Potency to cause systemic toxicity of different local anesthetics (LA)

The binding of short-acting LA (SALA) to the sodium channel is often characterized as ‘fast in-fast out’, whereas long-acting LA (LALA) are known as ‘fast in-slow out’. Thus, if systemic complication do occur, the duration of the toxicity is much longer and more serious when using long-acting than short-acting compounds (Table 1) (1).

The difference between SALA and LALA can be illustrated by a comparison between lidocaine and racemic bupivacaine. In a seminal study, Reiz & Nath (1) infused lidocaine or bupivacaine into the coronary circulation of dogs. In line with the LA potency ratio of 1 : 4 between lidocaine and bupivacaine, the effect on cardiac contractility was also observed to be 1 : 4. However, the effect on cardiac conductivity was found to be 1 : 16, and the time to normalization of the electrocardiogram (EKG) was 6 and 48 min for lidocaine and bupivacaine, respectively (Table 1). Based on these data, it can be concluded that the potential for serious toxicity of LALA is higher compared with SALA and that the main negative cardiac effect of LALA is their adverse influence on cardiac electrophysiology.

Because of the quite pronounced potential for serious systemic toxicity of racemic bupivacaine, more concentrated solutions than 0.5% are no longer commercially available. The more recently marketed alternatives to racemic bupivacaine, levo-bupivacaine, and ropivacaine, have been shown to be associated with a wider margin of safety compared with racemic bupivacaine. The relative safety of racemic bupivacaine, levo-bupivacaine, and ropivacaine has been reported by Santos & DeArmas and coworkers (2). The three various LALA were infused intravenously in nonpregnant sheep, and the dose associated with symptoms of serious systemic toxicity was assessed. As is clearly shown in Figure 1, the order of toxicity was found to be racemic bupivacaine > levo-bupivacaine > ropivacaine.

Thus, ropivacaine appears to be the least toxic of the LALA. However, the study referred to above does not take into account the relative LA potency of these agents. Based on obstetric epidural studies, the minimal local anesthetic concentration of the three LALA has been established and compared. Thus, racemic bupivacaine and levo-bupivacaine have been found equipotent (3), whereas ropivacaine was found to be only 60% as potent as racemic bupivacaine (4). Against this background, the wider safety margin
associated with ropivacine potentially can be explained by a reduced LA potency compared with racemic bupivacaine and levo-bupivacaine. With regard to the relative toxicity of racemic bupivacaine and levo-bulivacaine, it has been shown that levo-bupivacaine does bind to the cardiac sodium channel in a different and more benign way compared with racemic bupivacaine (5), thereby explaining the fact that levo-bupivacaine is less cardiotoxic compared with racemic bupivacaine.

The author’s conclusion concerning the aforesaid is that levo-bupivacaine and ropivacaine are associated with a reduced risk for serious systemic toxicity compared with racemic bupivacaine and should therefore routinely be used in children (with the exception of spinal anesthesia). However, in fact, whether ropivacaine is associated with a lower risk for systemic toxicity than levo-bupivacaine remains unclear. Thus, the choice between these two more modern LALA can be based on personal preference or market availability.

### Dosage recommendations of LALA in children

During the resurge of interest in pediatric regional anesthesia during the second half of the 1980s, no clear knowledge existed with regard to the safe dosing of racemic bupivacaine. Based on adult dosing, most centers used their own dosage regimens that often were found to be excessive, as evidenced by a number of case reports reporting both seizures and cardiac arrhythmias (6–8). This resulted in a large-scale American Patient Safety Foundation sponsored study that ultimately was able to define safe dosage guidelines for the use of racemic bupivacaine in newborns and older children (Table 2) (9).

Because of the reduced systemic toxicity of levo-bupivacaine and ropivacaine, a common question is whether it is possible to give an increased dose of these agents compared with racemic bupivacaine and still be within safe limits. This issue deserves to be divided into two different parts. First, if a regional block does not work after using the maximum dose defined for racemic bupivacaine according to Table 2, it will not work better if you inject an even larger quantity of LALA. Thus, in this setting, it can be recommended to adhere to the maximum dose of racemic bupivacaine also when using levo-bupivacaine and ropivacaine to avoid the risk of systemic toxicity and instead change analgesic strategy (e.g., administer adjunct or change to systemic analgesia).

To discuss the use of a total bolus dosage in excess of 2.5 mg kg\(^{-1}\) is more valid in the situation where different regional anesthetic blocks are to be combined, e.g., lumbar plexus and sciatic nerve blocks or lateral and subcostal transverse abdominis plane blocks. Bösenberg et al. (10) have reported the use of 3 mg kg\(^{-1}\) of ropivacaine in children without observing symptoms of systemic toxicity or plasma levels of ropivacaine in the range of potential risk for systemic

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Table 1

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<tr>
<td>Anesthetic potency: 4 : 1</td>
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<td>Depression of cardiac contractility: 4 : 1</td>
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<td>Prolongation of QRS complex: 16 : 1</td>
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<td>Time to recover normal conduction (min): 48 vs 6</td>
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### Figure 1

toxicity. Against this background, it may, in the setting of combined blocks, be reasonable to allow the use of 3 mg kg$^{-1}$ as a maximum dose of ropivacaine or levo-bupivacaine. However, if doing so, one must always bear in mind that the plasma levels, depending on the type of block, may be in the gray zone for systemic toxicity (11,12).

**Protein binding and the issue of the free fraction of LA**

Most LA, and especially LALA, are extensively subjected to plasma protein binding (PPB) (typical values for protein binding of LALA are >90%). Unspecific binding of LA occurs with many plasma proteins, with albumin being the most important unspecific plasma protein binder. Much more specific binding occurs to the acute-phase protein alpha-1 acid glycoprotein (orosomucoid; AAG), which is responsible for the major PPB of LA.

Lerman et al. (13) have shown that AAG plasma levels are low in newborns and toddlers and that normal adult values are not reached before 1 year of age. This will, thus, result in an increased free fraction of LA and thereby a potential for increased risk for systemic LA toxicity in newborns and infants.

Tucker, a main researcher and expert in the field of PPB of LA, previously argued that reduced PPB because of low levels of plasma proteins, including low levels of AAG, did result in an increased free fraction of LA and thereby a potential for increased risk for systemic LA toxicity. However, the free concentration of LA is in equilibrium with both the fraction bound to plasma proteins and the fraction bound to the tissues, there will be a dynamic interchange between these three compartments that may ameliorate the potential adverse effects of reduced AAG binding. Thus, Tucker later has modified and moderated his view on the importance of PPB for the occurrence of systemic LA toxicity (14). However, the relative importance of this issue in small children is still debated (15).

Furthermore, it should be noted that even newborns are capable to react with a significant acute-phase response when subjected to stress, thereby substantially increasing their AAG levels, which in turn will increase the binding capacity of LALA during continuous infusions (16) (Figure 2).

**Symptoms, signs, and treatment of systemic toxicity in children**

As the vast majority of pediatric patients are asleep when the block is placed, early symptoms are not possible to detect. Thus, the first signs of toxicity in this setting are seizures, tachyarrhythmias, or cardiovascular collapse.

The use of a test dose (LA with added epinephrine) is advocated by some authorities for the early identification of an inadvertent intravascular injection of LA. However, it is important to realize that the test dose will not provide any early warning signs of rapid absorption of LA from the injection site.

Studies simulating intravascular injection with epinephrine-containing LA have investigated the sensitivity and specificity of the test dose. Various different indicators or end points have been used, e.g., increase in heart rate, increase in blood pressure, and changes in T-wave configuration on the EKG (17–20). Unfortunately, the most informative clinical sign of intravascular injection is dependent on anesthetic technique (20,21), and sensitivity and specificity values are not conclusive enough to merit universal mandatory use. Thus, practice with regard to mandatory use of a test
dose varies considerably between institutions as well as countries, and its use appears to be linked, at least in part, to the existing medicolegal situation.

Early signs of LA toxicity (e.g., alterations of mental state and muscular twitching) may be possible to detect if awake regional techniques are used (i.e., awake caudal blockade in ex-premature babies) (22) or in the postoperative period if continuous infusion techniques are used. However, these signs are easily missed or misinterpreted and may even be taken as signs of inadequate pain-relief, resulting in either bolus dosing or increasing the rate of the continuous infusion of LA, thereby producing overt signs of systemic toxicity. Thus, when faced with the clinical situation of unclear postoperative problems in a child with an ongoing infusion of LA, one should always consider whether the symptoms may reflect early signs of systemic LA toxicity or not.

Treatment algorithms of suspected or overt LA toxicity are currently readily available http://www.aagbi.org/publications/guidelines/docs/la_toxicity_2010.pdf (23) (Figure 3). The most recent addition to the treatment armamentarium of severe systemic LA toxicity is the Lipidrescue concept (24–26). The mechanism behind the efficacy of this new treatment is still largely unknown but a useful metaphor is the ‘Lipid sink’ (27). As LA are lipophilic drugs, it can be assumed that the free unbound LA in the circulation will be ‘taken up’ by the lipid part of the plasma and thereby being sequestered from having its effect. As there exists an equilibrium between LA present in the blood and the LA residing in the different body tissues (most importantly the heart and the CNS), it can be presumed that LA will move from the tissues to the blood and then again into the lipid component of the plasma until a new equilibrium has been established.

Recent animal experiments have suggested that the efficacy of the Lipidrescue is influenced by the amount of epinephrine used during resuscitation as well as by the type of LALA. These studies point to Lipidrescue being less effective if large doses of epinephrine has been administered or if ropivacaine has been used (28,29). However, these new data have so far not been incorporated in treatment guidelines, and successful resuscitation of ropivacaine toxicity has been reported also in children (30).

The main current discussion is the time-point when Lipidrescue should be instituted. Current algorithms indicate that Lipidrescue should be used as a last resort, whereas as early administration as possible is being advocated by some researchers and clinicians as the efficacy of Lipidrescue from a theoretical standpoint must be better before cardiovascular collapse has already occurred (31). However, a recent study performed in piglets showed that epinephrine 3 μg kg⁻¹ is more effective than lipid if treatment is started before cardiovascular collapse has already occurred (treatment started at 50% reduction in blood pressure) (32). Thus, the efficacy of Lipidrescue may depend on when it is administered during the course ultimately leading to cardiovascular collapse.

In conclusion, Lipidrescue is a novel and effective method to reverse serious systemic toxicity of LA. With regard to the time-point when Lipid should be started, it appears appropriate to administer it as soon as it is available and not only to use it as a last resort. However, it is important to remember that Lipidrescue is not a substitute for normal resuscitation measures.

**Local tissue toxicity**

Although slightly beside the core of this text, it may be prudent to remind the reader that LA, especially LALA, may cause local tissue toxicity (most frequently local muscle tissue necrosis) (33). Although no data currently exist, it is reasonable to expect that the risk increase with the use of more concentrated LALA. In most patients, the occurrence of limited local muscle necrosis may not be associated with more than localized pain that eventually will subside without long-term problems or sequelae.

So far, no pediatric case reports have been published concerning this, but it can be speculated that premature babies and neonates may be a population at specific risk for this complication. Furthermore, in this specific population, even moderate myonecrosis could
potentially produce myoglobinemia with concomitant adverse renal effect.

No specific treatment for this complication of LALA is currently available, but systemic analgesics and physiotherapy appear to be logic treatment options. In animal studies, local administration of beta-2 agonists has been found to produce a positive effect (34) and may potentially be used if the patient has a very severe muscle necrosis deemed to be because of prior injection of LALA.

References