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The Role of Lipids in Local Anaesthetic Intoxication (Intralipids in Short Supply)

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Abstract **Review Article**

Systemic toxicity of local anaesthetics (LA) is a rare but often serious event. The clinical cases reported in the literature show that its clinical expression can be very polymorphous. The use of a peripheral block with ultrasound guidance reduces the incidence of vascular puncture and systemic toxicity Systemic toxicity is often delayed after L A injection. Therefore, close monitoring during the first 30 minutes after ALR (especially with ultrasound guidance) seems recommended. In case of a systemic accident, the administration of an intravenous lipid emulsion ELI is now part of the recommendations to be followed in case of cardiorespiratory arrest induced by a systemic overdose of local anaesthetic. The mechanisms of ELI are complex and probably multiple. Their use should therefore not replace other means of resuscitation, but appears to be an effective additional element. Further experimental studies and a clinical case registry will probably make it possible to better characterise the effects of an ELI-AL combination and to better understand the elements which, today, maintain the controversy of their use.

Keywords: lipids, local anaesthetic, intoxication, intralipids, lidocaine and bupivacaine, oliclinomel n4, generalized tonic-clonic convulsion.

INTRODUCTION

Systemic toxicity of local anaesthetics (LA) is a rare but often serious event. The clinical cases reported in the literature show that its clinical expression can be very polymorphous, often delayed after injection of LA. In fact, close monitoring during the first 30 minutes after ALR is performed seems to be recommended.

In the event of a systemic accident, the administration of an intravenous lipid emulsion ELI is now part of the recommendations to be followed in the event of cardiorespiratory arrest induced by a systemic overdose of local anaesthetic.

The mechanisms of ELI are complex and probably multiple. Their use should therefore not replace other means of resuscitation, but appears to be an effective additional element.

In our clinical case and in the absence of intravenous lipid emulsion in the Moroccan market, the use of the lipid component of oliclinomel as an alternative to ELI has proven to be effective in combination with resuscitative measures.

MEDICAL OBSERVATION

A 66 year old patient with no specific pathological history was admitted to the operating room for a cataract treatment of the left eye. On preoperative monitoring, the patient was hemodynamically and respiratorily stable with a blood pressure of 132/78, heart rate of 79 beats per minute, oxygen saturation of 98% at free airway and respiratory rate of 17 cycles per minute. A safety vascular line was placed in the right forearm.

After injection of local anaesthetic (lidocaine and bupivacaine) by retrobulbar route for cataract surgery, the evolution was marked in 2 minutes after injection by the installation of generalized tonic-clonic convulsion with post critical coma and respiratory distress (spO2 at 40% in free air) associated with a bradycardia at 40 beats per minute with arterial pressure at 90/42.

The patient was intubated, ventilated and sedated; with administration of 5 mg medazolam, loading dose of gardinal, 250 microgram atropine and early administration of the lipid component of oliclinomel N4 by peripheral venous route (equivalent to 40 g lipid), with a 20 ml kilogram saline filling 9% his capillary blood glucose is 1.05.

The immediate evolution was marked by the disappearance of convulsions, heart rate normalised and blood pressure stabilised without recourse to inotropes.

The examination on admission to the multipurpose resuscitation service of the 20 August hospital found a patient with IVS pupil in stable miosis on the haemodynamic level: PA: 128/75 MAP at 70, FC= 64bpm an ECG was carried out without anomaly, On the respiratory level: SpO2 at 100% under mechanical ventilation with Volume Controlled Ventilation mode with the following parameters FiO2= 50% / PEP= 4/ Vt= 500/ FR= 12.

After stabilisation, placement of a central venous catheter and administration of oliclinomel N7 lipid emulation over 12 hours 80g.

The patient underwent a cerebral CT scan which revealed no abnormalities; a full biological work-up was requested with no abnormalities including a lipid panel.

The evolution after 24 hours was favourable with a conscious Patient 1, PSR, no DSM, no more convulsions with spontaneous ventilation and hemodynamically stable: BP= 11/07, HR = 68 bpm; extubated by the following without incident with SPO2 at 98% in the open air, then he was transferred to the ophthalmology department for further specialised care.

DISCUSSION

Locoregional anaesthesia in ophthalmic surgery has grown considerably in recent years. In the short and medium term, this technique allows for faster patient rehabilitation and reduces the incidence of complications from general anaesthesia.

This technique is based on the use of local anaesthetics (LA), mostly of the amino-amide type. These molecules block voltage-gated sodium channels in nerve structures and thus prevent the propagation of the action potential along the axon. On the other hand, these molecules have other cellular targets such as the calcium channel, the mitochondria or the endoplasmic reticulum. These different interactions account for the toxicity of LA. During accidental intravascular administration or passive diffusion, a high plasma concentration of LA is manifested by systemic toxicity (TSAL), which is potentially fatal. Locally, these agents also have toxicity with less morbidity, which manifests itself on nearby structures such as the neuron, myocyte and chondrocyte.

A review of the literature shows that the first clinical signs of ALS are observed in less than one minute in 9% of cases [7].

TSAL is manifested by the appearance of clinical neurological and/or cardiac signs [4, 7, 8].

An increase in the plasma concentration of AL induces a blockage of cerebral cortical inhibitory pathways, resulting in the appearance of CNS symptoms and signs of excitation, including sensory or visual disturbances and muscle spasms. At very high plasma concentrations, CNS failure is observed, with impaired consciousness, coma and respiratory arrest.

LAs block potassium and calcium channels in myocardial cells. Associated pathophysiological effects are dysrhythmias, myocardial depression and collapse of systemic vascular resistance. Clinically, prolongations of PR, QRS and ST intervals may be observed, with an increased risk of bradycardia and reentrant tachycardia [9].

In addition to a dose-dependent effect, LA toxicity is also characterised by an increase in effect when the heart rate increases: this is *use-dependence* or phase block [10]. On the electrocardiogram, a widening of the QRS is classically described with possible modification of the QT. This effect is stereospecific with less toxicity of levobupivacaine and ropivacaine compared to racemic bupivacaine [10].

The clinical presentation of ALS in the cardiovascular system can therefore also be very multifaceted.

The physicochemical properties of LA molecules are associated with different levels of toxicity which are also dose dependent [10, 52, 55].

In 1998, Guy Weinberg's team described the first effects of intravenous coadministration of bupivacaine and ELI in rats [66]. The animals were divided into two groups: intravenous injection of bupivacaine associated or not with an injection of ELI. Two types of results were obtained: i) the toxic dose of bupivacaine necessary to induce cardiorespiratory arrest increases if it is preceded by an IV injection of Intralipid® 20%, and this is proportional to the dose of Intralipid® 20% pre-administered ii) during the injection of a lethal dose of bupivacaine, the mortality of the rats is significantly lower if they receive, during resuscitation, an IV solution of Intralipid® 20%. Numerous experimental studies have subsequently explored the mechanisms of action that could explain these phenomena.

Today, several mechanisms can probably account for this effect [67]. Among these different mechanisms, we could mention:

- The formation of a lipid trap: the formation of lipid droplets was initially observed by electron microscopy during a mixture of 20 ml of propofol in a lipid solution (1%) and 40 mg of lidocaine [68]. The authors describe an increasing diameter of the droplets over time, which may correspond to a capture of LA. This effect is described up to 24 hours after the two molecules are brought together. Dureau *et al.,* report that the administration of ELI after an intravascular injection of LA in healthy volunteers reduces the maximum concentrations of ropivacaine and levobupivacaine [69]. However, the ratio of free and protein-bound LA concentrations may not be altered [70].
- The likely involvement of cellular metabolism: In 1961, Shipp *et al*., demonstrated that lipids are essential energy substrates for cardiomyocytes [71]. Lipids are metabolised by the beta-oxidation cycle and allow mitochondrial ATP synthesis [72]. In the case of LA-induced cardiac toxicity, the administration of ELI, as the energy substrate of choice, could have a cyto-protective role with regard to the various stresses to which cardiomyocytes are subjected (Figure 1) [73, 74].
- The inherent haemodynamic effect of ELI: in the absence of LA, isolated administration of ELI in rats significantly increases aortic flow and arterial pressure compared to isotonic saline administration [73]. This positive inotropic effect may partly explain the return to a stable haemodynamic state observed in many clinical cases [75-78].
- Direct modulation of the sodium channel configuration: lipids interfere with the action of LA on the sodium channel. Experimentally, they decrease the intensity of the tonic and phasic block induced by LA.

The literature has been enriched since 2006 by the publication of some forty clinical cases highlighting the beneficial effects of ELI administration in the event of LA overdose, such as bupivacaine or ropivacaine [76, 77]. In one of the first two clinical cases published in 2006, a 58-year-old man underwent an interscalene block with a mixture of mepivacaine and bupivacaine [77]. At the end of the injection, the patient presented severe neurological signs followed by cardiorespiratory arrest. After 20 minutes of resuscitation and the persistence of haemodynamic instability, the administration of 100 ml of Intralipid® 20% allowed a very rapid improvement of the haemodynamic and electrical parameters, the patient not presenting any neurological complication afterwards. Similar results were subsequently described in other adult patients, but also in children [79, 80]. The majority of clinical cases report that, in the event of asystole following LA overdose, while the patient is receiving cardiopulmonary resuscitation with external cardiac massage, titrated adrenaline injections, oxygenation with a 100% inspired oxygen fraction and appropriate ventilation, additional administration of ELI is most often accompanied by haemodynamic restoration within a rapid timeframe of 5- 10 minutes.

A professional consensus has therefore legitimately included ELI in the treatment of ALS. In 2012, North American recommendations were published [81, 82]. However, the lack of high-level human studies and the heterogeneity of the results of experimental studies have given rise to controversy concerning the beneficial effects of the ELI-AL association. However, it seems legitimate to remain vigilant about cause and effect relationships because: i) an underestimation of the number of failures of ELI therapy cannot be excluded, ii) prospective and randomised studies on this subject are obviously ethically impossible.

Among the causes of failure of ELI therapy, animal experimental studies suggest that hypoxia, respiratory acidosis and excessive doses of adrenaline are factors in resuscitation failure.

In addition, the administration of ELI should be cautious. In the event of systemic LA overdose, some authors recommend that the maximum dose of 10 ml/kg of ELI should not be exceeded during the first 30 minutes [83]. This recommendation can be explained by the following arguments. In animal models, infusion of ELI during cardiopulmonary arrest induced by LA overdose inhibits vasodilation and thereby increases adrenaline-induced hyperlactatemia [84]. During a large volume injection of ELI in rats, an increase in triglycerides is observed during the first 48 hours, associated with an increase in amylase and ASAT [85]. These results have also been described in humans, with pancreatic [86], respiratory [82] or metabolic disorders such as hyperlipaemia.

The French Society of Anesthesia and Resuscitation (SFAR) and the American Society of Regional Anesthesia and Pain Medicine (ASRA) have published a *checklist* to be followed in the event of cardiopulmonary arrest related to an LST. The first three points are the subject of a clearly identified common consensus [81, 87]:

- Call for help
- Initial approach
- Airway management and ventilation with 100% oxygen.
- Management of severe neurological disorders: benzodiazepines first, do not inject propofol.
- Organising the possibility of an ECC.

- Management of asystole
- Prolonged cardiac massage.
- Avoid vasopressin, calcium channel blockers, beta-blockers, or other local anaesthetics.
- Adrenaline dose titration (<1mcg/kg).

The administration of ELI is less standardised. Overall, two protocols are published, which differ in the recommended initial doses and the presence or absence of continuous infusion (Table 2**)** [87]. In view of these differences, it is clear that the haemodynamic status of the patient will guide the practitioner to best apply these recommendations.

PARAMETERS	**Treatment with ELI (Intralipid® 20%) published on the SFAR website [87]**	**Treatment with ELI (Intralipid® 20%) published on the ASRA website [81]**
INITIAL DOSE	Initial bolus of 3 ml/kg IV	Initial bolus of 1.5 ml/kg IV over 1 minute
CONTINUOUS INFUSION	Continuous maintenance infusion is not essential	Continuous infusion of 0.25 ml/kg/min, possible up to 0.5 ml/kg/min in case of collapse
BOLUS REPETITION	-	Repeat bolus once or twice if cardiovascular collapse persists
DURATION	-	Continuous infusion at least 10 min after return to satisfactory hemodynamic balance
MAXIMUM DOSE	-	Avoid exceeding the maximum dose of 10ml/kg in the first 30 minutes
DURATION OF MONITORING	A minimum of 6 hours of rhythmic monitoring is recommended	Prolonged monitoring for more than 12 hours, justified by a risk of recurrence on discontinuation of the ELI

OLICLINOMEL (N4-550^{E} and N 7-1000**)** is an emulsion for infusion. It is presented in a 3-compartment bag.

One compartment contains a solution of glucose with calcium, a second a lipid emulsion and the third a solution of amino acids with other electrolytes.

Composition of a 1000 ml bag

Active substances	**20% lipid emulsion compartment (corresponding to 20 g/ 100 ml) (200 ml)**	**10% amino acid solution compartment (corresponding to 10 g/ 100 ml) (400 ml)**	**40% glucose solution compartment (corresponding to 40 g/100 ml) (400 ml)**
Refined olive oil + refined soybean oil*	**40,00 g**		
Alanine		8,28 g	
Arginine		4,60 g	
Glycine		4,12 g	
Histidine		1,92 g	
Isoleucine		2,40 g	
Leucine		2,92 g	
Lysine		2,32 g	
(as lysine hydrochloride)		(2,90 g)	
Methionine		1,60 g	
Phenylalanine		2,24 g	
Proline		2,72 g	
Serine		2,00 g	
Threonine		1,68 g	
Tryptophan		0,72 g	
Tyrosine		0,16 g	
Valine		2,32 g	
Sodium acetate, 3 H_2 O		2,45 g	
Sodium glycerophosphate, 5 H_2 O		2,14 g	
Potassium chloride		1,79 g	
Magnesium chloride 6 H_2 O		0,45 g	
Anhydrous glucose			160,00 g
(as glucose monohydrate)			(176,00 g)
Calcium chloride 2 H_2 O			0,30 g

CONCLUSION

Systemic toxicity of LA is a rare but often serious event. The clinical cases reported in the literature show that its clinical expression can be very polymorphous. It is often delayed after injection of LA. In fact, close monitoring during the first 30 minutes after ALR seems recommended.

Locally, the injection of LA is accompanied by cytotoxicity on the neighbouring structures, particularly affecting muscle and nerve cells. This cytotoxicity involves complex mechanisms and requires further experimental studies to understand them in more detail.

The key to LA toxicity lies above all in its prevention. This implies a judicious choice of LA, giving preference to the least cardiotoxic. The use of ultrasound guidance when performing ALR should encourage us to reduce the doses and concentrations of LA used.

In the event of a systemic accident, the administration of a LDE is now part of the recommendations to be followed in the event of cardiorespiratory arrest induced by a systemic overdose of a local anaesthetic. The mechanisms of ELI are complex and probably multiple. Their use should therefore not replace other means of resuscitation, but appears to be an effective additional element. Further experimental studies and a clinical case registry will probably make it possible to better characterise the effects of a combination of ELI and LA and to better understand the elements which, today, maintain the controversy of their use. Similarly, further work will help to better define the role of ELIs during overdosing with other fat-soluble agents.

REFERENCES

1. Sun Y, Li T, Gan TJ. The Effects of Perioperative Regional Anesthesia and Analgesia on Cancer Recurrence and Survival after Oncology Surgery: A Systematic Review and Meta-Analysis. Reg Anesth Pain Med 2015; 40:589-98.
2. Auroy Y, Benhamou D, Bargues L, Ecoffey C, Falissard B, Mercier FJ, Bouaziz H, Samii K. Major complications of regional anaesthesia in France: The SOS Regional Anaesthesia Hotline Service. Anesthesiology 2002; 97:1274-80.
3. Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. Reg Anesth Pain Med 2013; 38:289-99.
4. Liu SS, Ortolan S, Sandoval MV, Curren J, Fields KG, Memtsoudis SG, YaDeau JT. Cardiac Arrest and Seizures Caused by Local Anesthetic Systemic Toxicity After Peripheral Nerve Blocks: Should We Still Fear the Reaper? Reg Anesth Pain Med 2016; 41:5-21.
5. Abboud RT, Nelson TN, Jung B, Mattman A. Alpha1-antitrypsin deficiency: a clinical-genetic overview. Appl Clin Genet 2011; 4:55-65.
6. Kuo I, Akpa BS. Validity of the lipid sink as a mechanism for the reversal of local anesthetic systemic toxicity: a physiologically based pharmacokinetic model study. Anesthesiology 2013; 118:1350-61.
7. Vasques F, Behr AU, Weinberg G, Ori C, Di Gregorio G. A Review of Local Anesthetic Systemic Toxicity Cases Since Publication of the American Society of Regional Anesthesia Recommendations: To Whom It May Concern. Reg Anesth Pain Med 2015; 40:698-705.
8. Di Gregorio G, Neal JM, Rosenquist RW, Weinberg GL. Clinical presentation of local anesthetic systemic toxicity: a review of published cases, 1979 to 2009. Reg Anesth Pain Med 2010; 35:181-7.
9. Knudsen K, Beckman Suurkula M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth 1997; 78:507-14.
10. Mazoit JX, Decaux A, Bouaziz H, Edouard A. Comparative ventricular electrophysiologic effect of racemic bupivacaine, levobupivacaine, and ropivacaine on the isolated rabbit heart. Anesthesiology 2000; 93:784-92.
11. Meunier JF, Goujard E, Dubousset AM, Samii K, Mazoit JX. Pharmacokinetics of bupivacaine after continuous epidural infusion in infants with and without biliary atresia. Anesthesiology 2001; 95:87-95.
12. Paqueron X, Boccara G, Bendahou M, Coriat P, Riou B. Brachial plexus nerve block exhibits prolonged duration in the elderly. Anesthesiology 2002; 97:1245-9.
13. Muravchick S, Levy RJ. Clinical implications of mitochondrial dysfunction. Anesthesiology 2006; 105:819-37.
14. Heavner JE, Dryden CF, Jr, Sanghani V, Huemer G, Bessire A, Badgwell JM. Severe hypoxia enhances central nervous system and cardiovascular toxicity of bupivacaine in lightly anesthetized pigs. Anesthesiology 1992; 77:142-7.
15. Porter JM, Markos F, Snow HM, Shorten GD. Effects of respiratory and metabolic pH changes and hypoxia on ropivacaine-induced cardiotoxicity in dogs. Br J Anaesth 2000; 84:92-4.
16. Santos AC, DeArmas PI. Systemic toxicity of levobupivacaine, bupivacaine, and ropivacaine during continuous intravenous infusion to nonpregnant and pregnant ewes. Anesthesiology 2001; 95:1256-64.
17. Moller RA, Datta S, Strichartz GR. Beta-estradiol acutely potentiates the depression of cardiac excitability by lidocaine and bupivacaine. J Cardiovasc Pharmacol 1999; 34:718-27.

18. Santos AC, Karpel B, Noble G. The placental transfer and fetal effects of levobupivacaine, racemic bupivacaine, and ropivacaine. Anesthesiology 1999; 90:1698-703.
19. Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: a multifactorial concept. Reg Anesth Pain Med 2004; 29:564-75; discussion 24.
20. Nouette-Gaulain K, Capdevila X, Rossignol R. Local anesthetic 'in-situ' toxicity during peripheral nerve blocks: update on mechanisms and prevention. Curr Opin Anaesthesiol 2012; 25:589-95.
21. Cohen EN. Distribution of local anesthetic agents in the neuraxis of the dog. Anesthesiology 1968; 29:1002-5.
22. Mazoit JX, Boico O, Samii K. Myocardial uptake of bupivacaine: II. Pharmacokinetics and pharmacodynamics of bupivacaine enantiomers in the isolated perfused rabbit heart. Anesth Analg 1993; 77:477-82.
23. Collura V, Letellier L. Mechanism of penetration and of action of local anesthetics in Escherichia coli cells. Biochim Biophys Acta 1990; 1027:238-44.
24. Brull R, McCartney CJ, Chan VW, El-Beheiry H. Neurological complications after regional anesthesia: contemporary estimates of risk. Anesth Analg 2007; 104:965-74.
25. Gomez-Arnau JI, Yanguela J, Gonzalez A, Andres Y, Garcia del Valle S, Gili P, Fernandez-Guisasola J, Arias A. Anaesthesia-related diplopia after cataract surgery. Br J Anaesth 2003; 90:189-93.
26. Hogan Q, Dotson R, Erickson S, Kettler R, Hogan K. Local anesthetic myotoxicity: a case and review. Anesthesiology 1994; 80:942-7.
27. Malinovsky JM, Charles F, Baudrimont M, Pereon Y, Le Corre P, Pinaud M, Benhamou D. Intrathecal ropivacaine in rabbits: pharmacodynamic and neurotoxicologic study. Anesthesiology 2002; 97:429-35.
28. Zink W, Seif C, Bohl JR, Hacke N, Braun PM, Sinner B, Martin E, Fink RH, Graf BM. The acute myotoxic effects of bupivacaine and ropivacaine after continuous peripheral nerve blockades. Anesth Analg 2003; 97:1173-9.
29. Zink W, Bohl JR, Hacke N, Sinner B, Martin E, Graf BM. The long term myotoxic effects of bupivacaine and ropivacaine after continuous peripheral nerve blocks. Anesth Analg 2005; 101:548-54.
30. Padera R, Bellas E, Tse JY, Hao D, Kohane DS. Local myotoxicity from sustained release of bupivacaine from microparticles. Anesthesiology 2008; 108:921-8.
31. Amaniti E, Drampa F, Kouzi-Koliakos K, Kapoukranidou D, Pourzitaki C, Tsalie E, Vasilakos D. Ropivacaine myotoxicity after single intramuscular injection in rats. Eur J Anaesthesiol 2006; 23:130-5.
32. Duguez S, Feasson L, Denis C, Freyssenet D. Mitochondrial biogenesis during skeletal muscle regeneration. Am J Physiol Endocrinol Metab 2002; 282:E802-9.
33. Nouette-Gaulain K, Jose C, Capdevila X, Rossignol R. From analgesia to myopathy: When local anesthetics impair the mitochondrion. Int J Biochem Cell Biol 2011; 43:14-9.
34. Zink W, Graf BM, Sinner B, Martin E, Fink RH, Kunst G. Differential effects of bupivacaine on intracellular Ca2+ regulation: potential mechanisms of its myotoxicity. Anesthesiology 2002; 97:710-6.
35. Zink W, Missler G, Sinner B, Martin E, Fink RH, Graf BM. Differential effects of bupivacaine and ropivacaine enantiomers on intracellular Ca2+ regulation in murine skeletal muscle fibers. Anesthesiology 2005; 102:793-8.
36. Johnson ME, Saenz JA, DaSilva AD, Uhl CB, Gores GJ. Effect of local anesthetic on neuronal cytoplasmic calcium and plasma membrane lysis (necrosis) in a cell culture model. Anesthesiology 2002; 97:1466-76.
37. Leffler A, Fischer MJ, Rehner D, Kienel S, Kistner K, Sauer SK, Gavva NR, Reeh PW, Nau C. The vanilloid receptor TRPV1 is activated and sensitized by local anesthetics in rodent sensory neurons. J Clin Invest 2008; 118:763-76.
38. Haller I, Hausott B, Tomaselli B, Keller C, Klimaschewski L, Gerner P, Lirk P. Neurotoxicity of lidocaine involves specific activation of the p38 mitogen-activated protein kinase, but not extracellular signal-regulated or c-jun N-terminal kinases, and is mediated by arachidonic acid metabolites. Anesthesiology 2006; 105:1024-33.
39. Werdehausen R, Braun S, Essmann F, Schulze-Osthoff K, Walczak H, Lipfert P, Stevens MF. Lidocaine induces apoptosis via the mitochondrial pathway independently of death receptor signaling. Anesthesiology 2007; 107:136-43.
40. Wakata N, Sugimoto H, Iguchi H, Nomoto N, Kinoshita M. Bupivacaine hydrochloride induces muscle fiber necrosis and hydroxyl radical formation-dimethyl sulphoxide reduces hydroxyl radical formation. Neurochem Res 2001; 26:841-4.
41. Irwin W, Fontaine E, Agnolucci L, Penzo D, Betto R, Bortolotto S, Reggiani C, Salviati G, Bernardi P. Bupivacaine myotoxicity is mediated by mitochondria. J Biol Chem 2002; 277:12221-7.
42. Lambert LA, Lambert DH, Strichartz GR. Irreversible conduction block in isolated nerve by high concentrations of local anesthetics. Anesthesiology 1994; 80:1082-93.
43. Radwan IA, Saito S, Goto F. The neurotoxicity of local anesthetics on growing neurons: a comparative study of lidocaine, bupivacaine, mepivacaine, and ropivacaine. Anesth Analg 2002; 94:319-24, table of contents.
44. Johnson ME, Uhl CB, Spittler KH, Wang H, Gores GJ. Mitochondrial injury and caspase activation by

the local anesthetic lidocaine. Anesthesiology 2004; 101:1184-94.
45. Muguruma T, Sakura S, Kirihara Y, Saito Y. Comparative somatic and visceral antinociception and neurotoxicity of intrathecal bupivacaine, levobupivacaine, and dextrobupivacaine in rats. Anesthesiology 2006; 104:1249-56.
46. Muguruma T, Sakura S, Saito Y. Epidural lidocaine induces dose-dependent neurologic injury in rats. Anesth Analg 2006; 103:876-81.
47. Sztark F, Nouette-Gaulain K, Malgat M, Dabadie P, Mazat JP. Absence of stereospecific effects of bupivacaine isomers on heart mitochondrial bioenergetics. Anesthesiology 2000; 93:456-62.
48. Sztark F, Malgat M, Dabadie P, Mazat JP. Comparison of the effects of bupivacaine and ropivacaine on heart cell mitochondrial bioenergetics. Anesthesiology 1998; 88:1340-9.
49. Nouette-Gaulain K, Sirvent P, Canal-Raffin M, Morau D, Malgat M, Molimard M, Mercier J, Lacampagne A, Sztark F, Capdevila X. Effects of intermittent femoral nerve injections of bupivacaine, levobupivacaine, and ropivacaine on mitochondrial energy metabolism and intracellular calcium homeostasis in rat psoas muscle. Anesthesiology 2007; 106:1026-34.
50. Nouette-Gaulain K, Bringuier S, Canal-Raffin M, Bernard N, Lopez S, Dadure C, Masson F, Mercier J, Sztark F, Rossignol R, Capdevila X. Time course of mitochondrial metabolism alterations to repeated injections of bupivacaine in rat muscle. Can J Anaesth 2010; 57:836-42.
51. Nouette-Gaulain K, Dadure C, Morau D, Pertuiset C, Galbes O, Hayot M, Mercier J, Sztark F, Rossignol R, Capdevila X. Age-dependent bupivacaine-induced muscle toxicity during continuous peripheral nerve block in rats. Anesthesiology 2009; 111:1120-7.
52. Nouette-Gaulain K, Bellance N, Prevost B, Passerieux E, Pertuiset C, Galbes O, Smolkova K, Masson F, Miraux S, Delage JP, Letellier T, Rossignol R, Capdevila X, Sztark F. Erythropoietin protects against local anesthetic myotoxicity during continuous regional analgesia. Anesthesiology 2009; 110:648-59.
53. Galbes O, Bourret A, Nouette-Gaulain K, Pillard F, Matecki S, Py G, Mercier J, Capdevila X, Philips A. N-acetylcysteine protects against bupivacaine-induced myotoxicity caused by oxidative and sarcoplasmic reticulum stress in human skeletal myotubes. Anesthesiology 2010; 113:560-9.
54. Jose C, Bellance N, Chatelain EH, Benard G, Nouette-Gaulain K, Rossignol R. Antiproliferative activity of levobupivacaine and aminoimidazole carboxamide ribonucleotide on human cancer cells of variable bioenergetic profile. Mitochondrion 2012; 12:100-9.
55. Valenzuela C, Snyders DJ, Bennett PB, Tamargo J, Hondeghem LM. Stereoselective block of cardiac sodium channels by bupivacaine in guinea pig ventricular myocytes. Circulation 1995; 92:3014-24.
56. Kapral S, Greher M, Huber G, Willschke H, Kettner S, Kdolsky R, Marhofer P. Ultrasonographic guidance improves the success rate of interscalene brachial plexus blockade. Reg Anesth Pain Med 2008; 33:253-8.
57. Schnabel A, Meyer-Friessem CH, Zahn PK, Pogatzki-Zahn EM. Ultrasound compared with nerve stimulation guidance for peripheral nerve catheter placement: a meta-analysis of randomized controlled trials. Br J Anaesth 2013; 111:564-72.
58. Abrahams MS, Aziz MF, Fu RF, Horn JL. Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block: a systematic review and meta-analysis of randomized controlled trials. Br J Anaesth 2009; 102:408-17.
59. Walker KJ, McGrattan K, Aas-Eng K, Smith AF. Ultrasound guidance for peripheral nerve blockade. Cochrane Database Syst Rev 2009; CD006459.
60. O'Donnell BD, Iohom G. An estimation of the minimum effective anesthetic volume of 2% lidocaine in ultrasound-guided axillary brachial plexus block. Anesthesiology 2009; 111:25-9.
61. Danelli G, Ghisi D, Fanelli A, Ortu A, Moschini E, Berti M, Ziegler S, Fanelli G. The effects of ultrasound guidance and neurostimulation on the minimum effective anesthetic volume of mepivacaine 1.5% required to block the sciatic nerve using the subgluteal approach. Anesth Analg 2009; 109:1674-8.
62. Sites BD, Taenzer AH, Herrick MD, Gilloon C, Antonakakis J, Richins J, Beach ML. Incidence of local anesthetic systemic toxicity and postoperative neurologic symptoms associated with 12,668 ultrasound-guided nerve blocks: an analysis from a prospective clinical registry. Reg Anesth Pain Med 2012; 37:478-82.
63. Orebaugh SL, Kentor ML, Williams BA. Adverse outcomes associated with nerve stimulator-guided and ultrasound-guided peripheral nerve blocks by supervised trainees: update of a single-site database. Reg Anesth Pain Med 2012; 37:577-82.
64. Barrington MJ, Watts SA, Gledhill SR, Thomas RD, Said SA, Snyder GL, Tay VS, Jamrozik K. Preliminary results of the Australasian Regional Anaesthesia Collaboration: a prospective audit of more than 7000 peripheral nerve and plexus blocks for neurologic and other complications. Reg Anesth Pain Med 2009; 34:534-41.
65. Neal JM, Barrington MJ, Brull R, Hadzic A, Hebl JR, Horlocker TT, Huntoon MA, Kopp SL, Rathmell JP, Watson JC. The Second ASRA Practice Advisory on Neurologic Complications Associated With Regional Anesthesia and Pain Medicine: Executive Summary 2015. Reg Anesth Pain Med 2015; 40:401-30.
66. Weinberg GL, VadeBoncouer T, Ramaraju GA, Garcia-Amaro MF, Cwik MJ. Pretreatment or resuscitation with a lipid infusion shifts the dose-

response to bupivacaine-induced asystole in rats. Anesthesiology 1998; 88:1071-5.
67. Nouette-Gaulain K, Capdevila X, Robin F, Beloeil H. [Intravenous lipid emulsion and local anesthetic-induced systemic toxicity: mechanisms and limits]. Ann Fr Anesth Reanim 2014; 33:411-7.
68. Masaki Y, Tanaka M, Nishikawa T. Physicochemical compatibility of propofol-lidocaine mixture. Anesth Analg 2003; 97:1646-51.
69. Dureau P, Charbit B, Nicolas N, Benhamou D, Mazoit JX. Effect of Intralipid(R) on the Dose of Ropivacaine or Levobupivacaine Tolerated by Volunteers: A Clinical and Pharmacokinetic Study. Anesthesiology 2016.
70. Litonius E, Tarkkila P, Neuvonen PJ, Rosenberg PH. Effect of intravenous lipid emulsion on bupivacaine plasma concentration in humans. Anaesthesia 2012; 67:600-5.
71. Shipp JO, LH; Challoner,D. Fatty acid and glucose metabolism in the perfused heart. Nature 1961; 189:1018-9.
72. Nouette-Gaulain K, Quinart A, Letellier T, Sztark F. The mitochondria: roles and implications in anaesthesia-reanimation. Ann Fr Anesth Reanim 2007; 26:319-33.
73. Fettiplace MR, Ripper R, Lis K, Lin B, Lang J, Zider B, Wang J, Rubinstein I, Weinberg G. Rapid Cardiotonic Effects of Lipid Emulsion Infusion*. Crit Care Med 2013; 41:e156-e62.
74. Halestrap AP, Clarke SJ, Javadov SA. Mitochondrial permeability transition pore opening during myocardial reperfusion--a target for cardioprotection. Cardiovasc Res 2004; 61:372-85.
75. Ludot H, Tharin JY, Belouadah M, Mazoit JX, Malinovsky JM. Successful resuscitation after ropivacaine and lidocaine-induced ventricular arrhythmia following posterior lumbar plexus block in a child. Anesth Analg 2008; 106:1572-4.
76. Litz RJ, Popp M, Stehr SN, Koch T. Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. Anaesthesia 2006; 61:800-1.
77. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. Anesthesiology 2006; 105:217-8.
78. Schaeffer E, Rayaud L, Landy C, Boulland P, Favier JC. Local anaesthetic intoxication during an echo-guided axillary block treated with Intralipid. Ann Fr Anesth Reanim 2010; 29:929-30.
79. Shah S, Gopalakrishnan S, Apuya J, Shah S, Martin T. Use of Intralipid in an infant with impending cardiovascular collapse due to local anesthetic toxicity. J Anesth 2009; 23:439-41.
80. Aya AG, Ripart J, Sebbane MA, de La Coussaye JE. Lipid emulsions in the treatment of systemic toxicity of local anaesthetics: effectiveness and limitations. Ann Fr Anesth Reanim 2010; 29:464-9.
81. Neal JM, Mulroy MF, Weinberg GL. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. Reg Anesth Pain Med 2012; 37:16-8.
82. Weinberg GL. Lipid emulsion infusion: resuscitation for local anesthetic and other drug overdose. Anesthesiology 2012; 117:180-7.
83. Hayes BD, Gosselin S, Calello DP, Nacca N, Rollins CJ, Abourbih D, Morris M, Nesbitt-Miller A, Morais JA, Lavergne V, Lipid Emulsion W. Systematic review of clinical adverse events reported after acute intravenous lipid emulsion administration. Clin Toxicol (Phila) 2016; 54:365-404.
84. Hiller DB, Gregorio GD, Ripper R, Kelly K, Massad M, Edelman L, Edelman G, Feinstein DL, Weinberg GL. Epinephrine impairs lipid resuscitation from bupivacaine overdose: a threshold effect. Anesthesiology 2009; 111:498-505.
85. Hiller DB, Di Gregorio G, Kelly K, Ripper R, Edelman L, Boumendjel R, Drasner K, Weinberg GL. Safety of high volume lipid emulsion infusion: a first approximation of LD50 in rats. Reg Anesth Pain Med 2010; 35:140-4.
86. Bucklin MH, Gorodetsky RM, Wiegand TJ. Prolonged lipemia and pancreatitis due to extended infusion of lipid emulsion in bupropion overdose. Clin Toxicol (Phila) 2013; 51:896-8.
87. http://www.sfar.org/article/340/toxicite-systemique-aigue-des-anesthesiques-locaux.
88. Simon L, Kariya N, Edouard A, Benhamou D, Mazoit JX. Effect of bupivacaine on the isolated rabbit heart: developmental aspect on ventricular conduction and contractility. Anesthesiology 2004; 101:937-44.
89. Lin EP, Aronson LA. Successful resuscitation of bupivacaine-induced cardiotoxicity in a neonate. Paediatr Anaesth 2010; 20:955-7.