropivacaine has been extensively studied

in the pediatric population and it may be the agent of choice for long-term infusion analgesia in infants and children.

Levobupivacaine and Ropivacaine Toxicity in Children

A complete Medline® search was conducted by your authors from 1997 through May 2005. This search was facilitated through the use of Procite®. We can say without reservation that there seems to be zero adverse outcomes or reactions in pediatric patients associated with the use of either levobupivacaine or ropivacaine during the placement of axis or peripheral blocks. However, there are two recent adverse reaction case reports in adult patients that clearly show that toxic reactions can occur with either of these new local anesthetic agents.[58,59]

However, there are several studies involving infants and children in which ropivacaine has been successfully used to provide intraoperative anesthesia and postoperative analgesia without any adverse outcomes or complications.[60–66] There are advantages to using ropivacaine in lieu of bupivacaine. However, the most important advantage of ropivacaine is its well-established reduced cardiotoxicity profile which has been clearly demonstrated in animal models.[67] It has also been shown that when ropivacaine and bupivacaine are used in equipotent doses in pediatric patients, the resultant peak plasma concentrations are much lower in the ropivacaine group.[62] The pharmacokinetics of ropivacaine has been recently studied in the pediatric population. Apparently, the use of ropivacaine in children is associated with a longer elimination half-life and a larger volume of distribution when compared with adults.[63] The pharmacodynamic profile for ropivacaine has also been defined in pediatric patients. Concentrations of 0.2% ropivacaine or less have been shown to produce both excellent intraoperative and postoperative analgesia.[64] In fact, dangerously high peak plasma concentrations were noted when higher concentrations of ropivacaine (0.375%–0.5%) were used with a total dose of 3.5 mg/kg.[65] These relatively high doses were associated with peak plasma levels of 4.33–5.6 μg/mL.[65] Although no toxic side effects were noted in the aforementioned study, it would be prudent to limit total doses of ropivacaine to 3.0 mg/kg or less. If more intense intraoperative motor blockade is needed and higher concentrations of ropivacaine are used, then one can decrease peak plasma ropivacaine levels by using epinephrine (1:200,000).[66] Van Obbergh and colleagues[66] recently showed that the addition of epinephrine reduced peak ropivacaine plasma levels by approximately 33% after caudal injection. However, caution is warranted when applying the above ropivacaine data to neonates and chronically ill pediatric patients because neither of these groups were specifically targeted.

Spinal Opioids, Clonidine, and Respiratory Depression

The use of either epidural opioids or clonidine alone or in concert with local anesthetic agents has gained widespread acceptance with many pediatric anesthetists during the past decade. However, delayed respiratory depression is always possible, whether the opioid is administered via the caudal, epidural, or spinal route, especially in young infants. This is particularly true with concomitant administration of systemic opioids.

Nichols and colleagues[68] studied the disposition and respiratory effects of subarachnoid morphine in 10 infants and children undergoing craniofacial surgery. All of these children required cerebrospinal fluid (CSF) drainage as part of the surgical procedure; this was accomplished by placing a subarachnoid catheter at the L4-L5 interspace. The same catheter was used to administer subarachnoid morphine (2.0 μg/kg) before the conclusion of surgery, and then to sample and measure the CSF concentration of morphine at 6, 12, and 18 hours. Corresponding plasma concentrations of morphine were determined by radioimmunoassay. Subarachnoid morphine produced a reduction in both the slope and the intercept of the ventilatory response curve; this reduction was greatest 6 hours after morphine administration, and the ventilatory

response only partially recovered 12 and 18 hours later. This study documents that infants and children may experience respiratory depression for at least 18 hours after subarachnoid morphine administration and that appropriate monitoring and safeguards are essential.

The pharmacokinetic parameters observed after epidural morphine administration in older children have been found to be similar to those previously measured in adults, including a significant decrease in the minute ventilatory response to breathing an end-tidal CO_2 pressure of 55 torr. Breathing such a mixture caused a significant shift in the CO_2 response curve for more than 22 hours after epidural morphine administration.[69] Krane and colleagues[70] demonstrated that caudal morphine in a dose of 33 μg/kg provides excellent analgesia with a lower incidence of the delayed respiratory depression. Such delayed respiratory depression was previously reported by Krane[71] when a larger dose of 100 μg/kg was administered to a 2.5-year-old boy. Valley and Bailey[72] reported the use of caudal morphine (70 μg/kg diluted with normal saline) in 138 children undergoing major abdominal, thoracic, and orthopedic surgery. Children weighing less than 5 kg received 3.0 mL of solution, whereas those weighing 5–15 kg received 5.0 mL and those weighing more than 15 kg received 10 mL of solution. Of note is the high incidence of respiratory depression that occurred in 11 children in this study.[72] Of these 11 children, 10 were younger than 1 year of age and most had received concomitant systemic opioids along with the extradural opioids. The mean time from the administration of caudal morphine until the onset of respiratory depression in this group was 3.8 hours; *no respiratory depression occurred in any child more than 12 hours after the administration of the last dose of caudal morphine.* All episodes of respiratory depression were successfully managed with naloxone (5–20 μg/kg) followed by the infusion of naloxone at the rate of 2–10 μg/kg/h.

Bailey and colleagues[73] compared the efficacy of caudal, epidural, and intravenous butorphanol in reducing the incidence of adverse side effects associated with epidural morphine. They found that there was no difference in the incidence of adverse side effects between the children who had received butorphanol and those who had not. However, Lawhorn and Brown[74] found a decreased incidence of opioid-related complications when butorphanol (40 μg/kg) was added to epidural morphine (80 μg/kg).

The addition of clonidine to epidural morphine seems to provide prolonged analgesia without increasing the incidence of adverse side effects.[75] However, as reported earlier in this chapter, there has been a recent case report in which a former 32-week gestational-age neonate, who was 38 weeks' postconceptional age at the time of his elective inguinal hernia repair, received epidural clonidine and experienced significant periods of apnea and bradycardia.[11] This child essentially served as his own control because he received two separate caudal epidural anesthetics. The caudal blocks served as his total anesthetic during both surgeries. The first hernia repair was conducted with caudal bupivacaine (0.25%) and no periods of apnea were observed. One week later, a second herniorrhaphy was required. This time he received a caudal block that contained both bupivacaine (0.125%) and clonidine (1.8 μg/kg). Unfortunately, the infant experienced profound periods of apnea and bradycardia for more than 12 hours after the second anesthetic. Caution is warranted should one elect to administer either caudal or epidural clonidine to pediatric patients at risk for the development of apnea, bradycardia, or periodic breathing.

Conclusion

At the time of this writing, 2005, the safety and efficacy of pediatric regional anesthesia has been well established. That being said, there are still rare but serious complications that can occur should one elect to use regional anesthesia techniques in infants and children; however, many of these problems can be avoided by using good techniques, selecting the proper materials and patients, and by providing appropriate

follow-up care to detect early signs and symptoms of serious complications. The benefits of using regional anesthesia either alone or in conjunction with general anesthesia in pediatric patients are not limited to just obtaining better postoperative pain control,[76] but also to a decreased need for postoperative ventilation[77] and a decreased response to stress.[78] Even in pediatric cardiac surgery where patients may be at an increased risk of developing an epidural hematoma because of total body heparinization during bypass, expert opinion has weighed in favor of using spinal axis anesthesia/analgesia to provide our pediatric patients with profound postoperative pain relief.[79]

Acknowledgments

The authors thank Heather Harris, Emily Stewart, Karen Holt, and David Chasey for their assistance in the research and preparation of this chapter.

References

1. Broadman LM. Complications of pediatric regional anesthesia. In: Finucane BT, ed. Complications of Regional Anesthesia. 2nd ed. Philadelphia: Churchill Livingstone; 1999: 245–256.
2. Dalens B, Hasnouai A. Caudal anesthesia in pediatric surgery: success rate and adverse effects in 750 consecutive patients. Anesth Analg 1989;68:83–89.
3. Broadman LM, Rice LJ. Neural blockade for pediatric surgery. In: Cousins MJ, Bridenbaugh PO, eds. Neural Blockade in Clinical Anesthesia and Pain Management. 3rd ed. Philadelphia: JB Lippincott; 1998:615–636.
4. Veyckemans F, Van Obbergh LJ, Gouverneur JM. Lessons from 1100 pediatric caudal blocks in a teaching hospital. Reg Anesth 1992;17:119–125.
5. Giaufré E, Dalens B, Gombert A. Epidemiology and morbidity of regional anesthesia in children: a one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists. Anesth Analg 1996;83:904–912.
6. Cheney FW, Domino KB, Caplan RA, Posner KL. Nerve injury associated with anesthesia: a closed claims analysis. Anesthesiology 1999;90:1062–1069.
7. Fox MAL, Webb RK, Singleton R, et al. Problems with regional anaesthesia: an analysis of 2000 incident reports. Anaesth Intensive Care 1993;21:646–649.
8. Zadra N, Giusti F. Il Blocco caudale in pediatria. Minerva Anestesiol 2001;67(suppl 1): 126–131.
9. Puncuh F, Lampugnani E, Kokki H. Use of spinal anaesthesia in paediatric patients: a single centre experience with 1132 cases. Pediatr Anesth 2004;14:564–567.
10. Wee LH, Lam F, Cranston AJ. The incidence of post dural puncture headache in children. Anaesthesia 1996;51:1164–1166.
11. Fellmann C, Gerber AC, Weiss M. Apnoea in a former preterm infant after caudal bupivacaine with clonidine for inguinal herniorrhaphy. Pediatr Anaesth 2002;12:637–640.
12. Guinard J-P, Borboen M. Probable venous air embolism during caudal anesthesia in a child. Anesth Analg 1993;76:1134–1135.
13. Schwartz N, Eisenkraft JB. Probable venous embolism during epidural placement in the infant. Anesth Analg 1993;76:1136–1138.
14. Nora JJ. Etiologic aspects of heart disease. In: Adams FH, Emmanouilides CG, eds. Heart Disease in Infants, Children and Adolescents. 3rd ed. Baltimore: Williams & Wilkins; 1983:14.
15. Desparmet J. Total spinal anesthesia after caudal anesthesia in an infant. Anesth Analg 1990;70:665–667.
16. Holt HM, Andersen SS, Andersen O, et al. Infections following epidural catheterization. J Hosp Infect 1995;30:253–260.
17. McNeely JK, Trentadue NC, Rusy LM, Farber NE. Culture of bacteria from lumbar and caudal epidural catheters used for postoperative analgesia in children. Reg Anesth 1997; 22:428–431.
18. Fujinaka W, Hinomoto N, Saeki S, et al. Decreased risk of catheter infection in infants and children using subcutaneous tunneling for continuous caudal anesthesia. Acta Med Okayama 2001;55:283–287.

19. Strafford MA, Wilder RT, Berde CB. The risk of infection from epidural analgesia in children. A review of 1620 cases. Anesth Analg 1995;80:234–238.
20. Baker AS, Ojemann RG, Swartz MN, Richardson EP. Spinal epidural abscess. N Engl J Med 1975;293:463–468.
21. Meunier JF, Norwood P, Dartayet B, et al. Skin abscess with lumbar epidural catheterization in infants. Is it dangerous? Report of two cases. Anesth Analg 1997;84:1248–1249.
22. Larsson BA, Lundberg S, Olsson GL. Epidural abscess in a one-year-old boy after continuous epidural analgesia. Anesth Analg 1997;84:1245–1247.
23. Roberts GJ, Simmons NB, Longhurst P, Hewitt PB. Bacteraemia following local anaesthetic injections in children. Br Dent J 1998;185:295–298.
24. Ecoffey C, Dubousset A-M, Samii K. Lumbar and thoracic epidural anesthesia for urologic and upper abdominal surgery in infants and children. Anesthesiology 1986;65:87–90.
25. Ruston FG. Epidural anaesthesia in infants and children. Can Anaesth Soc J 1954;1: 37–40.
26. Bösenberg AT, Bland BAR, Schulte-Steinberg O, Downing JW. Thoracic epidural anesthesia via caudal route in infants. Anesthesiology 1988;69:265–269.
27. Gunter JB, Eng C. Thoracic epidural anesthesia via the caudal approach in children. Anesthesiology 1992;76:935–938.
28. Blanco D, Llamazares J, Rincón R, et al. Thoracic epidural anesthesia via the lumbar approach in infants and children. Anesthesiology 1996;84:1312–1316.
29. Raskin NH. Lumbar puncture headache: a review. Headache 1990;30:197–200.
30. Tobias JD. Postdural puncture headache in children: etiology and treatment. Clin Pediatr 1990;33:110–113.
31. McHale J, O'Donovan FC. Postdural puncture symptoms in a child. Anaesthesia 1997; 52:688–690.
32. Purtock RV, Buhl JL, Abram SE. Epidural blood patch in a nine-year-old boy. Reg Anesth 1984;9:154–155.
33. Roy L, Vischoff D, Lavoie J. Epidural blood patch in a seven-year-old child. Can J Anaesth 1995;42:621–624.
34. Kumar V, Maves T, Barcellos W. Epidural blood patch for treatment of subarachnoid fistula in children. Anaesthesia 1991;46:117–118.
35. Desparmet J, Mateo J, Ecoffey C, Mazoit X. Efficiency of an epidural test dose in children anesthetized with halothane. Anesthesiology 1990;72:249–251.
36. Perillo M, Sethna NF, Berde CB. Intravenous isoproterenol as a marker for epidural testdosing in children. Anesth Analg 1993;76:178–181.
37. Tucker GT. Pharmacokinetics of local anaesthetics. Br J Anaesth 1986;58:717–731.
39. Sethna NF, Berde CB. Pediatric regional anesthesia. In: Gregory G, ed. Pediatric Anesthesia. 3rd ed. New York: Churchill Livingstone; 1994:281–317.
39. Morgan D, McQuillan D, Thomas J. Pharmacokinetics and metabolism of the anilide local anesthetics in neonates. Eur J Clin Pharmacol 1978;13:365–371.
40. Mazoit JX, Denson DD, Samii K. Pharmacokinetics of bupivacaine following caudal anesthesia in infants. Anesthesiology 1988;68:387–391.
41. Lerman J, Strong HA, Le Dez KM, et al. Effects of age on serum concentration of alpha$_1$-acid glycoprotein and the binding of lidocaine in pediatric patients. Clin Pharmacol Ther 1989;46:219–245.
42. Eyres RL, Kidd J, Oppenheimer R, Brown TCK. Local anaesthetic plasma levels in children. Anaesth Intensive Care 1978;6:243–247.
43. Rosen MA, Thigpen JW, Shnider S, et al. Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 1985;64:1089–1096.
44. Heavner JE, Dryden CF, Sanghani V, et al. Severe hypoxia enhances central nervous system and cardiovascular toxicity of bupivacaine in lightly anesthetized pigs. Anesthesiology 1992;77:142–147.
45. Timour Q, Freysz M, Mazze R, et al. Enhancement by hyponatremia and hyperkalemia of ventricular conduction and rhythm disorders caused by bupivacaine. Anesthesiology 1990;72:1051–1056.
46. Scott DB. Evaluation of clinical tolerance of local anesthetic agents. Br J Anaesth 1975; 47:328–333.
47. Eyres RL, Hastings C, Brown TCK, Oppenheim RC. Plasma bupivacaine concentrations following lumbar epidural anesthesia in children. Anaesth Intensive Care 1986;14: 131–134.

48. Eyres RL, Bishop W, Oppenheim RC, Brown TCK. Plasma bupivacaine concentrations in children during caudal epidural analgesia. Anesth Intensive Care 1983;11:20–26.
49. Stow PJ, Scott A, Phillips A, White JB. Plasma bupivacaine concentrations during caudal analgesia and ilioinguinal-iliohypogastric nerve block in children. Anaesthesia 1988; 43:650–653.
50. Desparmet J, Meistelman C, Barre J, Saint-Maurice C. Continuous epidural infusion of bupivacaine for postoperative pain relief in children. Anesthesiology 1987;67:108–110.
51. Richter O, Klein K, Abel J, et al. The kinetics of bupivacaine plasma concentrations during epidural anesthesia following intraoperative bolus injection and subsequent continuous infusion. Int J Clin Pharmacol Ther Toxicol 1984;22:611–617.
52. McIlvaine WB, Knox RF, Fennessey PV, Goldstein M. Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. Anesthesiology 1988; 69:261–264.
53. Agarwal R, Gutlove DP, Lockhart CH. Seizures occurring in pediatric patients receiving continuous infusion of bupivacaine. Anesth Analg 1992;75:284–286.
54. Ved SA, Pinosky M, Nicodemus H. Ventricular tachycardia and brief cardiovascular collapse in two infants after caudal anesthesia using a bupivacaine-epinephrine solution. Anesthesiology 1993;79:1121–1123.
55. Maxwell LG, Martin LD, Yaster M. Bupivacaine-induced cardiac toxicity in neonates: successful treatment with intravenous phenytoin. Anesthesiology 1994;80:682–686.
56. McCloskey JJ, Haun SE, Deshpande JK. Bupivacaine toxicity secondary to continuous caudal infusion in children. Anesth Analg 1992;75:287–290.
57. Berde CB. Convulsions associated with pediatric regional anesthesia. Anesth Analg 1992;75:164–166.
58. Klein SM, Pierce T, Rubin Y, et al. Successful resuscitation after ropivacaine-induced ventricular fibrillation. Anesth Analg 2003;97:901–903.
59. Crews JC, Rothman TE. Seizure after levobupivacaine for interscalene brachial plexus block. Anesth Analg 2003;96:1188–1190.
60. Ivani G, Lampugnani E, De Negri P, Lönnqvist P, Broadman L. Ropivacaine vs bupivacaine in major surgery in infants. Can J Anaesth 1999;46:467–469.
61. Broadman LM, Ivani G. Caudal blocks. Tech Reg Anesth Pain Manage 1999;3:150–156.
62. Ala-Kokko TI, Karinen J, Raiha E, et al. Pharmacokinetics of 0.75% ropivacaine and 0.5% bupivacaine after ilioinguinal-iliohypogastric nerve block in children. Br J Anaesth 2002; 89:438–441.
63. Habre W, Bergesio R, Johnson C, et al. Pharmacokinetics of ropivacaine following caudal analgesia in children. Paediatr Anaesth 2000;10:143–147.
64. Deng XM, Xiao WJ, Tang GZ, et al. The minimum local anesthetic concentration of ropivacaine for caudal analgesia in children. Anesth Analg 2002;94:1465–1468.
65. Paut O, Schreiber E, Lacroix F, et al. High plasma ropivacaine concentrations after fascia iliaca compartment block in children. Br J Anaesth 2004;92:416–418.
66. Van Obbergh LJ, Roelants FA, Veyckemans F, Verbeeck RK. In children, the addition of epinephrine modifies the pharmacokinetics of ropivacaine injected caudally. Can J Anaesth 2003;50:593–598.
67. Morrison SG, Dominguez JJ, Frascarolo P, Reiz S. A comparison of the electrocardiographic cardiotoxic effects of racemic bupivacaine, levobupivacaine, and ropivacaine in anesthetized swine. Anesth Analg 2000;90:1308–1314.
68. Nichols D, Yaster M, Lynn A, et al. Disposition and respiratory effects of intrathecal morphine in children. Anesthesiology 1993;79:733–738.
69. Attia J, Ecoffey C, Sandouk P, et al. Epidural morphine in children. Pharmacokinetics and CO_2 sensitivity. Anesthesiology 1986;65:590–594.
70. Krane EJ, Tyler DC, Jacobson LE. The dose response of caudal morphine in children. Anesthesiology 1989;71:48–52.
71. Krane EJ. Delayed respiratory depression in a child after caudal epidural morphine. Anesth Analg 1988;67:79–82.
72. Valley RD, Bailey AG. Caudal morphine for postoperative analgesia in infants and children: a report of 138 cases. Anesth Analg 1991;72:120–124.
73. Bailey AG, Valley RD, Freid EB, Calhoun P. Epidural morphine combined with epidural or intravenous butorphanol for postoperative analgesia in pediatric patients. Anesth Analg 1994;79:340–344.

74. Lawhorn CD, Brown RE. Epidural morphine with butorphanol in pediatric patients. J Clin Anesth 1994;6:91–94.
75. Jamail S, Monin S, Begon C, et al. Clonidine in pediatric caudal anesthesia. Anesth Analg 1994;78:663–666.
76. Callow LB, Rosen DA, Rosen KR, et al. Optimal pain relief following cardiac surgery in children. Circulation 1992;86:I-501.
77. Huang JJ, Hirshberg G. Regional anaesthesia decreases the need for postoperative mechanical ventilation in very low birth weight infants undergoing herniorrhaphy. Paediatr Anaesth 2001;11:705–709.
78. Tuncer S, Yosunkaya A, Reisli R, et al. Effect of caudal block on stress responses in children. Pediatr Int 2004;46:53–57.
79. Rosen D, Rosen KR, Hammer GB. Pro: regional anesthesia is an important component of the anesthetic technique for pediatric patients undergoing cardiac surgical procedures. J Cardiothorac Vasc Anesth 2002;16:374–378.