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Local Anesthetic Agents - Current perspectives on action, metabolism, excretion and toxicity effects

KEYWORDS: Anesthesia, pH, pKa, partition coefficient, alpha1-acid glycoprotein, voltage gated Sodium channel.

*Basheer Ahmed Khan	Mazarulla Khan
Department of Anaesthesiology	Deccan College of Medical Sciences, Hyderabad, Telangana, India.

Mohammed Ishaq	Parveen N
SalareMillat Sultan Salahuddin Owaisi Research Centre for Cellular and Molecular Medicine	Princess Esra Hospital, Deccan College of Medical Sciences, Hyderabad, Telangana, India

ABSTRACT *This article reviews the action, metabolism, excretion and toxicity effects of local anesthetics in the management of pain during surgical and dental procedures. In this article, the efficacy of various local anesthetics has been discussed. Local anesthetics have similar chemical structure but differing pharmacokinetic properties and spectra of pharmacodynamic effects that influence selection of agents for use in various clinical situations. The structure and mechanism of various local anesthetics may enable the clinicians to exploit the safety of using them. However, indepth mechanism and the toxicity of the LA are yet to be studied in detail.*

Introduction

Local anesthesia plays an important role in the management of pain during surgical and dental procedures. The term local anesthesia is used to describe any technique which can induce the absence of sensation in a part of the body i.e., local insensitivity to pain. The nerve blocking function is achieved by the use of local anesthetics (Hille. 2001). These are the membrane stabilizing drugs that stimulate anesthesia by acting on certain nerve pathways thereby stopping the pain signals being sent by the nerves to the brain. They also play an important role in the diagnosis of suxamethonium apnoea (dibucaine test) the treatment of cardiac arrhythmias (lidocaine for ventricular arrhythmias), as mucosal vasoconstrictors of the upper airway (cocaine) to obtund the pressor response to tracheal intubation (intravenous lidocaine) and recreationally, as a drug of abuse (cocaine).

The use of local anesthesia was started way back a century ago, when Carl Koller, (1928) a young Viennese ophthalmologist discovered that Cocaine introduced into his own conjunctival formix produced localized insensitivity to touch and injury. The use of Cocaine may lead to abuse potential. Therefore the hunt for a drug with less toxicity and less addictive substitute resulted in the discovery of synthetic local anesthetics such as aminoester local anesthetics, Stovaine in 1903 and Procaine in 1904. The structures of synthetically made anesthetics are very similar to cocaine but they are being deficient in abuse potential. There are several synthetic local anesthetic drugs available and put into clinical use, particularly lidocaine in 1943, bupivacaine in 1957 and prilocaine in 1959.

The clinically used local anesthetics were widely grouped into: aminoamide and aminoester local anesthetics. Although these are structurally related to cocaine but they do not have abuse potential and do not act on the sympathoadrenergic system thereby maintaining the normal blood pressure and have no local vasoconstriction of the blood vessel with very few exceptions like ropivacaine and mepivacaine that produce weak vasoconstriction. Though modern local anesthetics are safer but risks persist and sometimes the use of correct dose of LA proves to be fatal. There is a need to understand the pharmacology, toxicity and the mechanism of action of using LA.

Mostly the site of action is intracellular, requiring the local anesthetic to diffuse across the lipophilic lipoprotein membrane. The administration of the LA is done by using an acidic solution that keeps the drug in the ionized soluble form. To enter into the nerve cells from the tissue, this acidic ionized form of the drug has to be converted into the neutral unionized form (ion-trapping) which in turn depends on the pKa of LA and the pH of the tissue. After entering into the cell the lower intracellular pH regenerates the ionized form, which results in the blocking of the receptor (inner portion) within the Sodium channel thereby impeding the threshold potential preventing the progress of impulse conduction (Figure 1). Thus the action potential is temporarily halted. The local anesthetic action is augmented by blockade of potassium channels, calcium channels and G-protein-coupled receptors (Xiong, et al.1998, Hollam, et al. 2001, Olschewski, et al. 1998). The opening and closing of the voltage-gated Sodium channel depends on the membrane potential difference. Each consists of a pore with an alpha subunit and 1 or 2 beta subunits. The alpha subunit consists of 4 domains (DI-IV) which in turn consists of 6 helical trans-membrane segments (S1-6) (Figure 2).

Local anesthetics block the nerve conduction by reversibly binding with the DIV and S6 part of alpha subunit of the gated channel in the nerve membrane. The stimulation of the nerve results in a series of conformational changes in the following 4 states: resting, activated, inactivated and deactivated. The affinity of LA is highest when the sodium channel is open (activated or inactive) and lowest when it is closed (deactivated and resting) (Courtney, K. 1975).

Chemistry

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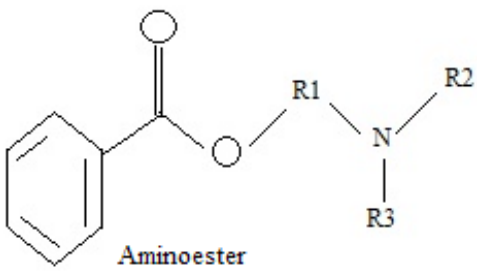
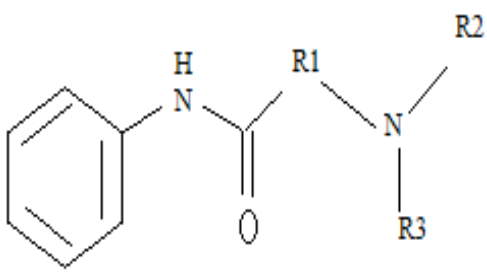
Most of the clinically used local anesthetics consist of structure similar to that of the first anesthetic, cocaine. The molecular configuration of LA consists of a lipophilic aromatic ring (allows nerve membrane penetration) attached to a hydrophilic amine groups. They are classified into esters, amide, ketone or ether.



Aminoester



Aminoamide

Ester linked anesthetics are metabolized quickly and are considered less toxic than amides. However they have short duration of action and cause more allergic reactions than amides. Esters include Procaine, cocaine, tetracaine benzocaine and 2-chloroprocaine.Though amide anesthetics are associated with high toxicity, they have prolonged duration of action, less allergic reactions, quicker onset, higher potency and more profound depth of anesthesia.

The local anesthetics are mostly chiral molecules i.e., they can exist in two non superimposable forms. Each form termed as an enantiomer or stereoisomer. They are named on the basis of the rotation of the polarized light as dextrorotatory (+) or levorotatory (-) or based on the absolute three-dimensional structure of the enantiomers they are designated as R and S forms.

Many synthetic LA are used as racemic mixtures (equal mixture of both R and S forms). The stereochemistry of these drugs plays an important role in terms of toxicity. Several pre-clinical studies showed that S-bupivacaine is less toxic than the R-form (Aberg, G. 1972). Both S and R forms exhibit same physiochemical properties but binding to biological receptor is different.

Pharmacodynamics and pharmacokinetics

In its natural form, LA are weak bases (pKa 7.6-8.9) with esters tending to have higher pKa, unstable in air, poorly soluble in water, and of little clinical value. To make clinically useful, they are dissolved in an acidic solution (pH 3-6) to form salts, which are stable and hydrophilic. At this pH they exist as a mixture of charged cationic molecule (RNH+) and neutral base (RN).The ratio of ionized to neutral base varies following the Henderson-Hasselbach equation with the dissociation constant (pKa) of that of local anesthetic and the pH of the solution.

log10 [base]/ [acid] = pH-pKa

The pKa is constant for any local anesthetic. The pKa value of most of the LA has a greater pKa than physiological pH (7.4). The lower the pKa of LA, the more basic the solution becomes resulting in quicker onset of action than with high pKa and less basic ones.

The efficacy of the LA action is affected by increase in the acidity of the environment (lower pH) of the tissue. The factors that contribute to this type of environment are tissue infection and inflammation and also use of vasoconstrictors and preservatives. Therefore, a LA with lowest pKa (e.g., mepivicaine) is used in cases of infections and inflammation.

Partition Coefficient of LA

The partition coefficient (PC) of LA plays an important role in determining the lipid solubility i.e ability of LA to diffuse across the lipid rich nerve membrane and access target receptors. PC is the distribution of the substance between aqueous and non-aqueous phase. It is directly proportional to the lipid solubility and the potency of the LA.

PCμ Lipid solubility μ Potency of LA

LA with high PC is required in lower concentration for the clinical purpose so as to achieve the same neuronal block (e.g. bupivacaine 0.25-0.5% of prilocaine 1-4%).

PC μ 1 / [LA]

Binding of the LA to Proteins

The LA bind to plasma proteins such as albumin and alpha1- acid glycoprotein (Orosomucoid) and tissue proteins. Albumin (molecular weight 60 KDa) is the low affinity and high volume plasma protein whereas the alpha1-acid glycoprotein (molecular weight 40-45 KDa) has high affinity and low volume. The binding of LA to proteins may increase in trauma, major surgery, chronic inflammation, cancer and uremia and decreases during pregnancy, in the newborn and with use of contraceptive pills (Tucker, G. 1994). LA are absorbed systemically, the plasma level rises slowly.

Effect of LA on blood vessels

The effect of LA on blood vessels is mostly dual i.e., they act as vasoconstrictors at very low concentration and vasodilators at concentrations that are used clinically. There are isomer specific differences with greater vasoconstriction with LA agents like L-bupivacaine compared to R-bupivacaine.

The following factors influence the potency of the LA

- LA with high partition coefficient increases the lipophilic properties thereby promoting the passage of the anesthetic into the lipid nerve membrane, enhancing the potency.
- The potency of the LA is decreased by vasodilation which promotes vascular absorption, reduces locally available drug.
- Addition of epinephrine or sodium bicarbonate increases the pH, thereby increasing the ionized particles, which are more lipids soluble.

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Absorption and distribution of LA

The absorption of LA into organs depends on several factors such as lipid solubility, pKa, protein binding as well as binding to other blood born sites (eg RBC), tissue binding affinity and clearance of LA and also on other features such as cardiac output and metabolic status of the patient. The site of injecting LA also plays an important role (Table 1). It has significant effect on plasma levels with the highest peak levels from intercostals and caudal injection followed by lumbar, epidural, brachial plexus, sciatic and femoral injections (Tucker, G. 1972). After administration, LA is distributed first by venous blood to the lungs, where they are taken up avidly during this first pass through the pulmonary circulation. This reduces the amount reaching the systemic circulation and protect against systemic toxicity. The distribution is more in highly perfused organs such as brain, kidneys and heart followed by skin, skeletal muscle and fat which are less well perfused tissues. The mechanism of systemically administered local anesthetics in relieving pain is well reported. Intravenous lidocaine administration has been reported to have analgesic effect in many acute and chronic conditions (Atkinson, R.L.1982 Cassuto, J. 1985, Kastrup, J. 1987, Glazer, S. 1991, Attal, N. 2004, Williams, D.R. 2003, Koppert, W. 2004, Finnerup, N.B.2005). Subcutaneously injected bupivacaine reportedly produces analgesia via a systemic effect (Duarte, A.M. 2005). In a preclinical study by Zhang et al (2004) it was demonstrated that in rats systemic lidocaine delivered via implanted osmotic pump reduces sympathetic nerve sprouting in dorsal root ganglion that is associated with some neuropathic pain behaviors.

Metabolism and Excretion of LA

The hydrolysis of aminoester LA occurs rapidly in the plasma by the action of non-specific esterase resulting in the formation of inactive metabolites and derivatives (PABA, p-amino benzoic acid) which can be allergenic. The rapid degradation of LA provides a degree of safety as plasma levels fall quickly. The degree and rate of hydrolysis of plasma cholinesterase vary according to the agent used e.g., Chloroprocaine get hydrolyzed readily than procaine and tetracaine. The risk of developing toxicity increases is patients with atypical plasma cholinesterase, where hydrolysis of LA will be minimal or completely absent.

However the aminoamide LA are metabolized by the action of phase I enzymes of the liver and excreted by the kidneys. In the liver LA undergo a complex process of biotransformation by microsomal enzymes (CYP P450) followed by renal excretion. The rate of metabolism of LA is mainly depended on the liver blood flow and differs between agents. Patients with liver diseases and renal diseases where there is compromised blood flow to the liver will have lowered toxicity thresholds.

Placental transfer

In general, LA is able to cross the placenta by diffusion (Ralston, D.H. 1978) . The binding of LA to the mother's protein decreases the availability of LA that is free and able to diffuse across the placenta. The concentration of alpha1 acid glycoprotein in the fetus is low, thereby reducing the concentration of LA binding sites. The pH of blood of fetus is lower than that of mother, which results in ion-trapping of agents with higher pKa values (Morishim, H.O, 1982). Aminoester LA is hydrolyzed rapidly in the blood, so do not cross the placenta in significant amounts. However, there are changes in the speed of placental transfer and degree of retention in case of amide LA. It is important to remember that fetal acidemia impedes the placental transport of amide compounds from fetus to mother and as a result, delay in elimination of local anesthetic amides occur in fetus. The amounts of LA drugs (lidocaine, mepivacaine, bupivacaine and etidocaine) present in fetal tissues and blood (i.e., the total placental transport) is equal as per the calculations based in terms of percentage of the drugs administered to mother (Table 2). Thus, all local anesthetic amides cross the placenta in proportionate amounts and the safety of these drugs in fetus should be considered following equipotent and clinically acceptable doses of these drugs to the mother. Recently, the usage of mepivacaine has come down because of its relatively longer half-life resulting in delay of its elimination in the neonate. In a study by Morishima et al (1982) it was demonstrated that an increased sensitivity of the asphyxiated fetus to toxic CNS and cardiovascular effects of lidocaine when compared to the non asphyxiated fetus in baboons. This may be due to higher uptake of lidocaine in tissues (brain and heart) through increased organ perfusion, decreased plasma protein binding and ion trapping of the drug in acidotic tissue in case of asphyxiated fetus. In such cases, the smallest possible dose of LA amide should be used for regional blocks when fetus is compromised or is at increased risk for asphyxia. In this condition, 2-chloroprocaine is the safest anesthetic which gets readily hydrolyzed.

Rate of metabolism of LA

The rate of metabolism of LA is in the order ofPrilocaine>Etidocaine >Lidocaine> Mepivacaine>Ropivacaine>Bupivacaine.

Systemic Toxicity

Local anesthetics are to be used with caution as they have potential to cause serious harm. The magnitude of the effect will depend on the toxicity of the drug, the dose administered, the speed and site of administration, as well as the physical status of the patient in terms of age, medical conditions and pregnancy. The mechanism involved in the action of LA is the blockage of voltaged-gated Sodium channel which affects action potential propagation throughout the body. Therefore the possibility of systemic toxicity may occur. The toxic effects of LA can be reduced by careful techniques of needle placement, administration of fractionated doses, and use of less toxic anesthetic.

Toxicity of the LAs depends upon the route of administration and speed at which toxic plasma levels occur. If plasma levels raise slowly the central nervous system (CNS) is affected first. CNS toxicity of LA marked initially as CNS excitation, followed by CNS depression. This biphasic effect occurs because LA first blocks inhibitory CNS pathways and then ultimately blocks both inhibitory and excitatory pathways. The neurological symptoms include tongue paresthesia, dizziness, tinnitus blurred vision, restlessness, agitation, nervousness, paranoia, slurred speech, drowsiness, unconsciousness muscle twitching heralds the onset of tonic-clonic seizures with respiratory arrest to follow. Elevated plasma levels lead to blockade of sodium channel with more generalized neuronal depression leading to coma. The management should be aimed at maintaining oxygenation, fluids, vasopressors, and inotropes with use of anticonvulsants whenever necessary.

Signs and symptoms of various degree of neuropathy have been reported with spinal anesthesia with 2 to 5% lidocaine. Comparison of the frequency of transient neurologic symptoms and neurologic complications after spinal

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anesthesia with other local anesthetics was done by Zaric et al (2005). They reported that the risk for developing transient neurologic symptoms after spinal anesthesia with lidocaine was higher than compared to other anesthetics such as bupivacaine, prilocaine, procaine and mepivacaine. The toxic potential of bupivacaine is more than that of ropivacaine was reported by Zink et al (2005). However, in the preclinical study both drugs produce morphologically identical patterns of calcified myonecrosis, formation of scar tissue and a marked rate of muscle fibre regeneration after continuous peripheral nerve blocks.

Overdose of LA by intravascular injection leads not only to malfunctioning of CNS but it also results in cardiovascular toxicity. Some of the symptoms of cardiovascular toxicity include bradychardia with a long PR interval. Increasing blood levels lead to varying degrees of block, reentrant arrhythmics, tachycardia and ventricular fibrillation. The arrhythmias precipitated by LA are a result of depression of the rapid depolarization phase (Vmax) of the cardiac action potential. Yet, the management will be the same as described above for CNS toxicity.

Cardiovascular effects occur because LA block sodium channels through a fast in slow out mechanism that affects impulse conduction through the heart of nerve tissue. Albright et al (1979) reported unexpected cardiovascular toxicity of bupivacaine. The pre clinical studies showed that convulsive activity and cardiovascular collapse was lower for bupivacaine than lidocaine as the same dose of both. Whereas, a clinical study demonstrated that the doses required for producing early features of CNS and cardiovascular toxicity by ropivacaine and levo-bupivacaine were about equal and were higher than for bupivacaine (Stewart, J. 2003).

Depending on the nature of toxicity, the cardiovascular toxicity is treated according to the guidelines of American Heart Association. Lipid emulsion infusion may be beneficial in treating cardiovascular toxicity in some cases. Intravenous infusion of 20% lipid emulsion will be used for the treatment for systemic toxicity from LA.

Lipid emulsion therapy

At the first signs of systemic toxicity from LA, after airway management, use of lipid emulsion will be carried out. This will provide more lipids in which the lipidic phase of LA can dissolve more. In a study by Rosenblatt (2007) the high solubility of LA in lipid emulsions and high binding capacity of these emulsions has been reported in in vitro cultures. Several preclinical studies showed the successful application of lipid emulsion infusion in resuscitation of LA induced cardiac arrest (Weinberg, G.L. 1998, Weinberg, G.L. 2003, Weinberg, G.L. 2007, Mayr, V.D. 2008, Di Gregorio, G. 2009, Harvey, M. 2009). Many clinical studies demonstrated that 20% lipid infusion to resuscitate a patient from prolonged cardiac arrest that followed an interscalene block with different LAs (Rosenblatt, M.A. 2007, Litz, R.J. 2006, Litz, R.J.2008, Foxall, G. 2007, Ludot, H. 2008, Marwick, P.C. 2009).

Conclusion

Local anesthetics are widely used to manage pain during surgical, dental procedures and diagnostics purposes. They are also used to manage cancer pain. Though modern LAs are safer but a risk persists and a detailed mechanism of action, binding of LA to proteins, rate of its metabolism and systemic toxicity will be more effective.

Lipid emulsion proves to be effective for treating toxicity caused by LA. However an in-depth study is required to identify its role in it effectiveness.

Table 1: Clinical use of Local anesthetics

LA	Site of injection	Max. Dose (mg/kg body wt.)	Effect	Duration
Benzocaine	Topical	-	-	30 min-1 hour
Chloroprocaine	Epidural	12	Infiltration, peripheral nerve block	30 min-1 hour
Cocaine	Topical	3	-	30 min-1 hour
Tetracaine	Spinal, topical	3	-	1.5 hrs-6 hrs
Bupicaine	Epidural, Spinal	3	Infiltration, peripheral nerve block	1.5hrs-8hrs
Lidocaine	Epidural, Spinal	4.5 With epinephrine	Infiltration, peripheral nerve block	0.75- 2 hrs
Mepivacaine	Epidural	4.5 With epinephrine	-	1-2 hrs
Prilocaine	Dental	8	peripheral nerve block	30min-1hour
Ropivacaine	Epidural, Spinal	3	Infiltration, peripheral nerve block	1.5-8hrs

Table 2: The half-life of local anesthetics in adults and newborn

Half-life	2-Chloroprocaine (Nesacaine)	Lidocaine (Xylocaine)	Mepivacaine (Carbocaine)	Bupivacaine (Marcaine)
Adult	21 sec	1.6 hr	1.9 hr	2.7 hr
Newborn	43 sec	3.0 hr	9.0 hr	8.1 hr

Lidocaine, mepivacaine and bupivacaine are amides local anesthetics which undergo slower biodegradation in the liver and its products are eliminated by the kidneys. However 2-Chloroprocaine, an ester LA is rapidly hydrolysed in both maternal and fetal blood by the enzyme pseudocholinesterase present in plasma.

Figure 1: Action of local anesthetics after Ionisation inhibition of Sodium entry

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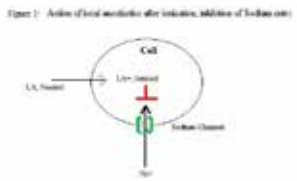
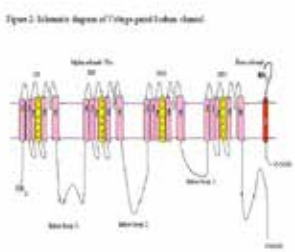


Figure 2: Schematic diagram of volatage gated Sodium channel



REFERENCE

1. Hille, B. Ionic channels of excitable membranes, 3rd ed. Sunderland, Massachusetts: Sinauer Associates, Inc.; 2001. | 2. Koller, C. (1928) Historical notes on the beginning of local anesthesia. JAMA., 90:1742-1743. | 3. Xiong Z, Strichartz G. (1998) Inhibition by local anesthetics of Ca2+ channels in rat anterior pituatary cells. Eur J Pharmacol., 363:81-90. | 4. Hollman, M, Wieczorek, K, Berger, A. (2001): Local anesthetic inhibition of G protein-coupled receptor signaling by interference with G alpha (q) protein function. Mol Pharmacol., 59:294-301. | 5. Olschewski, A, Hemplemann, G, Vogel, W. (1998): Blockade of Na+ currents by local anesthetics in the dorsal horn neurons of the spinal cord. Anesthesiology., 88: 172-179. | 6. Courtney, K.. (1975): Mechanism of frequency-dependent inhibition of sodium currents in frog myelinated nerve by the lidocaine derivative GEA 968. J Pharmacol Experiment. Ther., 195: 225-236. | 7. Aberg. G. (1972): Toxicological and local anaesthetic effects of optically active isomers of local anaesthetic compounds. Acta Pharmacol Toxicol., 31:444-450. | 8. Tucker, G. Local Anesthetic Drugs: Mode of Action and Pharmacokinetics. In: Nimmo W, Rowbotham D, Smith G, editors. Anesthesia. Oxford: Blackwell Scientific Publications; 1994.1371. | 9. Tucker, G.T, Moore, D.C, Bridenbaugh, P.O, Bridenbaugh, L.D, Thompson, G.E. (1972) Systemic absorption of mepivacaine in commonly used regional block procedures. Anesthesiology., 37: 277-287. | 10. Atkinson, R.L. (1982): Intravenous lidocaine for the treatment of intractable pain of adiposis dolorosa. Int J Obes., 56: 351–357. | 11. Cassuto, J, Wallin, G, Hagstrom, S, Faxen, A, Rimback, G. (1985): Inhibition of postoperative pain by continuous low-dose intravenous infusion of lidocaine. Anesth Analg., 64:971–974. | 12. Kastrup, J, Petersen, P, Dejgard, A, Hilsted, J. (1987): Intravenous lidocaine infusion: a new treatment of chronic painful diabetic neuropathy? Pain., 25:69–75. | 13. Glazer, S.A.B, Portenoy, K. (1991): Systemic local anesthetics in pain control. J Pain Symptom Manage., 6:30–39. | 14. Attal, N, Rouaud, J, Brasseur, L, Chauvin, M, Bouhassira, D. (2004): Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. Neurology., 62:218–225. | 15. Williams, D.R, Stark, R.J. (2003): Inravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. Cephalalgia., 23:963–971. | 16. Koppert, W, Weigand, M, Neumann, F, Sittl, R, Schuettler, J, Schmelz, M, et al. (2004): Perioperative intravenous lidocaine has preventive affects on postoperative pain and morphine consumption after major abdominal surgery. Anesth Analg., 98:1050–1055. | 17. Finnerup, N.B, Biering-Sorensen, F, Johannesen, I.L, Terkelsen, Astrid, J.M.D, Juhl Gitte, I.M.D, Kristensen, Anders, D, et al. (2005): Intravenous lidocaine relieves spinal cord injury pain: a randomized controlled trial. Anesthesiology., 102:1023–1030. | 18. Duarte, A.M, Pospisilova, E, Reilly, E, Mujenda, F, Hamaya, Y, Strichartz, G.R et al. (2005): Reduction of postincisional allodynia by subcutaneous bupivacaine. Anesthesiology., 103:113–125. | 19. Zhang, J.M, Li, H, Munir, M.A. (2004): Decreasing sympathetic sprouting in pathologic sensory ganglia: a new mechanism for treating neuropathic pain using lidocaine. Pain., 109:143–149. | 20. Ralston, D.H and Shnider, S.M. (1978): The fetal and neonatal effects of regional anesthesia in obstetrics. Anesthesiology., 48:34-64. | 21. Morishima, H.O and Covino, B.G. (1982): Toxicity and distribution of lidocaine in nonasphyxiated and asphyxiated baboon fetuses. Anesthesiology., 54:182-186. | 22. Zaric, D, Christiansen, C. Pace, N.L, Punjasawadwong, Yodying. (2005): Transient neurologic symptoms after spinal anesthesia with lidocaine versus other local anesthetics: a systematic review of randomized, controlled trails. Anesth Analg., 100:1811–1816. | 23. Zink, W, Bohl, J.R, Hacke, N, Sinner, B, Martin, E, Graf, B.M. (2005): The long term myotoxic effects of bupivacaine and ropivacaine after continuous peripheral nerve blocks. Anesth Analg., 101:548–554. | 24. Albright, G. (1979): Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology., 51:285-287. | 25. Stewart, J, Kellet, N, Castro, D. (2003): The central nervous system and cardiovascular effects of levobupivacaine and ropivacaine in healthy volunteers. Anesth Analg., 97: 412-416. | 26. Rosenblatt, M.A, Abel, M, Fischer, G.W, Eisenkraft, J.B. (2007) Anesthesiology., 106:637–638. | 27. Weinberg, G.L, VadeBoncouer, T, Ramaraju, G.A, Garcia-Amaro, M.F, Cwik, M.J. (1998): Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced a systole in rats. Anesthesiology., 88:1071–1075. | 28. Weinberg, G, Ripper, R, Feinstein, D.L, Hoffman, W. (2003): Lipid emulsion infusion rescues dogs from bupivacaine induced cardiac toxicity. Reg Anes Pain Med., 28:198–202. | 29. Weinberg, G.L. In reply [letter]. Anesthesiology 2007; 106:637. This paper discusses various clinical and experimental aspects related to the use of lipid emulsion to treat bupivacaine cardiotoxicity. | 30. Mayr, V.D, Mitterschiffthaler, L, Neurauter, A, Gritsch, C, Wenzel, V, Müller, T. (2008): A comparison of the combination of epinephrine and vasopressin with lipid emulsion in a porcine model of asphyxial cardiac arrest after intravenous injection of bupivacaine. Anesth Analg., 106: 1566-1571. | 31. Di Gregorio, G, Schwartz, D, Ripper, R, Kelly, K, Feinstein, D.L, Minshall, R.D et al. (2009): Lipid emulsion is superior to vasopressin in a rodent model of resuscitation from toxin-induced cardiac arrest. Crit Care Med., 37:993–999. | 32. Harvey, M, Cave, G, Kazemi, A. (2009): Intralipid infusion diminishes return of spontaneous circulation after hypoxic cardiac arrest in rabbits. Anesth Analg., 108:1163-1168. | 33. Rosenblatt, M.A, Abel, M, Fischer, G.W, Eisenkraft, J.B. (2007): Anesthesiology., 106:637–638. | 34. Litz, R.J, Popp, M, Stehr, S.N, Koch, T. (2006): Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. Anaesthesia., 61:800–801. | 35. Litz, R.J. (2008): Reversal of central nervous system and cardiac toxicity after local anesthetic intoxication by lipid emulsion injection. Anesth Analg., 106:1575-1577. | 36. Foxall, G, McCahon, R, Lamb, J, Hardman, J.G, Bedforth, N.M. (2007): Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid. Anaesthesia., 62:516–518. | 37. Ludot, H, Tharin, J.Y, Belouadah, M, Mazoit, J.X, Malinovsky, J.M. (2008): Successful resuscitation after ropivacaine and lidocaine-induced ventricular arrhythmia following posterior lumbar plexus block in a child. Anesth Analg., 106:1572-1574. | 38. Marwick, P.C, Levin, A.I, Coetzee, A.R. (2009): Recurrence of Cardiotoxicity after Lipid Rescue from Bupivacaine-Induced Cardiac Arrest. Anesth Analg., 108: 1344-1346. |