Regional anesthesia is being administered to an increasing number of infants and children, and there is a growing body of literature regarding age-related differences in local anesthetic pharmacology and toxicology, and in clinical application of various regional anesthetic techniques in pediatrics. This lecture will review some aspects of the basic, translational and clinical science of regional anesthesia in pediatrics. Despite the title “The Science of …”, as requested by the conference organizers, it will become apparent that much of what guides our current practice of pediatric regional anesthesia is based on art, belief and custom, rather than evidence (Broadman and Holt, 2007).

1. Sodium channels and ontogeny of nerve functions

Local anesthetics bind to voltage gated sodium channels and alter the relative stability of resting, open, and inactivated conformations (Figures 1 and 2).

Sodium channels and other ion channels are present early in the development of peripheral nerves. (Wada, 2006) Functioning of sodium, potassium, and calcium channels plays a number of crucial roles in the activity-dependent processes of axonal growth and projection to target tissues. In experimental models, prolonged interruption of nerve conduction and/or afferent activity can markedly alter the development of functional connections in the central and peripheral nervous systems. Myelination of peripheral nerves progresses gradually through pre-natal and post-natal life. The responses of the peripheral and central nervous systems to inflammation and to nerve injury change through development. (Ririe et al. 2003, 2006)

A variety of different sodium channel subtypes are expressed in different mammalian tissues. Variants in specific sodium channel subtypes may underlie a range of neurologic and cardiovascular diseases, as well as chronic pain syndromes such as erythromelalgia (Sheets et al, 2007). Targeting of specific sodium channel subtypes may be a promising approach for future development of analgesics for neuropathic pain (Ekberg et al, 2006).
2. Action of local anesthetics on developing nerves – development of surrogate animal models for studying efficacy and toxicity, correlation with human case series

Peripheral nerve blockade and neuraxial blockade has been studied in several infant animal models. Hu et al (1997) in our lab developed a model of neurobehavioral assessment of infant rats receiving percutaneous sciatic blockade. In this model, when younger and older rats are dosed with the same weight-scaled (mg/kg) doses, blocks wear off much faster in younger rats compared to older rats. This age-related trend in dose-response can be interpreted in part based on considering the dependence of minimum blocking concentration on absolute nerve length (Raymond and Strichartz, 1989). The infant rat sciatic block model was subsequently used (Kohane et al, 1998a) to evaluate relative potency and toxicity of bupivacaine and ropivacaine in rats of different ages. Infant rats tolerated a larger weight-scaled dose (higher LD50) for both agents, compared to adult rats, and ropivacaine appeared similarly safer (similar ratio of LD50s) than bupivacaine at all ages.

Howard et al. (2001) examined the effects of epidural blockade on inflammatory pain and hypersensitivity in infant rats. In their model, relatively dilute concentrations of bupivacaine were more effective in preventing hypersensitivity in younger rats compared to older rats.

One difficulty for interpreting studies of developing animals concerns age-related changes in baseline mechanical and thermal withdrawal thresholds (Berde and Cairns, 2000).

What information is available regarding the dose or concentration response of peripheral or neuraxial regional anesthesia as a function of age?

Case series for spinal anesthesia show that infants require much larger doses than adults to achieve high thoracic levels of blockade (e.g. 0.6 – 1 mg/kg for bupivacaine or tetracaine, compared to 0.2 – 0.3 mg/kg for adults). Even with 3-fold higher weight-scaled dosing in neonates, spinal anesthetic durations average roughly 1/3 the duration of comparable spinal anesthetics in adults (Dohi and Seino, 1986). There is a gradual change in dose requirements through childhood.

With other types of blocks, age-related trends in dose-response and duration are less clear. While there are a large number of studies available, the experimental paradigms differ significantly among the various studies, making comparisons difficult.

For example, Deng and coworkers determined that, for caudal anesthesia, a ropivacaine concentration of 0.11% was 50% effective for prevention of movement or changes in heart rate or blood pressure in 1 – 5 year old children under an estimated 0.5 MAC of enflurane anesthesia. This type of paradigm requires a number of assumptions about the interaction of local anesthesia and general anesthesia in blunting movement and cardiovascular responses, and it is not clear that this can translate readily into a recommended concentration required for postoperative analgesia for children, or to permit comparison of effects of age on concentration-response between children and
adults. Readers are encouraged to read a recent editorial (Fisher, 2007) on the statistical, clinical and ethical issues with study designs that examine “50% effective” doses.

The experience of Ganesh and Cucchiaro (2007) and others would suggest that continuous peripheral nerve or plexus infusions using comparatively dilute concentrations of ropivacaine (e.g. 0.1-0.15%) produces good analgesia postoperatively in children and adolescents, but it is difficult to find studies that show systematic trends with age in the minimally effective concentrations of local anesthetics for either bolus dosing or infusions for pediatric regional anesthesia.

3. **Pharmacokinetics: Local Uptake and Distribution into Nerves, Systemic Uptake and Clearance**

For most systemically acting drugs, there is a series relationship between the site of administration, the central circulation, and the effect site. For local anesthetics, systemic uptake competes with entry into the effect site, and there is a parallel relationship between the central circulation and the effect site (Figure 3). When radiolabeled local anesthetics are injected outside nerves in animal models, less than 3% of injected doses enter a nerve, and over 80% of an injected dose leaves the surrounding tissues within 30 minutes. This imposes structural requirements on drugs for local anesthesia: they must dissolve well and diffuse rapidly in both aqueous and lipid micro-environments. Factors that influence local blood flow and diffusion of drug into nerves can dramatically alter local anesthetic efficacy (Cairns et al, 2003a, Masuda et al, 2004).

Hepatic immaturity and reduced activity of CYP enzymes leads to slower clearance of the amino amide local anesthetics (including racemic bupivacaine, levo-bupivacaine, ropivacaine, and lidocaine) in neonates and younger infants compared to older children and adults (Larsson et al, 1997; Mazoit and Dalens, 2004). Active metabolites of local anesthetics, such as MEGX in the case of lidocaine, may also accumulate in neonates and younger infants and may contribute to risk of systemic toxicity. Reduced plasma concentrations of alpha-1-acid glycoprotein in the neonate lead to higher unbound plasma concentrations of these agents. The slower clearance of amide local anesthetics leads to gradually rising plasma concentrations with prolonged epidural infusions. In contrast, the ester local anesthetic 2-chloroprocaine is cleared efficiently even in former preterm neonates receiving comparatively high epidural infusion rates (Henderson et al, 1993).

Based on these considerations, my own practice is to use chloroprocaine for most neonatal epidural infusions.

4. **Cardiovascular and CNS toxicity**

Cardiac and CNS toxicity from local anesthetics remains an important clinical problem in pediatric regional anesthesia. Risks are increased by a number of factors, including: absence of premonitory signs or patient reports when regional anesthesia is performed under general anesthesia, narrower therapeutic index (dose to block a nerve scales weakly with body size, dose for systemic toxicity scales more directly with body size), reduced
protein binding of local anesthetics in infants, and possibly greater vulnerability of the neonatal myocardium to depressant actions per se.

a. Lipid Emulsions for Treatment of cardiovascular depression

Prevention of inadvertent intravascular injection and avoidance of excessive dosing remain the key elements for avoiding cardiovascular toxicity of local anesthetics.

However, even with good clinical practice, inadvertent intravascular injection may occur. Laboratory investigations (Weinberg et al, 2003) and recent clinical case reports (Rosenblatt et al, 2006) suggest that resuscitation following local anesthetic induced cardiac arrest may be facilitated by intravenous infusion of lipid emulsions, such as Intralipid®. Lipid emulsions have been also been used successfully for patients who have had cardiac arrests associated with ropivacaine and levo-bupivacaine as well as racemic bupivacaine. Based literature review, web-site search (www.lipidrescue.squarespace.com), and discussion with investigators (G. Weinberg, personal communication, August, 2007), it appears that at least 8 well-documented cases of successful resuscitation from cardiac arrest temporally associated with lipid infusion have occurred over the past 2 years.

In the past year, it has become a widespread recommendation for clinicians performing major regional anesthesia to keep available a supply of a lipid emulsion for resuscitation purposes. If kept unopened, these formulations have a long shelf-life, so that the cost of keeping a supply at hand is not prohibitive in most hospital settings in developed countries. While the commercial formulation “Intralipid®” is cited here, based on some of the animal and human publications, Weinberg (personal communication August 2007) believes that other widely used commercial intravenous lipid formulations would have similar benefit and could be used in similar dosing. Along with institution of standard PALS/ACLS protocols, a recommended regimen for Intralipid® 20% (or other lipid emulsions in equal weight of lipid) in the event of local-anesthetic-induced cardiac arrest is 1.5 ml/kg loading dose, followed by an infusion of 0.25 ml/kg/min.

Although propofol is supplied commercially in a lipid emulsion, the administration of propofol in this setting is ill-advised: animal data confirms that administration of a sufficient dose of lipid via propofol formulations results in a severely cardiodepressant dose of propofol, which overshadows the benefits of the lipid infusion and prevents successful cardiac resuscitation.

With regard to other components of PALS/ACLS protocol in the setting of local anesthetic-induced cardiac arrest, there is reason from animal studies and theoretical considerations to omit lidocaine and amiodarone from their standard protocol-based uses for ventricular fibrillation or pulseless ventricular tachycardia. Weinberg et al (personal communication, August, 2007) would recommend, based on animal experiments, adhering to standard dose, rather than high dose epinephrine, and avoiding vasopressin.
Animal experiments and case reports suggest that lipid emulsion may also be considered in cases of cardiac arrest due to overdoses of calcium channel blockers and tricyclic antidepressants.

Cardiopulmonary bypass has been life-saving in at least one case, and in hospital settings with rapid bypass or ECMO capability, these rapid response teams may be notified as the rest of resuscitation proceeds.

Chiral Local Anesthetics

Ropivacaine and levo-bupivacaine appear to offer modest advantages over racemic bupivacaine in terms of their therapeutic indices (Kohane et al, 1998a). In animal models, resuscitation following cardiac arrest is slightly more difficult with racemic bupivacaine compared to levo-bupivacaine or ropivacaine. Ropivacaine offers modest improvements in sensory selectivity compared to bupivacaine in some, but not all, clinical trials.

5. Failed Local Anesthesia: Differentiating Among Biological, Technical and Operational/Systems Failures

In many areas of medicine (as with aeronautics or auto manufacturing), there are systematic efforts to reduce failures. My view is that we should adopt more systematic approaches to reducing failures of regional anesthesia as well. It seems useful to differentiate between biological causes, technical causes, and operational/systems failures.

Biological Causes of Failed Local Anesthesia

Genetic Variants

Occasionally, patients report that “local anesthetics don’t work for me”. While many of us tend to ascribe this to technical failure on the part of previous practitioners, patient psychological factors, etc., there may be patients who have biological variants in sodium channel functioning or other aspects of somatosensory processing that render them resistant to local anesthetics. For example, patients with Ehlers Danlos syndrome (Arendt-Nielsen et al, 1990) and even redheads (Liem et al, 2005) show measurable degrees of resistance to local anesthesia. Future studies may identify patients with sodium channel variants that confer greater degrees of resistance to local anesthetic blockade.

Inflammation-Induced Local Anesthetic Failure

Local anesthetics frequently fail in sites of infection or inflammation: failure rates in the setting of a tooth abscess approach 70%. Inflammation-induced local anesthetic failure (Cairns et al 2003a, 2003b) appears to reflect a combination of pharmacokinetic factors (more rapid clearance from perineural injection compartments, greater drug diffusion distances due to perineural edema, impaired transmembrane diffusion of local anesthetics due to local tissue acidosis) and pharmacodynamic factors (peripheral sensitization with changes in membrane threshold and central sensitization, with increased summation of inputs). Changes in regional blood flow in perineural injection
compartments can produce dramatic changes in the effectiveness of regional anesthesia (Masuda et al, 2004).

Tachyphylaxis, Hyperalgesia and Chronic Pain

Tachyphylaxis to local anesthesia is probably quite prevalent in postoperative patients. It is facilitated by hyperalgesia, and interventions that prevent or treat hyperalgesia can diminish tachyphylaxis (Lee et al, 1994). In my opinion, a major rationale for the routine inclusion of some dorsal horn-active agent, e.g. clonidine, opioids, or (if available) preservative-free S+ ketamine, in most epidural infusions is to exploit their anti-hyperalgesic/anti-tachyphylactic actions. Patients with chronic pain generally require more dense epidural infusions and more liberal use of additives to achieve adequate analgesia (Mogensen et al, 1988).

6. Promoting Technical Success

In my opinion, there is a need for more science in evaluating methods of needle placement and in ensuring technical success of needle and/or catheter placement in sedated or anesthetized children.

Since most pediatric regional anesthesia is performed under sedation or general anesthesia, methods for confirming correct needle placement cannot rely on patient reports as much as in adult regional anesthesia. The issues of nerve injury with sedated or anesthetized placement are addressed below.

A number of pediatric case series have examined technical aspects of regional anesthesia in infants and children. Blind placement (i.e. loss of resistance for epidural anesthesia, use of surface landmarks for ilioinguinal/iliohypogastric or penile blocks) has appeared good, but not uniformly successful, in many case series. In addition, success rates in studies performed by experts with considerable experience in the “feel” of these techniques may not extrapolate to equal success among less experienced practitioners.

Ultrasound guidance is rapidly emerging as a method for confirming needle location and drug spread in a variety of forms of regional anesthesia (Marhofer and Chan, 2007). As the machines improve and the prices drop, it is likely that use of ultrasound will continue to grow.

In several side-by-side comparative studies between ultrasound and nerve stimulation guidance for peripheral or plexus blocks in adults, success rates appear higher, onset appear times shorter, median effective volumes are smaller, and/or quality and duration of analgesia appears better with ultrasound guidance. In a recent dose-finding randomized trial for femoral nerve blockade, the median volumes for 50% or 95% success in obtaining dense sensory and motor block at 30 minutes by use of ultrasound were 57% and 54% of the corresponding volumes obtained by use of nerve stimulation (Casati et al, 2007).

Pediatric case series have also shown high success rates when ultrasound is used for peripheral and plexus blocks.
For infants and children ages 0-6 years, a study by Willschke et al (2006) found that ultrasound facilitated rapid identification of the epidural space, and permitted visualization of epidural spread of injected local anesthetic.

Tsui et al (2004) have described use of nerve stimulation for confirmation that a catheter tip is in the epidural space and for determination of the spinal level of the tip. This involves use of a wire-wrapped epidural catheter that has been flushed with saline and electrical stimulation from the negative (black by convention) electrode of a two-lead nerve stimulator through a special adapter that connects to the hub of the catheter. An extensive series of prospective studies has shown good sensitivity, specificity and positive predictive value of this approach. My opinion is that Tsui’s technique is enormously useful for rapid confirmation of epidural catheter location (including sidedness) in awake, sedated, or anesthetized subjects, and I currently use this approach extensively, to direct cephalad catheter advancement of catheters and to confirm proper catheter tip locations with direct entry at the intended lumbar or thoracic level. For example, if a catheter is placed for one sided surgery, such as a lateral thoracotomy or a unilateral hip operation, and the twitches obtained are predominantly on the contralateral side, my practice is to reposition the catheter until I obtain either bilateral equal twitches or predominantly ipsilateral twitches. Wrong-sided epidural catheters are more likely to be ineffective.

Fluoroscopy is used widely in pain clinics for a wide range of regional anesthetic procedures, and may be considered for monitoring needle and catheter advancement and drug spread in selected pediatric regional anesthetic procedures. There are concerns related to radiation exposure and expense that should be considered. I use fluoroscopy for perioperative regional anesthesia for selected high risk patients, for patients with anatomic difficulties (e.g. significant scoliosis), for almost all epidural steroid injections for radiculopathy, and for placement of spinal ports for patients in palliative care.

7. Promoting Operational Success and Developing Systems for Management

Technical success is necessary, but not sufficient, for providing clinically useful regional anesthesia and analgesia. Successful application also requires proper initial drug and dose selection, pro-active anticipation and prevention of adverse events, prevention and treatment of side-effects, and a coordinated system of postoperative management. Postoperative regional analgesia can be labor intensive, and should be undertaken with a coordinated system of management and clear designation of the chain of command.

Effective side-effect management protocols are essential to improved care. As an example, consider pruritus, which is common and frequently very bothersome with either epidural or systemic opioids. Antihistamines are still prescribed widely for this symptom, despite a lack of evidence for efficacy, and a number of negative clinical trials. Nalbuphine and ultra-low dose naloxone infusions have evidence for efficacy, and should be used widely.
8. Choice of Techniques, Agents and Additives

Among major pediatric centers worldwide, there is substantial variation in the choices of techniques (e.g. single-shot versus continuous catheter techniques, cephalad advancement of caudal epidural catheters versus direct thoracic epidural placement, when to use peripheral blocks versus neuraxial blocks, etc.), in choice of local anesthetics, and in choice of additives to epidural and perineural infusions.

There are a large number of studies comparing different infusions and additives, with evaluation of pain scores, side-effects, and a variety of other outcome measures, for example, see De Negri et al (2001) or Vetter et al (2007) or a review by Ansermino et al (2003); some additional considerations regarding drug selection will be presented at the meeting. It is worth emphasis that considerations influencing drug selection and an optimal balance between analgesia and side-effects may vary widely among individual patients. Many children will choose mild or even moderate pain if sufficiently concerned about vomiting and nausea, for example (Cucchiaro et al, 2006).

9. Injury to nerves from local anesthetics and from needles (direct trauma and ischemia)

All local anesthetics are neurotoxic if they reach sufficiently high intra-neural concentrations (Bainton and Strichartz, 1994). The reported low frequency of clinically apparent nerve injury is due in part to the effects of dilution and spread through tissues, as well as inefficient entry of drug into nerves. Neurotoxicity can be multifactorial, and the risk may be exacerbated by pre-existing neurologic disorders and by a number of factors that produce reductions in nerve perfusion pressure, including local compression and systemic hypotension, and by “multiple hits” along the course of the nerve (Drasner, 2002).

Several investigators have examined effects of spinal administration of local anesthetics in developing animal models. For example, Lian and Di (2006) reported apoptotic neurodegeneration in the spinal cords of young (45-day old) rabbits receiving a large dose (4 mg/kg) of 2% tetracaine, but not doses of ropivacaine 0.25%-0.75% (0.5 – 1.5 mg/kg). Since equipotent doses of the two local anesthetics were not studied, and since only a single age was studied, it is difficult to draw any conclusions about the relative neurotoxicity of different spinal agents, or the age-dependence of neurotoxicity. Available animal studies differ in their choice of drugs, doses and concentrations, the methods of assessment of neurologic injury, the ages of animals studied, and the choice of species.

A number of case series suggest that the frequency of clinically-apparent neurotoxicity following pediatric peripheral or neuraxial regional anesthesia is quite low (Williams et al, 2006), though most have not performed careful neurologic examinations in all patients before and after conduct of regional anesthesia, and these reports cannot exclude minor deficits that are not grossly apparent or are not detected on follow-up visits to pediatric surgeons.
Most pediatric regional anesthesia is performed under general anesthesia, which precludes symptom reporting to detect needle contact with, and subsequent injury to, peripheral nerves, spinal nerve roots, or the spinal cord.

There has been considerable controversy regarding the relative safety of different types of regional anesthesia performed in adults or children awake, sedated or fully anesthetized.

A widely quoted adult study by Horlocker et al (2003) found no cases of identifiable nerve injury among 4298 adults receiving lumbar epidural catheter placement under general anesthesia. Extrapolation from this study should be cautious, since >98% were used solely for postoperative analgesia and > 98% of subjects received opioids alone through the catheters.

In awake subjects, presence of paresthesias is neither necessary nor sufficient for producing nerve injury. Cases of peripheral nerve injury, spinal nerve root injury, and spinal cord injury have occurred in awake adults who reported no paresthesias or pain with initial needle or catheter placement. One prospective study of adults (Bigeleisen, 2006) undergoing axillary blockade involved deliberate intraneural injection (observed via ultrasound) in subjects who first reported paresthesias. This study was surprising in two respects: first, it received ethics committee approval, and secondly, within the limits of a small sample size, clinically apparent nerve injury was not common. I am personally not very reassured by this study.

Available evidence suggests that ultrasound might have the potential to reduce the frequency of peripheral nerve injuries in anesthetized as well as awake subjects.

From the cumulative numbers of patients in available pediatric case series (which will be summarized in more detail by Drs. Moriary and Cucchiaro in the following lecture), the safety of lumbar epidural needle and catheter placement in anesthetized subjects appears quite good, despite the caveat that under-reporting may occur with infants and younger children.

Nevertheless, a small number of cases have been reported with poorly understood extensive spinal cord injury following needle insertion at caudal or lumbar levels (Flandin-Blety and Barrier, 1995). From available data, it has been difficult to conclude whether or not vascular mechanisms might have been involved (including arterial or venous air embolism or unusual anatomy of the arterial supply to the anterior spinal cord) or whether some of these cases represented unrecognized spinal placement.

There is much greater controversy regarding direct thoracic puncture in anesthetized infants and children (Bromage and Benumof, 1998; Krane et al, 1998, Kasai et al, 2002). Available case series suggest low frequencies of adverse events, but the cumulative numbers of direct thoracic placements in published pediatric case series probably comprise less than 5,000 cases.
My own current practice is to use direct methods (either Tsui’s nerve stimulation method or fluoroscopy and contrast epidurography) for confirming needle and/or catheter placement prior to injecting local anesthetics in most cases of direct thoracic puncture in anesthetized subjects. The choice between these two methods depends on clinical circumstances.

10. Infection

a. Epidemiology
Infection is a concern with regional anesthesia in infants and children, and a number of studies have examined frequencies of clinically apparent local or deep infection, local erythema, or surrogate measures, such as bacterial colonization of catheter tips at the time of catheter removal. Erythema at the catheter site correlates highly with bacterial colonization of catheter tips.

The frequency of catheter colonization increases with duration of epidural catheter placement. In several studies, the tips of untunneled caudal catheters had a much higher frequency of bacterial colonization than the tips of untunneled lumbar catheters.

b. Prevention

Bubeck et al (2004) reported, in a large, prospective open-label study, frequencies of bacterial colonization of untunneled caudal catheters, tunneled caudal catheters, and untunneled lumbar catheters of 29%, 11%, and 9%, respectively, suggesting that tunneling a caudal catheter can reduce the risk of catheter colonization to approximately that of untunneled lumbar catheters. My opinion is that tunneling of caudal catheters should be considered strongly, especially for catheters whose intended duration of use exceeds 2 days.

Traditionally, anesthesiologists have performed much of regional anesthesia with simple application of gloves, not necessarily with hand hygiene or removal of jewelry beforehand, and with aqueous iodine formulations (e.g. betadine) for skin preparation.

An ASRA consensus panel has recommended removal of jewelry and hand hygiene prior to gloving as a standard of care for regional anesthetic procedures.

Since (fortunately) the frequency of true epidural space infections is fairly low, the case for making specific modifications in sterile procedure is derived largely from surrogate measures (e.g. catheter tip colonization rates) and from extrapolation from other percutaneous procedures, especially central venous line placement.

A combined practice program that includes hand washing, removal of jewelry, gowning and draping, and alcoholic chlorhexidine for skin preparation appeared to significantly reduce central venous catheter associated infections compared to traditional practice.
In obstetric epidural practice, chlorhexidine produces a lower rate of catheter tip colonization compared to betadine. There has been a historical reluctance to recommend chlorhexidine for skin preparation for lumbar puncture and for epidural procedures because of concerns regarding neurotoxicity. It seems improbable that significant volumes of chlorhexidine can be tracked into contact with major nerve trunks during conduct of regional anesthesia. In view of the apparently greater efficacy of chlorhexidine compared to betadine, my practice is to use chlorhexidine for the overwhelming majority of regional anesthetic procedures beyond the newborn period.

11. “Major” Outcomes: Mortality and Neurologic Disability

Fortunately, a majority of infants and children do well after surgery. Death and major neurologic disability are becoming increasingly less common in pediatric cardiac surgery, and quite rare in most other types of pediatric surgery.

In adult postoperative care, the most impressive aspects of regional anesthetic outcome studies have examined impact of regional anesthesia on immediate postoperative recovery and rehabilitation (e.g. Kehlet and Mogensen, 1999) and on analgesia per se (Block et al, 2003). Effects of regional anesthesia and analgesia on mortality and major disability have been most apparent in very large studies, in studies restricted to particular high-risk subgroups of patients, or meta-analyses that pooled data from a large number of individual studies (Beattie et al, 2001; Rodgers et al, 2000).

In most situations, regional anesthesia in infants and children is unlikely to influence mortality or major neurologic disability. In one situation, however, there is a possible role. As per Prof. Maze’s discussion in the previous lecture, it remains unclear how to interpret the neurodevelopmental risks of general anesthesia in human infants in light of studies in infant rats by Olney’s group showing massive apoptotic neurodegeneration with anesthetic exposures in younger rats, but not older rats.

In response to this concern, a multicenter / multi-continental study, planned for over 700 subjects, is in progress with a randomized comparison between spinal anesthesia and general anesthesia for infants undergoing inguinal hernia repair, followed by long-term neurodevelopmental assessments at 2 years and 5 years of age. It is hoped that studies of this sort will help define the relative safety and potential long-term consequences of general anesthesia and regional anesthesia in infants.

12. Future Local Anesthetics

Work continues from several groups on several approaches to producing a 2 – 4 day local anesthetic, using both sustained release of existing local anesthetics and using novel agents, including site 1 sodium channel toxins (Kohane et al, 1998b; Rodriguez-Navarro et al, 2007). Although I am biased (and have conflicts of interest in this regard), I remain convinced that these will fill an unmet need for postoperative wound infiltration and prolonged perineural blockade.
References


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Zaric D, Christiansen C, Pace NL and Punjasawadwong Y: Transient neurologic symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics. Cochrane Database of Systematic Reviews. CD003006, 2003.
Figure 1  Hille’s Modulated Receptor Hypothesis

Local anesthetics produce conduction block by an allosteric mechanism, altering the kinetics of cycling among sodium channel conformations.
Figure 2  
Models of sodium channels

The theory is that the inactivation gate "swings" shut, turning off the channel.
Figure 3  Heuristic Model of Local Anesthetic Uptake into Nerves

A.  
Most Drugs

Injection or absorption site

Central circulation

Effect site

Metabolism and elimination

B.  
Local Anesthetics  
> 98% of dose  
<